NDA20-449

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FPL sheet

D. please

NDA 20-449

MAY 14 1996

Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 1200
Collegeville, Pennsylvania 19426-0107

Attention: Max W. Talbott, Ph.D.
Vice President
Worldwide Regulatory Affairs

Dear Dr. Talbott:

Please refer to your July 24, 1994 new drug application and your resubmission dated December 1, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere (docetaxel) for Injection Concentrate.

We acknowledge receipt of your amendments dated October 13 and November 7, 1994; January 20, May 23, and December 1, 1995; and February 28, 1996.

This new drug application provides for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

We have completed the review of this application, including the submitted draft labeling, according to the regulations for accelerated approval and have concluded that adequate information has been presented to approve Taxotere (docetaxel) for Injection Concentrate for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved under 21 CFR 314.510. Approval is effective on the date of this letter.

Products approved under the Accelerated Approval Regulations 21 CFR 500 require further adequate and well-controlled studies to verify and describe clinical benefit. In this regard, we acknowledge your commitment in your letter dated November 21, 1995 to completing the following four controlled clinical trials and request that you submit the complete finding of these studies as soon as possible for our review to satisfy the requirements of the Accelerated Approval Regulations.

1. Ongoing studies in advanced breast cancer comparing docetaxel at 100 mg/m^2 with paclitaxel (TAX311), with doxorubicin (TAX303), and with mitomycin C/vinblastine (TAX304). For studies TAX311 and TAX304, sufficient numbers of anthracycline-resistant patients should be accrued to

confirm the response rate and toxicity profile of docetaxel in the patient population for which approval is based and to assess the clinical benefit of Taxotere.

2. An ongoing study in second line breast cancer comparing docetaxel 100 with docetaxel 75 mg/m^2 and assessing the clinical benefit of Taxotere. Serious consideration should be given to adding a 60 mg/m^2 dose (patients progressing after 2 cycles on the low dose could be retreated at a higher dose, assuming the higher dose can be tolerated).

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-449. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated November 21, 1995 and our October 27, 1995 approvable letter. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

You have agreed to complete and submit results of the following studies:

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Dotti Pease, Project Manager, at (301) 594-5742.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc: Original NDA 20-449
HFD-150/Div. files
HFD-150/CSO/DWPease
HFD-150/RJustice
HFD-150/JBeitz
HFD-150/YHsieh
HFD-150/RWood
HFD-150/MBrower
HFD-150/JDeGeorge
HFD-150/710/SJWang
HFD-150/710/CGnecco
HFD-150/480/PZannikos
HFD-150/480/ARahman
HFD-2/M.Lumpkin
HFD-101/L.Carter
HFD-810/C.Hoiberg
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)
HFD-021/J.Treacy (with labeling)

drafted: dwp/May 6, 1996/c:pease\n20449.ltr
r/d Initials: LVaccari 5-6-96
JBeitz 5-7-96
YHsieh 5-7-96
RWood 5-7-96
JDeGeorge 5-7-96
SJWang 5-7-96
CGnecco 5-7-96
MBrower 5-10-96
ARahman 5-10-96

R Temple 5/14/96

final:dwp/5-10-96/revised 5-14-96 per RTemple

Dwpease 5-14-96

APPROVAL [with Phase 4 Commitments]

R Justice 5/14/96

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FPL Sheet

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NDA 20-449

Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 1200
Collegeville, Pennsylvania 19426-0107

OCT 27 1995

Attention: James T. Molt, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Molt:

Please refer to your July 27, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere (docetaxel) for Injection Concentrate.

We acknowledge receipt of your amendments dated October 13 and November 7, 1994 and January 20 and May 23, 1995.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit revised draft labeling and the following information:

MEDICAL/PHARMACOLOGY-TOXICOLOGY/CHEMISTRY

We would like you to provide the data from which you concluded that degradate RPR 110928 was not a prognostic factor for the onset of neurotoxicity. In addition, we would like you to provide the maximum level of degradate RPR 1122248 found in lots used for phase 1 and phase 2 clinical trials and the numbers of patients exposed to that maximum.

MEDICAL

As was explained at the October Oncology Drug Advisory Committee (ODAC) meeting, many of the critical subgroup analyses carried out by RPR and utilized by the Committee in its deliberations on Taxotere have not been provided in full to the FDA.

1. Please provide case report forms for the 15 second line breast cancer patients with combined abnormalities of transaminase and alkaline

phosphatase.

2. Please provide case report forms for all second line breast cancer patients with baseline edema and/or effusions, in support of the claim that Taxotere may be given to patients with baseline fluid retention (your slide 36).

3. Please provide tumor lesion measurements and your assessment for the 174 second line breast cancer patients treated in Japan and your assessment of anthracycline-resistance in this patient population. To expedite this submission, Japanese data could be submitted electronically, with minimal prior translation. If this data cannot be submitted in a timely manner, please explain why.

4. Please provide a detailed summary of all hematologic and non-hematologic toxicities observed in the 134 anthracycline-resistant patients on TAX233, TAX267, and TAX286, grouped according to baseline liver function (patients with combined elevations of alkaline phosphatase and transaminase vs. those without the combined elevations).

5. Please provide details of the assessment of performance status over time for responders and non-responders that was presented at the October 1995 ODAC Meeting. Your slides 61-65 should be submitted along with supporting electronic data.

6. Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. This update should provide the most recent information available on the cohort of patients premedicated with the 5-day dexamethasone regimen, including the median number of treatment cycles, median cumulative dose to onset of moderate/ severe toxicity, median cumulative dose to treatment discontinuation, rate of treatment discontinuation, and duration of fluid retention. Please also describe patient compliance with the regimen, adverse events attributable to dexamethasone (e.g., gastrointestinal perforation), supportive measures used to treat fluid retention, evolution of performance status during treatment, and response to docetaxel treatment.

7. We acknowledge your verbal commitment to conduct a physician education program. Please confirm in writing and provide a detailed proposal for review.

In addition, the following points should be clarified:

1. There were 26 deaths (out of 1327) reported to the NDA as of 2/17/95, of which 19 were sepsis-related. In addition, between 1/95 and the present (10/25/95), there have been 16 toxic deaths reported to IND# , of which only 5 were sepsis-related. Please explain the apparent preponderance of non-sepsis related deaths among the reports to the IND this year.

2. Please specify the number of toxic deaths and the cycle in which they occurred among the 95 patients with transaminase elevations in the March 1995 safety analysis of patients with liver dysfunction. Appendix V (3/95) indicates that there were a total of 5 toxic deaths, and 4 occurred at the first cycle. However, in your response of May 23, 1995, there were 4 toxic deaths occurring after the first cycle in this group.

3. Please describe the specific symptoms that led to the designation of "severe asthenia" for each anthracycline-resistant patient with this reported toxicity, and explain, to the extent possible, why the presence of this toxicity did not lead to a report of deterioration in performance status in these patients.

4. We would like to be able to describe in the labeling the fraction of patients who had infection complicated by the need for hospitalization or IV antibiotics. Please provide the incidence of infection requiring hospitalization of IV antibiotics by grade of neutropenia for anthracycline-resistant patients.

CHEMISTRY/MANUFACTURING/CONTROLS

The sensitivity and reactivity of the new drug substance, docetaxel, and its synthetic intermediates, towards oxidation, acids, bases, heat, light and other reagents have resulted in a substantial level of observed impurities in both the drug substance and the drug product. Because of a possible correlation between impurity levels and observed clinical toxicity, efforts must be made to reduce

impurity levels by improvements of in-process controls and the use of more sensitive analytical methods. Such changes will also result in improved batch-to-batch uniformity of both the drug substance and the drug product.

1. The following comment/request pertains to the drug substance HPLC analytical method:

   Your proposed changes of the method, by using a high performance detector and increasing the injection concentration (not specified), to improve the limit of detection (LOD) to 0.02% and limit of quantitation (LOQ) to 0.05% (appendix 19), are not adequate to detect the residual RP 61387 in the drug substance. The regulatory method selected to routinely control impurities in commercial lots should be capable of detecting all the impurities actually found. The LOD and LOQ of the HPLC method can be improved by injecting larger quantities of samples. However, we are unable to determine the proposed increased injection concentration from appendix 19. Please specify the proposed increased injection concentration of the drug substance and justify it, using the response curves of docetaxel provided in appendix 13.

2. The following comments/requests pertain to drug substance manufacturing process:

d. The second paragraph of page 40 of appendix 6 was mistakenly titled It should be "Filtration of DCU" instead.

e. The saponification after the Darzens reaction involves The procedure calls for maintaining the reaction mixture at room temperature for 20 hours. The reaction completion test and validation data to justify the reaction time need to be provided.

f. No data were provided to justify the reaction time of 4 hours for the esterification of phenylisoserine (

g. Neither test for completion nor data were provided to justify the reaction time for the protection of the side chain hydroxy group in the isoserine derivative, RPR 104493

3. The following comments/requests pertain to drug product specifications:

a. Levels of impurities RPR 101118, RPR 102049, RP66779 + A and RPR 102512 are not individually controlled. Instead, they are included into "total related substances" in the proposed Taxotere® drug product specifications. However, as shown in the limit for these "total related substances" is raised from % at the time of manufacture to % for the stability specification, indicating that these degradants increased significantly during the stability studies. These results clearly underline the need to better control these impurities. The justifications given to group them into "total related substances" and regulate with a total limit in the drug product specifications are not adequate. We recommend that individual specifications, based on appropriate preclinical and clinical data, be established for these impurities.

b. It is noted that:

(1) The increase of RP 61387 concentration during the stability study suggests that docetaxel is degraded into RP 61387 and N-t-butyloxycarbonyl-3-phenyl-isoserine in Taxotere solution; yet little data on the detection and quantitation of isoserine as degradant have been provided.

(2) The t-butyloxycarbonyl (Boc) group on the side chain amino function in the docetaxel molecule is heat-labile. However, the potential degradation pathway of the drug product through the cleavage of the Boc group has not been addressed.

We recommend that potential degradations of Taxotere through the 2 pathways discussed in 1. and 2. be comprehensively examined. Degradants should be identified and quantitated, if appropriate. Validation data to demonstrate that the analytical method is specific enough to detect the potential degradant(s) should be provided as well.

4. The following comments/requests pertain to the examination of the drug

product HPLC analytical method:

Validation data to demonstrate that the proposed LOD and LOQ of the prescribed HPLC analytical method is capable of detecting and quantitating potential process impurities and degradants have not been provided. Given that the same HPLC conditions and method of quantitation (normalized area percent) are used for analyzing docetaxel and Taxotere® and that the LOD and LOQ for assaying docetaxel are being adjusted to a more sensitive level, the Agency does not believe that the proposed LOD of % and LOQ of % for Taxotere® are acceptable. We have the following comments and recommendations:

a. The amount of sample injected μg) for the analysis has not been adequately justified.

b. Provide validation data to demonstrate that the proposed LOD and LOQ of the prescribed HPLC analytical method of the drug product is capable of detecting and quantitating potential process impurities and degradants.

c. The Agency acknowledges the applicant's concern that injecting a more concentrated solution would also introduce more polysorbate 80 on the HPLC column with potential adverse effects on its selectivity and/or lifetime; however, the amount of the surfactant injected on the column can be minimized if docetaxel and its degradants are recovered from the drug product concentrate before the analysis.

d. The procedures to prepare sample solutions for the drug product analysis as provided in page 3-3-89 in the original NDA application (first paragraph, 3.1-Solution S) read:

Please explain.

5. The following comments/requests pertain to the drug product manufacturing process:

a. The time limit for the distillation of (conducted at should be

specified.

b. Please verify whether the temperature of the drug product solution in the distillation step

original NDA application.

POST-APPROVAL STUDIES AND ANALYSES

We note that you have committed verbally to us and before the Oncology Drugs Advisory Committee to the completion of several ongoing and proposed studies. We will need a letter documenting your intent to complete and submit results of the following studies as soon as possible after marketing:

LABELING

We have enclosed our preliminary comments on your July 21, 1995 draft package insert. You will need to revise this according to the new indication and we anticipate that additional revisions will be needed once we have completed our reviews of the information requested above.

In addition, a patient package insert should be provided, outlining specific directions, precautions, warnings or safety information patients should know to take this drug safely (e.g., patients should be alert to the signs and symptoms of fluid retention; the importance of taking premedication, etc.). Please provide a draft patient package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Dotti Pease, Project Manager, at (301) 594-5742.

Sincerely yours,

Robert Temple 10/27/95

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Revised Draft Labeling

cc: Original NDA 20-449
HFD-150/Div. File
HFD-2/M.Lumpkin
HFD-80
HFD-100
DISTRICT OFFICE
HFD-244/SSherman (with draft labeling)
HFD-638 (with draft labeling)
HFD-730
HFD-8
HFD-9/ASeifried
HFD-150/DWPease
HFD-150/JBeitz
MBrower
JDeGeorge
YHsieh
RWood
MMehta
PZannikos
SJWang
SWilson

drafted: DWPease/10-19-95/n20449.ltr
r/d initialed by: LVaccari 10-23-95
YHsieh 10-23-95
RWood 10-23-95
SJWang 10-23-95
SWilson 10-23-95
PZannikos 10-23-95
MMehta 10-23-95
MBrower 10-24-95
JDeGeorge 10-24-95
JBeitz 10-24-95
F/T: dwp 10-25-95: initialed by RJustice 10-25-95 RJustice 10/27/95
RDeLap 10-25-95
Revised: dwp 10-26-95/n204492.ltr
dwp 10-27-95/n20449.ltr
APPROVABLE (AE)
10-27-95

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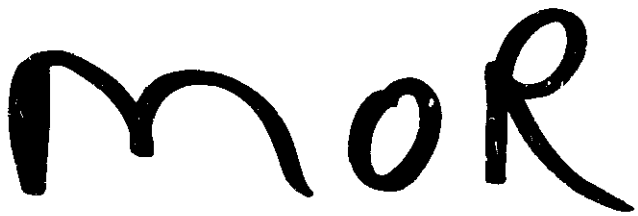
FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.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D. Prac

FEB 23 1996

MEDICAL OFFICER REVIEW OF AMENDMENT TO NDA # 20-449

TAXOTERE® (docetaxel) for Injection Concentrate

November 3, 6, 21, 1995 and December 1, 1995 Submissions

1. Description of Clinical Data Sources

RPR has submitted the following responses and documents as requested under the "MEDICAL" heading of the October 27, 1995 Approvable Letter:

Response/Document	Date Submitted
Request #1: Case report forms - liver dysfunction	11/3/95
Request #2: Case report forms - fluid retention	11/3/95, 11/6/95
Request #3: Japanese clinical experience	11/21/95
Request #4: Toxicity profile in anthracycline-resistant breast cancer	11/21/95
Request #5: Evolution of performance status	11/21/95
Request #6: Safety update	11/21/95
Request #7: Physician education program	11/21/95
Clarification #1: Recent deaths reported to the IND	11/3/95
Clarification #2: # deaths in 95 patients with transaminase elevations reported in 3/95	11/3/95
Clarification #3: Severe asthenia and performance status	11/21/95
Clarification #4: Patients with infections requiring hospitalization or IV antibiotics	Not submitted
Draft product labeling and patient package insert	12/1/95
Post-Approval Commitments #1 - #7	11/21/95

In addition, the following information was submitted in the 11/21/95 document: RPR's response to the Pharmacology/Toxicology questions regarding docetaxel degradates (RPR110928 and RPR112248), univariate and logistic regression analyses of febrile neutropenia (dataset upon request), and a discussion of the influence of baseline α-1-acid glycoprotein levels on PK and PD. These materials will be reviewed by the Pharm/Tox and BioPharm Divisions, respectively.

[redacted]

2. Maximum Level of Degradate RPR-112248

RPR has submitted a list of seven patients who received a higher level (> 0.8%) of degradate RPR112248, a degradate with questionable neurotoxicity in preclinical studies (Pharmacology/ Toxicology request in the Approvable Letter). Two of these patients developed neurotoxicity in cycles following initial exposure; severe neurotoxicity may have contributed to treatment discontinuation in one of these patients, despite a clinical response. Four patients came off study early due to disease progression, before it may have been possible to observe neurotoxicity, and there is no clinical information available on one patient.

Comment: This group of seven patients is not representative of the patients treated on pivotal trials. While the incidence of neurotoxicity (2/7) is in keeping with the 65% incidence of neurotoxicity reported (N=134 anthracycline-resistant breast cancer patients), the incidence of early withdrawals due to disease progression (4/7) is more than double that observed in the pivotal trials. In these trials, only 27/134 or 20% of patients had disease progression as the best response to docetaxel. **The clinical experience with exposure > 0.8% of RPR112248 is insufficient to rule out the possibility for the development of severe neurotoxicity. If additional clinical data is not available to clarify this point, then further toxicologic evaluation in mice (as previously described) may be required.**

Information on these patients was derived from annotated case report forms submitted to the original NDA on patients who died on study. Docetaxel clearance was known for one patient.

Study 224:
Patient : 46 year old male with small cell lung cancer who received docetaxel 100 mg/m^2 for five cycles. Docetaxel clearance was 34.4 L/min in cycle 1. He was "exposed" in cycle 3, and developed grade 3 neurosensory and neuromotor toxicity, and moderate neuralgia in cycle 5. He was taken off study due to adverse events (those listed above plus severe skin toxicity) after cycle 5, despite a partial response.

Study 225:
Patient 71 year old male with adenocarcinoma of the lung who received docetaxel 100 mg/m^2 for three cycles. He was "exposed" in cycle 1, but was taken off study after cycle 3 due to disease progression.

Study 245:
Patient exposed in cycle 1, no clinical information available

Patient 65 year old male with malignant fibrous histiocytoma who received one dose of docetaxel 100 mg/m^2. He had baseline grade 2 neuromotor symptoms (difficulty with walking, dexterity, gross movements, strength). He was "exposed" in cycle 1, but was taken off study after this cycle due to disease progression.

Patient 34 year old female with malignant fibrous histiocytoma who received docetaxel 100 mg/m^2 for two cycles. She was "exposed" in cycle 1, but was taken off study after cycle 2 due to disease progression.

Patient 55 year old female with leiomyosarcoma who received docetaxel 100 mg/m^2 for three cycles, then reduced to 75 mg/m^2 for one cycle. She was "exposed" in cycle 1, developed moderate paresthesias in cycle 4, and was taken off study after cycle 4 due to drug toxicity (including febrile neutropenia, grade 4 stomatitis and skin toxicity, and grade 3 elevation of bilirubin).

Patient 63 year old male with leiomyosarcoma who received docetaxel 100 mg/m^2 for two cycles. He was "exposed" in cycle 1, but was taken off study after cycle 2 due to disease progression.

3. Japanese Clinical Experience with Docetaxel 60 mg/m^2

RPR has submitted a new analysis of the efficacy data in 174 breast cancer patients previously treated with chemotherapy ("MEDICAL" Request #3 of the Approvable Letter). This data was assessed by a committee of Japanese investigators in accordance with the "Criteria for Assessment of Direct Efficacy of Chemotherapy for Solid Tumors" proposed by the Japanese Society for Chemotherapy, and with "Rules on Dealing with Breast Cancer" proposed by the Society for the Study of Breast Cancer. According to RPR, this data has not been "reviewed by an independent panel as were the pivotal US and European breast cancer clinical trials".

Comments on Baseline Characteristics:

1. In the Japanese trials, the breakdown of patients by intent of prior chemotherapy or number of prior chemotherapy regimens is not appreciably different from that found in the 3 pivotal trials, TAX233, TAX267, and TAX286. The median time elapsed between last chemotherapy and start of docetaxel was one month longer in the Japanese trials. See Table 1 below.

2. Four patients in Japanese trials had received additional chemotherapy after anthracycline and prior to docetaxel. Note that the TAX233 and TAX267 protocols permitted patients to receive up to 4 cycles of a non-anthracycline-containing regimen after documentation of anthracycline-resistance. The study reports, however, do not indicate the number of such patients entered.

3. The median duration of prior anthracycline therapy was longer in the Japanese studies (3.5 months, range 1-11 months) as compared to the 3 pivotal trials (1.6 months, range 1 day - 8.6 months). This difference may be related to the numbers of patients entered with PD as best response to prior anthracycline in the various trials. In the pivotal trials, there were, in fact, only 106 (of 134) patients who had a documented response to prior anthracycline. Of these, 53 or 50% had PD as best response to prior anthracycline, as compared to 21 of 92 (23%) patients in late phase 2 Japanese trials. (See MO Review of Amendment to NDA # 20,449, 10/24/95, p. 67,

for docetaxel response rates in the 3 pivotal trials by response to prior anthracycline).

Table 1
Comparison of Baseline Patient Characteristics in Japanese and US/EORTC Trials

Characteristic	Japanese 60 mg/m² N=174	TAX233[a] 100 mg/m² N=41	TAX267[b] 100 mg/m² N=42	TAX286[c] 100 mg/m² N=51
Prior Tx				
Adj/neoadj only	32 (18%)	4 (10%)	2 (5%)	6 (12%)
Adv only	70 (40%)	22 (54%)	14 (33%)	20 (39%)
Adj/neoadj + Adv	72 (41%)	15 (36%)	26 (62%)	25 (49%)
# of Prior Regimens				
1	64 (37%)	15 (37%)	9 (21%)	23 (45%)
2	72 (41%)	19 (46%)	20 (48%)	23 (45%)
3	30 (17%)	7 (17%)	12 (29%)	5 (10%)*
> 3	8 (5%)	0	1 (2%)	-
Time since last chemo				
Median (mos)	2.5	1.3	1.2	1.4
Range (mos)				

[a] Table 13, 8-38-70
[b] Table 13, 8-44-71
[c] Table 18, 9-12-203
* 3 or more prior regimens

Comments on Response Rates in Patient Subgroups:

1. Table 3.2 of the November 1995 submission (page 8) lists objective response rates in Japanese trials related to the number of prior chemotherapy regimens received. These were: 41% for 1 prior regimen, 49% for 2 prior regimens, 53% for 3 prior regimens, and 25% for more than 3 regimens. Comparable analyses were not provided in the NDA for the TAX233, TAX 267 or TAX286 trials.

2. Objective response rates to docetaxel by intent of prior chemotherapy (patients with prior adjuvant/neoadjuvant treatment only vs patients with prior treatment for advanced disease) were similar across trials. See Table 2 below.

3. Early phase 2 Japanese trials included 35 patients who had received prior anthracycline therapy. Of these, 7 had either NC or PD as best response to prior anthracycline. The objective response rate in this group was 29% (2/7). This finding is similar to the objective response rate in the TAX286 trial which demonstrated a 29% response rate (12/41 patients) with anthracycline resistance defined in this way. Note that this definition is more restrictive than that used in the TAX233 and TAX267 trials, or for the proposed indication for docetaxel.

4. Late phase 2 Japanese trials included 92 patients with prior anthracycline exposure. Of these, 21 were reported to have PD as best response to prior anthracycline; the objective response rate in this group was 33%. This compares favorably to response rates in this patient subgroup treated on the TAX233, TAX267, and TAX286 trials (see Table 2). Again, this definition of anthracycline-resistance is more restrictive than that for the proposed indication.

Table 2
Comparison of Response Rates in Patient Subgroups in Japanese and US/EORTC Trials

ORR by Patient Subgroup	Japanese 60 mg/m² N=174	TAX233 100 mg/m² N=41	TAX267 100 mg/m² N=42	TAX286 100 mg/m² N=51
ORR by Prior Tx Adj/neoadj Only Advanced	 18/32 (56%) 61/142 (42%)	 3/4 (75%)[a] 16/37 (43%)[a]	 1/2 (50%)[b] 20/40 (50%)[b]	 0/5[c] 12/33 (36%)[c]
ORR in Pts with PD as Best Response to Prior Anthracycline	7/21 (33%)	4/13 (31%)	5/15 (33%)	9/25 (36%)

[a] Table 4.10, 8-39-188 [b] Table 4.10, 8-45-232 [c] Table 30, 9-12-221, N= 38 evaluable patients only

5. Recall that similar response rates have been noted with 3- and 24-hour infusions of paclitaxel for the subgroup of patients having PD as best response to prior anthracycline. A response rate of 27% (8/30) for paclitaxel 175 mg/m² over 3-hours (Bristol-Myers Squibb randomized phase 3 trial) was confirmed by this Division, and a response rate of 32% (10/31, 95% CI: 18-40%) has been reported for paclitaxel 250 mg/m² over 24-hours (Seidman et al., 13, JCO, 1995).

6. **RPR's submission fails to discuss the 50 additional responses that occurred among the remaining 99 patients previously treated with anthracycline in the Japanese trials.** (Table 16, Japanese Clinical Experience, 7/21/95 submission, stated that there were a total of 59 responses among 127 patients (47%) previously treated with anthracycline.) These responses presumably occurred in patients who either a) had a prior CR or PR to anthracycline in the early phase 2 trials, or b) had a prior response of CR, PR, or NC to anthracycline in the late phase 2 trials. **To completely describe the responses seen in Japan and to perform a fair comparison to responses seen in the 3 pivotal trials, RPR should provide the number of responses that occurred in patients in the following groups: a) those with an initial CR or PR, then PD on anthracycline, b) those with an initial response of NC, then PD on anthracycline, and c) those with progression on adjuvant anthracycline.** Given the similarity in response rates for the 60 and 100 mg/m² doses among patients presenting with the "worst case scenario" (i.e., PD as best response to prior anthracycline), it is unlikely that the response rates in Japan will be inferior in patients with more responsive disease.

7. The proposed indication for docetaxel as treatment for anthracycline-resistant breast cancer does not specify that patients must have disease that was unresponsive or responsive to

anthracycline prior to progression. Recall that the response rate among docetaxel-treated patients on pivotal trials (100 mg/m²) with unresponsive disease was not statistically different from the response rate among patients with responsive disease (p=0.312, MOR, 10/24/95, p. 67). Similar conclusions have also been reported for paclitaxel by Seidman et al., 13, JCO, 1995, and by Wilson et al., 12, JCO, 1994 [and personal communication with Dr. Wilson]).

Comments on Appendices I and II:

1. Appendix I provided the "overall response" assessment for each of the 174 previously treated breast cancer patients in Japanese trials. A total of 79 objective responses are listed. This corresponds to the information previously reported to the Agency (Table 14, Japanese Clinical Experience, 7/20/95). The methodology used to determine these responses was not provided.

2. Appendix II tabulated the tumor measurements in 152 of these patients who had measurable disease. There were several discrepancies in how the indicator lesion was described in Appendix I vs II (e.g., "breast" was often listed as "skin", "soft tissue" or "subcutaneous"). Different indicator lesions were listed for the same patient in the two appendices. This reviewer was able to confirm "lesion" responses in 48 patients using the indicator lesions noted in Appendix II. The responses in the remaining 31 patients could not be confirmed for the following reasons:

Table 3
Status of "Lesion" Responses in Japanese Trials as Presented in Appendix II

"Lesion" Responses (N=79 Patients)	Patient ID
Response in indicator lesion(s) confirmed by reviewer (N=48)	
Response not confirmed 4 weeks later (N=16)	
Tumor measurements missing on-study, or disease not measurable (N=7)	
Measurement of indicator lesion was unidimensional (N=4)	
Reviewer disagreement with assessment of response as noted in Appendix I (N=4)	

Comments: Appendix II tabulations were incomplete in several respects as noted in the table above. Data on all indicator lesions for all cycles would allow confirmation of objective responses lasting $\geq$ 4 weeks. **If RPR has not audited the Japanese sites, it should be strongly encouraged to do so.**

Even if additional data is not forthcoming, and/or the 45% "overall response" rate has been overestimated in Appendix I, a response rate of 28% (48/174, intent-to-treat, assuming all measurable indicator lesions have been counted) is not insignificant in patients with previously treated breast cancer. Prior exposure to anthracycline in these patients has not been provided, but should be easily retrievable.

The product label should include accurate and complete safety and efficacy information on docetaxel. For some patients, doses below 100 mg/m² will undoubtedly be used. To the extent possible, the proposed label should be amended so that practicing oncologists are made aware of the risks and benefits of administering doses below 100 mg/m².

4. Serious Adverse Events - Update

The following updated information on fatal and non-fatal adverse events was submitted in response to "MEDICAL" Request #6 of the Approvable Letter.

- **Deaths**

RPR reported a total of 145 treatment-related deaths among 5,083 patients treated with docetaxel 100 mg/m² every 21 days, regardless of tumor type or pretreatment characteristics. These patients were treated between 10/2/90 and 10/31/95. Of these, 88 deaths were due to infection and 57 to "other" treatment-related adverse events, not otherwise described in this submission. See Table 4 below.

RPR also reported a total of 88 treatment-related deaths among 4,452 patients treated with docetaxel 100 mg/m² every 21 days, regardless of tumor type or pretreatment characteristics. These patients were treated between 7/1/94 and 10/31/95. Of these, 56 were due to infection and 32 to "other" treatment-related adverse events, not otherwise described in this submission.

Comment: If the second cohort described above is, in fact, a subset of the total number of patients treated, then there would have been 631 patients treated early on (between 10/2/90 and 6/30/94) that experienced 57 treatment-related deaths, for a 9% toxic death rate. Of these, 32 would have been due to infection, and 25 to "other" adverse events. These events should have been captured in the original NDA, submitted 7/27/94. However, that document reports a total of 17 treatment-related deaths among 912 patients treated at 100 or 75 mg/m², for a 1.9% toxic death rate (8-117-69). Of these, 14 were due to infection, and 3 to other adverse events (one patient with cardiac failure/pulmonary edema, one with hemiparesis and drowsiness, and one with gastro-intestinal hemorrhage due to thrombocytopenia in the setting of liver

dysfunction). That document also reported one toxic death and 21 unrelated deaths among 256 patients receiving a range of doses (5-130 mg/m²/cycle) on phase 1 trials.

Table 4
Fatal Adverse Events Among Patients Treated with Docetaxel at an Initial Dose of 100 mg/m²

Cause of Death	N= 5,083 10/2/90-10/31/95	N= 4,452 7/1/94 - 10/31/95	[illegible]	N= 912* ISS, Original NDA (phase 2 only) 7/27/94
Treatment-Related				
Total	145 (2.8%)	88 (2.0%)	[illegible]	17 (1.9%)
Infection	88 (1.7%)	56 (1.3%)	[illegible]	14 (1.5%)
Other	57 (1.1%)	32 (0.7%)	[illegible]	3 (0.4%)
Unrelated	511 (10.1%)	325 (7.3%)	[illegible]	55 (6.0%)
All deaths	656 (12.9%)	413 (9.3%)	[illegible]	72 (7.9%)

*Study cut-off date 10/31/93 in US trials, 12/15/93 in European trials; N includes 75 patients who were treated at an initial dose of 75 mg/m². Deaths reported here were on-study, i.e., within 30 days of the last docetaxel infusion. In fact, there were a total of 104 fatalities if those occurring after 30 days are included, for an overall death rate of 15.4%.

1. RPR must explain the apparent treatment-related death rate of 9% among the 631 patients treated prior to 7/1/94 as described in this submission. This figure is in serious disagreement with the 1.9% toxic death rate reported among 912 patients in the original NDA, and the 2% toxic death rate reported among 1327 patients at the ODAC Meeting in October 1995. The number of treatment-related deaths occurring on-study (within 30 days of docetaxel infusion) and beyond 30 days should be enumerated for the "infection" and "other" categories for the early (N=631) and later (N=4,452) cohort of patients.

2. Assuming that the majority of infectious deaths likely occurred on-study, this data raises the concern of late-occurring "other" treatment-related deaths not previously reported to the Agency. RPR must submit its assessment of the 57 "other" treatment-related deaths occurring among the total cohort of 5,083 patients, along with case report forms for each of these patients.

- **Additional Concerns Regarding Treatment-Related Deaths**

1. Clarification point #1: There were 26 deaths (out of 1327) reported to the NDA as of 2/17/95, of which 19 were sepsis-related. In addition, between 1/95 and the present (10/25/95), there have been 16 toxic deaths reported to IND , of which only 5 were sepsis-related. Please explain the preponderance of non-sepsis-related deaths among the reports to the IND this year.

RPR stated that all safety reports "were filed for unexpected serious adverse events. The preponderance of non-septic, related deaths in the 1995 Safety Reports reflects the fact that Safety Reports are no longer required to be filed for Septic Deaths which are now considered 'expected'."

Following receipt of this response, the Division requested that all treatment-related deaths, including sepsis-related deaths, continue to be reported as Safety Reports to the IND. RPR has agreed to do this.

Since 1/95, there have been a total of 32 treatment-related deaths reported to the IND, with 16 deaths reported since the Approvable Letter was issued on 10/27/95. A brief description of these events is tabulated below. There were 16 deaths reported among breast cancer patients, 9 of which occurred in cycle one. Additional clinical details are appended.

Table 5
Patient Deaths Reported to IND (January 1, 1995 - Present)

Study/Patient#	Demographics	Docetaxel Dose/Cycle	Cause of Death/ Related Symptoms
TAX-EAP			
	43 yo female, breast ca	75 mg/m^2, cycle 1	Diabetic ketoacidosis
	51 yo female, breast ca	50 mg/m^2, cycle 1	Myocardial infarction
	63 yo female, breast ca	100 mg/m^2, cycle 1	Neutropenic sepsis, ?PE
	58 yo female, breast ca	75 mg/m^2, cycle 1	Intracerebral event, CNS mets
	62 yo female, breast ca	100 mg/m^2, cycle 2	Renal failure, pneumonia
	43 yo female, breast ca	100 mg/m^2, cycle 1	Neutropenic sepsis, PE
	55 yo female, breast ca	100 mg/m^2, cycle 1	Unexplained death
	47 yo female, breast ca	185 mg, cycle 3	Pulmonary edema, infection
TAX-264			
	74 yo female, breast ca	100 mg/m^2, cycle 7	GI, vaginal bleeding, prolonged PT
TAX-V-301			
	61 yo male, lung ca	100 mg/m^2, cycle 5	Unexplained death, disease progression
	71 yo female, breast ca	100 mg/m^2, cycle 1	Cardiac arrhythmia (pre-existing)
	56 yo female, breast ca	75 mg/m^2, cycle 3	Anasarca, ascites (no liver mets), jaundice, hemorrhage
	58 yo female, breast ca	125 mg, cycle 2	Neutropenic sepsis
	35 yo female, breast ca	100 mg/m^2, cycle 1	Acute CNS bleed, grade 4 thrombocytopenia
TAX-SI-001			
	58 yo female, breast ca	100 mg/m^2, cycle 3	Unexplained death

Table 5 - Continued

Study/Patient#	Demographics	Docetaxel Dose/Cycle	Cause of Death/ Related Symptoms
TAX-V-Compa	62 yo female, breast ca 71 yo female, breast ca	not reported, cycle 1 75 mg/m², cycle 3	DIC, liver failure, liver mets Neutropenia, mucositis, diarrhea
TAX-SI-002	61 yo male, lung ca 57 yo male, lung ca 63 yo male, lung ca 73 yo female, lung ca	100 mg/m², cycle 2 100 mg/m², cycle 1 100 mg/m², cycle 1 75 mg/m², cycle 4	Pulm abscess, pericarditis, renal failure Sudden death, WBC 0.4, severe diarrhea Sudden death, dyspnea, cardiac pain, WBC 0.3 GI bleed, neuropathy
TAX201	65 yo male, lung ca 68 yo male, lung ca	75 mg/m², cycle 4 55 mg/m², cycle 6	Sepsis, respiratory distress Unexplained death
TAX320	60 yo male, lung ca	100 mg/m², cycle 1	Severe dyspnea
TAX-V-298	50 yo male, lung ca	75 mg/m², cycle 1 + navelbine	Neutropenic sepsis, CVA
TXB-201	53 yo male, lung ca	100 mg/m², cycle 3	Dyspnea, hemoptysis
TAX020	69 yo male, lung ca	75 mg/m², cycle 1 + cisplatin	Cardiac arrest, history of heart disease, diabetes mellitus
TAX-V-216	61 yo male, head & neck cancer	100 mg/m², cycle 2 + cisplatin	Unexplained death, grade 2 neutropenia
TAX-V-238	70 yo male, tonsil ca	100 mg/m², cycle 3	Unexplained death, grade 4 neutropenia, asthenia
TAX-V-042	55 yo male, leiomyosarcoma	75 mg/m², cycle 3 + ifosphamide	Neutropenic sepsis, pulmonary infection
TAX-037	52 yo male, lymphoma	70 mg/m², cycle 3	Intestinal perforation
TAX-UK203	64 yo female, ovarian cancer	75 mg/m², cycle 1	Severe nausea, vomiting

2. Clarification point #2: Please specify the number of toxic deaths and the cycle in which they occurred among the 95 patients with transaminase elevations in the March 1995 safety analysis of patients with liver dysfunction. Appendix V (3/95) indicates that there were a total of 5 toxic deaths, and 4 occurred in the first cycle. However, in your response of May 23, 1995, there were 4 toxic deaths occurring after the first cycle in this group.

The data as presented in March 1995 are correct. The May 23, 1995 submission "should have read that there were 'four toxic deaths at first cycle'."

- **Non-Fatal Docetaxel-Related Serious Adverse Events**

RPR reported a total of 1861 serious adverse events related to docetaxel among 4,452 patients treated with an initial planned dose of docetaxel 100 mg/m^2. These patients were treated between 7/1/94 and 10/31/95 and include all tumor types. The "estimated incidence" of these events is far lower than that reported among 912 patients evaluable for safety in the original NDA, except for the incidence of sepsis which has doubled for the cohort of recently-treated patients. See below.

Table 6
Non-Fatal Serious Adverse Events Related to Docetaxel Initial Dose of 100 mg/m^2

Adverse Event	N= 4,452 "Estimated Incidence" 7/1/94 - 10/31/95	N= 912 ISS, Original NDA* 7/27/95
Neutropenia	3.0%	8.0%
Febrile Neutropenia	11.0%	24%
Infection	1.7%	9.4%
Pneumonia	1.2%	1.2%
Sepsis	1.8%	0.8%
Allergy/AHSR	0.6%	5.2%
Asthenia	1.1%	3.2%
Fluid Retention	0.6%	4.7%
Neurologic Disorders	0.5%	3.3%
Skin Toxicity	0.5%	2.3%
Stomatitis	0.6%	1.1%
Nausea/vomiting	2.8%	4.2%
Diarrhea	1.9%	3.0%

*N includes 75 patients who were treated at an initial dose of 75 mg/m^2; Table 38, 8-117-72

1. These results should be interpreted with caution, given that information is not provided on the duration of follow-up for the new cohort of patients. This is most critical for the chronic non-hematologic toxicities (fluid retention, neurologic disorders, skin toxicity, asthenia). Despite the declines reported in neutropenia and febrile neutropenia events, and stable incidence of pneumonia, the incidence of sepsis has doubled. **Clarification of the methods used in the follow-up of these patients, duration of follow-up, and RPR's assessment of the increased incidence of sepsis events should be requested. Given the vast number of patients treated with docetaxel at the proposed dose and schedule since submission of the original NDA, and the time elapsed since the last formal safety update (4-month safety update, November 1994, reported on 1010 patients treated at 100 or 75 mg/m^2), a more comprehensive safety summary is warranted at this time. This summary should include annotated case report forms for patients withdrawn from treatment for adverse events and for patients dying on study (excluding the 57 patients above whose complete case report forms are being requested).**

- **Fluid Retention**

There are now 201 breast cancer patients from 5 studies who are evaluable for the effect of 5-day dexamethasone premedication on fluid retention. These patients were enrolled on phase 2 (TAX264, TAX296) and phase 3 (TAX303, TAX304, and TAX311) trials, and have received a median of 4 treatment cycles (range 1-14+) and a median cumulative dose of docetaxel of 393 mg/m^2 (range 5-1081+ mg/m^2). Recall that the experience reported at ODAC included only 104 evaluable breast cancer patients who had received a median of 3 treatment cycles. Of these, 32 patients had received a median of 5 cycles (range 1-13), and a median cumulative dose of 405 mg/m^2 (range 99-975 mg/m^2). The table below summarizes the experience in the cohort of 201 patients compared to the original 32 patients.

Table 7
Effect of 5-Day Dexamethasone on Fluid Retention

	N= 32 patient cohort	N= 201 patient cohort
Severity of Fluid Retention		
-any grade	**44%**	**50%**
-mild	**19%**	**26%**
-moderate	**19%**	**17%**
-severe	**6%**	**6%**
Treatment Discontinuations	**3.1%**	**1.5%**
Median cumulative dose to onset		
-any grade	**508**	**396+**
-moderate/severe	**746**	**705+**

The median duration of fluid retention among the 201 patients was 26 weeks (range 0.1-46+

weeks), calculated from the onset of any fluid retention. Altogether 59 of these patients required diuretic therapy during 89 treatment cycles. No information was provided on the frequency of drainage procedures. Evolution of performance status scores was provided for the 201 patients at cycles 2, 4, and 6. RPR stated that these scores demonstrate stabilization or improvement for the majority of patients.

Full doses of 5-day dexamethasone as recommended (8 mg bid for 5 days) were taken in 745 (83%) of 902 docetaxel cycles administered to the 201 patients.

RPR reported the following occurrence of gastrointestinal side effects potentially attributable to docetaxel. Bowel perforation has been reported in 3 out of 3,036 patients (0.1%) who received the 5-day dexamethasone premedication vs 1 case out of 1,416 patients (0.07%) who did not receive 5-day steroids. Gastrointestinal hemorrhage has been reported in 7 out of 3,036 patients (0.2%) who received the 5-day dexamethasone premedication vs 1 case out of 1,416 patients (0.07%) who did not receive 5-day steroids.

Comments:

1. The findings in the 201 patient cohort (incidence of moderate/severe fluid retention, median cumulative dose to onset, duration of fluid retention) appear to be comparable to those previously reported.

2. The data provided on performance scores are difficult to interpret as only one-third to one-half as many patients remained on study at cycle 6 compared to cycle 2, and PS was unknown for up to 35% of patients at some of the time points.

3. Gastrointestinal hemorrhage or perforation are potentially life-threatening adverse events. GI hemorrhage has resulted in at least 4 deaths (3 out of 1327 patients reported at ODAC in October 1995, plus 1 or 2 patient deaths reported as Safety reports to IND since 1/95 as indicated in Table 5). In addition, there have been two cases of bowel perforation recently reported to the Agency on 10/24 and 11/16/95 that would not be included in RPR's report above. Details regarding use of 5-day premedication in these cases, and RPR's assessment of the causality of these events would be helpful.

3. **Data available on the 3,036 patients who received the 5-day dexamethasone premedication should be submitted in a formal safety update.**

5. Safety Profile in Anthracycline-Resistant Breast Cancer Patients

RPR has submitted the safety profile of docetaxel for the 134 anthracycline-resistant breast cancer patients treated on the pivotal trials TAX233, TAX267, and TAX286 ("MEDICAL" Request #4 of the Approvable Letter). This profile was reported, in part, at the October ODAC Meeting. Seven of these patients were considered to have liver impairment at baseline defined as: SGOT/SGPT > 1.5 x ULN and AP > 2.5 x ULN. The remaining 127 patients had either completely normal liver function or isolated elevations of transaminases or alkaline phosphatase and were considered to have "normal" liver function at baseline. Tables 8 and 9 below summarize the common hematologic and non-hematologic toxicities for the subset of anthracycline-resistant patients. The findings reported for 1070 patients (treated on phase 2 studies, all tumor types) and for the subset of 297 second line breast cancer patients are shown for sake of comparison. At the October meeting, ODAC recommended that patients with liver dysfunction defined in the manner described be excluded from treatment with docetaxel.

Table 8
Patients without Liver Dysfunction

Toxicity	ALL N= 1028	Second Line Breast CA N= 282	Anthracycline-Resistant Breast CA N= 127
Neutropenia	97%	99%	99%
Neutropenia, grade 4	80%	92%	95%
Febrile Neutropenia	13%	16%	22%
Infections	19% (5%)	23% (6%)	25% (7%)
Thrombocytopenia	9%	14%	12%
Septic Deaths	1.5%	1.4%	0.8%
Stomatitis	44% (6%)	57% (9%)	56% (9%)
Skin Toxicity	61% (7%)	57% (8%)	62% (10%)
Fluid Retention	52% (9%)	59% (10%)	57% (9%)
Neurosensory	52% (4%)	53% (4%)	66% (7%)
Asthenia	69% (12%)	71% (19%)	80% (23%)
Nonseptic Deaths	0.3%	0	0

Figures in parentheses refer to grades 3 + 4 or severe toxicities

Table 9
Patients with Liver Dysfunction

Toxicity	ALL N= 42	Second Line Breast CA N= 15	Anthracycline-Resistant Breast CA N= 7
Neutropenia	93%	100%	100%
Neutropenia, grade 4	79%	87%	100%
Febrile Neutropenia	24%	40%	43%
Infections	33% (17%)	40% (27%)	71% (57%)
Thrombocytopenia	29% (7%)	53% (20%)	71% (14%)
Septic Deaths	4.8%	6.7%	14.3%
Stomatitis	43% (17%)	60% (40%)	71% (57%)
Skin Toxicity	62% (12%)	67% (20%)	57% (14%)
Fluid Retention	36% (10%)	53% (13%)	57% (14%)
Neurosensory	33% (0)	33% (0)	43% (0)
Asthenia	52% (14%)	47% (20%)	43% (29%)
Nonseptic Deaths	7.1%	13.3%	14.3%

Figures in parentheses refer to grades 3 + 4 or severe toxicities

The most recent version of the proposed package insert, submitted December 1, 1995, indicates that there were 29 patients of the 127 with normal liver function tests at baseline that received the recommended premedication regimen. Of these, only 3 (11%) experienced any fluid retention and 1 patient (3.6%) had severe fluid retention. In addition, there were 3 patients of the 7 with abnormal liver function tests at baseline that received the recommended premedication. Of these, two patients experienced fluid retention, and one of these cases was severe. Comment: The 11% overall incidence reported here is much lower than the 50% overall incidence reported for the 201 patient cohort (see Table 7).

- **Additional Concerns Regarding Adverse Events**

1. Clarification point #3: Please describe the specific symptoms that led to the designation of "severe asthenia" for each anthracycline-resistant patient with this reported toxicity, and explain, to the extent possible, why the presence of this toxicity did not lead to a report of deterioration in performance status in these patients.

Severe asthenia was reported in 43/786 cycles (5.5%) administered to 31/134 anthracycline-resistant patients (23%). Twenty-nine of these patients had normal liver function at baseline,

while 2 had abnormal liver function. Of the 43 events of severe asthenia, 30 were reported as fatigue, 6 were reported as weakness, 5 were reported as asthenia, and 2 were reported as fatigue and weakness. "The duration of these events was usually a few days, therefore, the overall performance status reported for the cycle was not adversely affected. Among the 43 cycles with severe asthenia, no PS > 2 was reported, and PS = 2 was reported only in 7 cycles."

Comments:

1. Valero et al., JCO 13:2886-2894, 1995, state that there were 19 patients with severe asthenia on the TAX233 trial vs 16 in RPR's study report (Table 43). **If this is the case, then the number of anthracycline-resistant patients with severe asthenia is 34 or 25%.**

2. Case report forms of 15 second line breast cancer patients with abnormal liver function at baseline and of 56 patients with baseline fluid retention were reviewed. Performance status scores were recorded by checking the appropriate box, at the start of a treatment cycle. For some studies, investigators were required to write in each adverse event for each cycle, while for other studies, adverse events, including asthenia, were listed on the case report forms, and investigators would write in comments when appropriate. **Thus, direct correlation between performance status and the occurrence of asthenia or other adverse events was generally not possible if these events were short-lived. Conversely, chronic, serious adverse events would be expected to affect performance status recorded at the start of subsequent cycles.**

Specific examples below suggest that fatigue, and associated symptoms of myalgias or weakness, could be chronic in nature, and/or associated with PS > 2, especially when drug-related toxicities developed concurrently with disease progression. Note that patients , on the TAX233 trial, patient on TAX267, and patient on the TAX264 trial were anthracycline-resistant.

TAX233, patient Chronic fatigue, PS = 2
46 year old female with breast cancer metastatic to lymph nodes who received 5 cycles of docetaxel. Baseline PS= 80% on 1/5/93, the day docetaxel was started, declining to 70% at the start of cycle 4 (3/12/93). Moderate fatigue was recorded beginning 2/18, worsening to **severe** between 3/12 through 4/15. This patient also had severe edema between 3/30 and 4/15. On 4/15, PS remained at 70%, and a fifth dose was given. The patient continued to have moderate fatigue from 4/15 through to her last follow-up visit on 8/31. She was considered to have had a partial response for 17 weeks.

TAX233, patient : Chronic fatigue and weakness, PS > 2
48 year old female with breast cancer metastatic to liver who received 4 cycles of docetaxel. Baseline PS= 80% on 3/18/93, one day prior to the first docetaxel dose. Moderate fatigue was first noted on 3/21 and continued during cycle 2, although no date of resolution was given. Following the third dose (5/13), moderate fatigue was recorded between 5/15 and 5/27. Following the fourth dose (6/10, PS=80%), **severe fatigue** was noted on 6/14 and was ongoing,

though reduced to moderate, at last follow-up on 10/21. Moderate myalgias were noted 4/17-4/25 following the second dose on 4/15. **Severe neuromotor weakness** was recorded beginning on 5/13, and severe bilateral pleural effusions requiring drainage beginning 6/7; both were ongoing at last follow-up, although weakness was reduced to moderate. The patient's **PS was 50%** at end-of-study on 7/12, although she was considered to be in partial response. No PS was recorded for the last follow-up on 10/21. The patient died of malignant disease on 11/21.

TAX233, patient Chronic fatigue and myalgias
49 year old female with breast cancer metastatic to bone and liver who received 8 cycles of docetaxel. Baseline PS= 70% on 4/21/93, one day prior to the first docetaxel dose. **Severe fatigue** was first noted on 4/24, and was deemed probably related to study drug. At the start of cycle 2 (5/13), her PS was still recorded as 70%, although severe fatigue did not improve to mild until 5/25. Mild fatigue continued until 7/8, then worsened to moderate until the end of study (10/27). **Severe myalgias** began on 4/24, improved to moderate on 5/16, and ceased on 6/9. Following the third docetaxel dose on 6/9 (PS 70%), moderate myalgias were experienced 6/11-6/29; and following the fourth dose on 7/2 (PS 80%), moderate myalgias resumed on 7/3. Moderate myalgias continued until the end of study. Although the patient lived until 12/30, the exact duration of moderate fatigue and myalgias is not known. This patient's dose was adjusted several times due to thrombocytopenia and neutropenic sepsis (3 cycles were given at 55 mg/m²). She was considered to have had a partial response lasting 25 weeks.

TAX267, patient Chronic weakness
69 year old female with breast cancer, metastatic to lung and chest wall, who received 7 cycles of docetaxel. She had a baseline PS= 60% on 7/6, one day prior to her first docetaxel dose. Her PS improved to 90% at the start of cycle 2 on 7/26, and remained stable throughout treatment. However, beginning in cycle 5, from 10/18 until she was discontinued from study 12/30 due to disease progression, **severe weakness** was recorded. In cycle 7, hospitalization was required. Her best response to docetaxel was disease stabilization.

TAX221, patient Severe asthenia and PS > 2
48 year old female with breast cancer, metastatic to liver, who received one cycle of docetaxel. She had a left pleural effusion, ascites and a PS= 0 at baseline. The patient received her first dose of docetaxel on 5/29/92. She developed grade 4 neutropenia, moderate total body edema, DIC, and increased bilirubin, alkaline phosphatase and transaminases. **Severe asthenia** was noted on 6/3, **PS= 3 on 6/4, declining to PS= 4 on 6/15**. She expired on 6/15 with malignant disease.

TAX221, patient : Chronic severe asthenia and PS > 2
44 year old female with breast cancer metastatic to liver who received two doses of docetaxel on 7/24/92 and 8/11/92. Baseline PS= 2, dropping to PS= 3 at start of cycle 2. **Grade 4 asthenia** was recorded between 8/11 and the date of death, 9/19. The case report form described grade 4 asthenia as "bedridden or unable to care for self" in the case report form. Patient's course was complicated by persistent ascites, treated with albumin and paracenteses x 4 (cytology negative), grade 4 neutropenia, grade 4 stomatitis, and grade 3 skin toxicity with desquamation in cycle 2.

The patient's liver function tests worsened and she was taken off study due to disease progression on 9/15, shortly before her death.

TAX235, patient Severe asthenia, PS unknown, toxic death
46 year old female with breast cancer, metastatic to liver; no prior anthracycline. The patient received her first dose of docetaxel on 12/3/93. She experienced fever and neutropenia, requiring IV antibiotics starting 12/13, grade 3 stomatitis starting 12/13, severe fluid retention and **severe asthenia**, starting 12/20. GI bleeding with DIC developed on 12/25. The patient died on 12/27 due to drug toxicity.

TAX264, patient : Chronic fatigue
54 year old female with breast cancer, metastatic to soft tissue and bone, who received eight doses of docetaxel. The patient had a PS of 100% at baseline, declining to 90% at the start of cycle 4 (10/7/94). On FACT-B questionnaires, she consistently reported "very much" or "quite a bit" to the question regarding lack of energy between 9/16 and 11/18. **Severe or moderate fatigue** was recorded beginning on 8/12/94 and continuing until 5/15/95 (both severities were noted in different locations). The patient stopped therapy on 2/3/95 and was considered to have had a partial response for 26 weeks.

TAX264, patient : Acute severe weakness, PS $\leq$ 50%
74 year old female with breast cancer metastatic to bone and liver, received prior adjuvant anthracycline, was treated with 7 doses of docetaxel. Baseline PS= 70%. PS remained stable, although at the start of cycle 6, she reported "very much" to the question regarding lack of energy on FACT-B questionnaires for the first time. PS declined to 50% at the start of cycle 7 on 1/6/95. Her course was complicated by **severe neuromotor weakness**, melanotic stools, vaginal hemorrhage. She became unresponsive and died on 1/8. She was considered to have had stable disease, although elevations of alkaline phosphatase and SGOT were noted beginning at cycle 6.

TAX264, patient : Chronic PS of 60%, severe weakness noted briefly
46 year old female with anthracycline-resistant breast cancer, metastatic to lung, liver and bone, who received three doses of docetaxel. The patient had a PS of 60% at baseline and at the start of each treatment cycle. On FACT-B questionnaires, she consistently reported "very much" or "quite a bit" to the question regarding lack of energy. **Severe weakness** was recorded for 3 days in cycle 3, in association with grade 4 neutropenia, severe nausea, vomiting, diarrhea and dehydration. The patient died of malignant disease 4 weeks after the third dose.

6. Evolution of Performance Status

At the October 1995 ODAC Meeting, RPR presented a series of graphs depicting the evolution of performance status in anthracycline-resistant patients. The sponsor's conclusions (slide 66) were:

1) In this anthracycline-resistant patient population, most symptomatic patients improved or maintained their performance status while on Taxotere, and

2) In those instances where a deterioration was observed, the degree of this deterioration was rarely profound.

Comments:

1. Since performance scores are recorded at the start of each treatment cycle, deterioration in scores due to serious, though reversible, adverse events occurring in mid-cycle would not be captured in this analysis. Nevertheless, using the PS scores provided in the EXCEL spreadsheet, there were a total of 55 responders. There was a consistent improvement in PS in only 4 (all with a baseline PS of 2), a stable PS in 34, and a worsened PS in 17. Using end-of-study PS scores from the data listings, the PS of 6 of these responders would be downstaged from stable to worsened (see below).

2. Performance scores were recorded at end-of-study (within 30 days of the last int n) for several patients in the data listings (Table 12 for each study report) but were not used in this analysis. Thus, treatment-related morbidity for the following patients is not captured:

TAX233:

Patient : 48 year old female with breast cancer metastatic to liver who received 4 cycles of docetaxel. Baseline PS= 80%. Patient developed severe skin toxicity, severe pleural effusions, and severe fatigue after 4 cycles and discontinued treatment despite a partial response. Her PS at end-of-study was 50%.

Patient 70 year old female with metastatic breast cancer who received three doses of docetaxel. Baseline PS= 80%. In cycle 3, she developed fever and pneumonia complicated by severe dyspnea and hypoxia. She withdrew from treatment with a PS of 50%, despite a partial response.

TAX267:

Patient 60 year old female with metastatic breast cancer who received three doses of docetaxel. Baseline PS= 70%. She discontinued treatment due to moderate fatigue with stable disease and an end-of-study PS of 50%.

Patient 59 year old female with metastatic breast cancer who received five doses of docetaxel. Baseline PS= 80%, improving to 90% at the start of cycles 2-5. Despite a partial response, the patient withdrew from treatment due to severe neurosensory and neuromotor toxicities and severe myalgias, with an end-of-study PS of 70%.

Patient 45 year old female with metastatic breast cancer who received five doses of docetaxel. Baseline PS= 60%, improving to 90% at the start of cycles 4 and 5. Patient, however, withdrew from treatment due to severe neurosensory and neuromotor toxicities with an end-of-study PS of 50%. The patient had stable disease.

Patient 57 year old female with metastatic breast cancer who received five doses of docetaxel. Baseline PS= 90%. Patient, however, withdrew from treatment due to severe neurosensory toxicity and associated depression, with an end-of-study PS of 60%. The patient had stable disease.

TAX286:
Patient 72 year old female with a baseline PS of 1. She was withdrawn after 6 doses of docetaxel with severe neurotoxicity and severe generalized edema. Her end-of-study PS was 2. She had stable disease.

Patient 58 year old female with a baseline PS of 1 who withdrew after 4 cycles with stable disease. Her end-of-study PS declined to 2, but no information was provided as to the reason for this decline.

3. The three anthracycline-resistant patients on pivotal trials who had treatment-related deaths, and presumably a decline in PS to 4, were included, but only their baseline PS was used in the sponsor's analysis

TAX233:
Patient 62 year old female with breast cancer metastatic to bone, liver, soft tissue, and lymph nodes. Baseline PS= 1. She received one dose of docetaxel, and was hospitalized four days later with grade 4 neutropenia, grade 4 vomiting and diarrhea, and severe chest and abdominal pain. Blood cultures grew *Pseudomonas aeruginosa*. Patient expired on day 6.

TAX286:
Patient 63 year old female with metastatic breast cancer and a baseline PS of 2. On day 6 of the first cycle, she developed acute pulmonary edema and hypotension in the setting of grade 4 neutropenia. She died the next day, her death presumed to be due to septic shock.

Patient : 42 year old female with breast cancer, progressive liver metastases and a baseline PS of 2. On day 7 she developed oral and genital bleeding and hypotension concurrent with febrile neutropenia, grade 4 thrombocytopenia, grade 4 stomatitis, prolonged PT, increased hepatic enzymes (bilirubin, grade 4, alkaline phosphatase, grade 2, and transaminases, grade 3), and increased creatinine. The patient died the next day due to hemorrhage that was unresponsive to transfusion and intensive support. This fatality was considered probably related to docetaxel, with toxicities exacerbated by the patient's underlying liver dysfunction which "could have contributed to a reduction in clearance of docetaxel".

4. End-of-study PS was not recorded in the data listings for four patients withdrawn with toxicity who likely had deterioration in performance status from baseline. These were:

TAX267:
Patient with a baseline PS= 90% withdrew after 3 cycles due to severe dyspnea from a

grade 4 interstitial pneumonia considered probably related to study drug. She had stable disease.

Patient , with a baseline PS= 100% withdrew after 5 cycles due to moderate asthenia with stable disease.

Patient with a baseline PS= 100% withdrew after 5 cycles despite a partial response. She was hospitalized for shortness of breath and increasing pleural effusions requiring thoracentesis; the cytology of the pleural fluid was negative.

TAX286:

Patient with a baseline PS= 100% was withdrawn for severe neurotoxicity (paresthesias) despite a partial response.

5. On the TAX286 trial, there were three patients who withdrew treatment for moderate to severe fluid retention whose PS scores do not appear to accurately reflect what the patient was experiencing. Either these patients did not truly have symptomatic fluid retention or their PS scores are incorrect:

Patient had consistent PS scores of 0 at baseline, during treatment, and end-of-study despite the development of severe generalized edema and bilateral pleural effusions after 4 doses. Her response was not evaluable.

Patient had consistent PS scores of 1 at baseline, during treatment, and end-of-study despite the development of severe edema and bilateral pleural effusions after six doses. She had stable disease.

Patient had consistent PS scores of 1 at baseline, during treatment, and end-of-study despite the development of moderate fluid retention after 5 doses. In addition, she was hospitalized twice in cycle 5 requiring IV antibiotics for febrile neutropenia, and subsequently, for purulent conjunctivitis. She had a partial response.

In summary then, perhaps as many as 18 out of 134 anthracycline-resistant patients (13%) in pivotal trials experienced a deterioration of performance concurrent with treatment-related adverse events that lead to treatment discontinuation or death. Of these, 6 were responders, 8 had stable disease, and 4 were not evaluable for response. Perhaps a more accurate assessment of PS among the 55 responders might be: improved in 4, stable in 28, and worsened in 23. Of course, these estimates do not fully capture the morbidity of serious adverse events occurring in mid-cycle and resolving at the start of the next cycle.

7. Case Report Forms on Patients with Liver Dysfunction

Fifteen case report forms on patients with second line breast cancer and combined abnormalities of SGOT/SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN were submitted (MEDICAL Request #1 of the Approvable Letter). See Table 9 for the docetaxel toxicity profile in this cohort of patients. Upon review of these documents, the following observations could be made:

1. **Three toxic deaths in cycle 1 were confirmed:** gram negative sepsis in patient on TAX233; hemorrhage in the setting of rapidly rising liver function tests, thrombocytopenia, and stomatitis in patient on TAX286; toxicities as in patient plus severe fluid retention requiring drainage in patient on TAX235.

2. **Five patients withdrew for adverse events:** severe pleural effusion and three episodes of febrile neutropenia with stable disease after 3 cycles in patient on TAX296; severe effusions, ascites, and fatigue with a partial response after 4 cycles in patient on TAX233; moderate edema, dyspnea, and neurosensory toxicity with stable disease after 6 cycles in patient on TAX286; severe fluid retention with a partial response after 7 cycles in patient on TAX235; and patient on TAX233 failed to return after cycle 1 following an episode of febrile neutropenia.

3. **One patient withdrew due to "consultant's decision":** patient on TAX235 suffered a pulmonary embolism, unrelated to docetaxel in cycle 2, with a decline in PS to 3 and remained dyspneic on supplemental oxygen; she was withdrawn after the fourth cycle.

4. **Six patients were withdrawn for disease progression:** patient on TAX221 died on study after 1 dose; patient on TAX221 died on study after 2 doses; patient on TAX264 died on study after 3 cycles; patient on TAX221 progressed after 4 cycles; patient on TAX233 progressed after 7 cycles; and patient on TAX233 progressed after 8 cycles. Only patient had a partial response lasting 25 weeks prior to progression.

8. Case Report Forms on Breast Cancer Patients with Fluid Retention at Baseline

Fifty-six case report forms of patients with second line breast cancer who had fluid retention at baseline were submitted and reviewed. These patients had been treated with an initial planned dose of docetaxel 100 mg/m² on nine different studies. Case report forms for each of the studies differed with respect to how information on fluid retention was recorded. Thus, it was not always possible to determine the severity or duration of each event. Altogether, there were 22 anthracycline-resistant patients (treated on the three pivotal trials, TAX233, TAX267, and TAX286), and 34 second line breast cancer patients, some of whom received prior anthracyclines but had not progressed on anthracyclines.

A partial response to docetaxel was observed in 10/22 or 45% of anthracycline-resistant patients; among the remaining second line patients, a partial response was noted in 6/33 or 18%. A single case report form was submitted for the TAX311 trial which randomizes patients to docetaxel or paclitaxel. This document covered the first 3 cycles of treatment for patient 2905, presumably with treatment ongoing; assignment to docetaxel vs paclitaxel in this patient is not known and tumor assessments were not provided.

The table below summarizes the baseline findings in these patients. Baseline fluid retention consisting of upper extremity lymphedema, ipsilateral to the mastectomy site, was noted in 31 patients. Peripheral edema alone was noted in 8 patients, and in combination with effusions/ascites in 6 patients. Pleural effusions were noted in 19 patients and ascites in 5 patients.

Moderate or severe fluid retention was recorded, with an estimated duration for each event whenever possible. No moderate or severe events were noted for 8 patients. For 12 patients, moderate/severe events that were present at baseline persisted during treatment (noted as "ongoing"). New moderate/severe events, including generalized edema, pleural effusions, weight gain, ascites or combinations thereof, developed in 32 patients. Two patients clearly improved (233/644 and 267/275, shown in highlighted areas) and two patients had a mixed response (267/267 and 267/293) with respect to fluid retention.

Among the 16 partial responders, 1 patient had no moderate/severe events recorded, 4 patients had "ongoing" symptoms, 8 patients had new symptoms during treatment, 2 had mixed responses and one had complete resolution.

Twenty-seven patients were treated with diuretics, 8 required drainage procedures, four had their docetaxel doses delayed, reduced or withdrawn, and one patient died in acute pulmonary edema in cycle 1, day 6. One of the two patients with improvement, and both patients with mixed responses also received diuretics.

In this group of patients there were a total of 8 deaths on treatment, 6 occurring in cycle 1. Three deaths were due to toxicity, four due to disease progression, and one due to unknown causes.

Among the 22 anthracycline-resistant patients, the death rates due to toxicity or to disease progression were identical (4.5%). Among the remaining 33 second line breast cancer patients, the death rate due to toxicity was 6%, and to other causes, 12%.

Comment: At the October 1995 ODAC Meeting, sponsor's slide 36 stated that 49% of patients with baseline edema and 59% of patients with baseline effusion were "improved on treatment". Review of the case report forms submitted in support of this statement do not appear to substantiate this claim.

Table 10
Outcomes Among Second Line Breast Cancer Patients with Baseline Fluid Retention

Study/ Patient ID	Baseline Findings	Moderate/Severe Adverse Events	Action(s) Taken	Best Resp
233	Arm edema, moderate	Generalized edema - 8+ wk Pleural effusion - 30 wk	Diuretics Dose delayed, reduced	PR (17 wks)
233	Peripheral edema, mild Pleural effusion, small	None noted	Diuretics	SD
233	Arm edema, mild	Peripheral edema - 49 wk Pleural effusion - 24 wk 10 kg wt gain	Diuretics Thoracentesis	PR (39 wks)
233	Arm edema, mild Pleural effusion	None noted	None	PR (9 wks)
233	Arm edema, mild Breast edema, mild	Cellulitis of breast - 3 wk Breast edema - 1+ wk	Antibiotics	SD
233	Arm edema, mild	None noted	None	PD
233	Pleural and Pericardial effusions mod size, no symptoms	Resolved on study: Pleural eff in 12 wk Pericardial eff in 14 wk	Diuretics	PR (15 wks)
233	Arm edema, mild Peripheral edema, mod Pl eff, s/p thoracentesis	Ongoing	Diuretics	SD
267	Pleural effusion, mild	Tachypnea - 4 wk Pain, chest tube site- 19 wk	Sclerotherapy	SD
267	Arm edema, mild	Bilat arm edema - 25 wk Pleural effusion - 23 wk 7 kg wt gain	Dose delayed Diuretics Hickman for access	PR (20 wks)
267	Arm edema, moderate Pleural effusion, small	Leg (?) edema, moderate - 4 wk	Diuretics Dose delayed	PR (22 wks)

Study/ Patient ID	Baseline Findings	Moderate/Severe Adverse Events	Action(s) Taken	Best Resp
267	Arm edema, mild Pleural effusion, mild	Arm edema, mod - 8 wk Pl eff resolved in 7 wk, recurred 17 wk later, large for 8+ wk	Compression device Thoracentesis	PR (28 wks)
267	Arm edema, moderate	Arm edema, severe - 8 wk	None	SD
267	Ankle edema, mild Pleural effusion s/p thoracentesis	Ankle ed resolved in 7 wk Pleural eff: PR in 6 wk, then stable for 20 wk	None	SD
267	Peripheral edema, mild Bilat pl eff, large on Rt Ascites, moderate	Generalized edema - 13 wk Pl eff, ascites stable 15 wk, then bilat effusions became severe 5 kg wt gain	Diuretics Thoracentesis x5, chest tube Sclerotherapy Prolonged hosp	SD
267	Arm edema, moderate Bilat pleural effusions	Arm edema improved for 9 wk, then became mod Ed legs, breast, mod 27 wk Pl eff resolved in 6 wk	Diuretics	PR (20+ wks)
286	Arm edema, mild	None noted	None	PD
286	Arm edema, mild	Arm edema, mod - 24+ wk Leg edema, mod - 16 wks Pl eff, ?severity - 23 wks	Diuretics	PR (26+ wk)
286	Arm edema, mild	Peripheral edema - 12+ wk 8 kg wt gain	Diuretics	SD
286	Arm edema, moderate	Ongoing	None	PR (21+ wk)
286	Arm edema, moderate Pleural effusion - ? severity	Acute pulmonary edema, severe - 1 day	Diuretics Pressors	Death: Edema Cycle 1
286	Arm edema, moderate Pleural effusion - ? severity	Ongoing	None	Death: PD Cycle 1
311	Arm edema, moderate	Ongoing	Diuretics	NA
029	Arm edema, mild	None noted	None	PD
296	Peripheral edema, mild	None noted	None	NE
296	Peripheral edema, mild Pleural effusion, mild	Periph edema, sev - 5 wk Pl eff & ascites, mod - 2 wk	Diuretics Albumin	PR (20 wks)
296	Ascites, mild	Pleural effusion - ? duration	Diuretics Tx withdrawn	SD

Study/ Patient ID	Baseline Findings	Moderate/Severe Adverse Events	Action(s) Taken	Best Resp
221	Peripneral edema, Pleural effusion Ascites	Generalized edema	Albumin	Death: PD Cycle 1
235	Peripheral edema, mild	Generalized edema - 10 wk 5 kg wt gain	Diuretics Tx withdrawn	PR (21 wks)
235	Ascites	Generalized edema - 1 wk	Albumin Diuretics Drainage	Death: Toxicity Cycle 1
235	Leg edema, mild	Generalized edema - 4 wk 8 kg wt gain	Diuretics	SD
235	Arm edema, mild	Arm edema, mod/sev- 6 wk	None	SD
235	Edema, arm & hand, moderate	Bilat leg edema - ? severity, ? duration 5 kg wt gain	Diuretics	PD
235	Arm edema, moderate	Ongoing	Bandaging	SD
235	Arm edema, moderate Pleural effusion, severe s/p pleurodesis	Ongoing	Diuretics Thoracentesis x2	PR (21 wks)
235	Arm edema, moderate	Ongoing	None	PD
235	Arm edema Congestive heart failure Pericardial effusion, small	Edema face & ankles, ? severity, ? duration	Diuretics ACE inhibitor Thoracentesis	SD
235	Bilat leg edema, mild Pleural effusion	Edema arm & legs - ? severity	Thoracentesis x2	PD
235	Breast edema, moderate	Progression of breast edema	None	PD
235	Lymphedema, mild	None noted	None	SD
235	Arm edema, mild	Leg edema, moderate ? duration	None	SD
235	Arm edema, severe	4 kg wt gain	Analgesics	SD
235	Peripheral edema, mild Pleural effusion	New facial, eyelid edema - ? severity	Diuretics	SD
235	Bilat pleural effusions	Ongoing	None	Death: PD Cycle 1

Study/ Patient ID	Baseline Findings	Moderate/Severe Adverse Events	Action(s) Taken	Best Resp
264	Bilat leg edema, mild	Bilat leg edema, mod/sev - 3 wk	Diuretics	Death: Toxicity Cycle 2
264	Arm edema, severe	Ongoing	None	PR (26 wks)
264	Arm edema, moderate	Ongoing	None	PR (21 wks)
264	Arm edema, mild	Venous thrombosis - UE	Anticoagulants	PD
264	Ankle edema, mild	Peripheral edema, mod - 8 wks	Diuretics	SD Death: ? cause
264	Arm edema, mild	Peripheral edema, mod- 48 wks	Diuretics	SD
264	Peripheral edema, mod	Ascites, moderate - 13 wks	Diuretics	PR (22 wks)
264	Arm edema, mild	SVC thrombosis	Anticoagulants	SD
264	Peripheral edema, mild	None noted	None	NE
264	Peripheral edema, mod Ascites, moderate	Ongoing	None	Death: PD Cycle 1
264	Peripheral edema, mod Pleural effusion, severe s/p thoracentesis	Ongoing 15 kg wt gain	Diuretics	NE
264	Peripheral edema, mild	Peripheral edema, mod - 4 wks Pleural eff, mod - 3 wks	None	PD

9. Draft Product Labeling (December 1, 1995)

A. Upon review of the most recent version of the draft product labeling (dated December 1, 1995), the following changes are recommended.

CLINICAL STUDIES

A footnote below the tables on pages 9 and 10 should be added, stating that "Normal Liver Function includes patients with SGOT and/or SGPT $\leq$ 1.5 times ULN or with alkaline phosphatase $\leq$ 2.5 times ULN".

WARNINGS

The heading "HEMATOLOGIC EFFECTS", page 12, line 2, should be moved to the next line.

PRECAUTIONS

FLUID RETENTION: In the second paragraph, change "severe fluid retention was 5%" to "severe fluid retention was 6%". Also change "median cumulative dose to onset of fluid retention was 705 mg/m^2" to "median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m^2" (see Table 6.5, November 21, 1995 submission).

NEUROLOGIC: Change "Severe peripheral neurotoxicity is infrequent" to "Severe peripheral neurotoxicity was observed among 7% of 134 patients with anthracycline-resistant breast cancer".

ASTHENIA: Change the second sentence to read, "Severe asthenia was reported in 23% of 134 patients with anthracycline-resistant breast cancer and in 5.5% of 786 cycles received." Note that Valero et al., JCO 13:2886-2894, 1995, state that there were 19 patients with severe asthenia on the TAX233 trial vs 16 in RPR's study report (Table 43, original NDA, 7/27/94). If this is the case, then the number of anthracycline-resistant patients with severe asthenia is 34 or 25%.

DRUG INTERACTIONS: In line 6, place a period following "enzyme" and begin the next sentence with "Caution".

ADVERSE REACTIONS

In the first paragraph and in the footnote below the table on page 18, change "Abnormal liver function: SGOT and/or SGPT $\geq$ 1.5 times ULN concomitant with alkaline phosphatase $\geq$ 2.5 times ULN" to "Normal liver function includes patients with SGOT and/or SGPT $\leq$ 1.5 times ULN or with alkaline phosphatase $\leq$ 2.5 times ULN".

In the ADVERSE EVENT table on page 18, the incidence of fluid retention with recommended premedication (n=201) should be 49.8% for "any" and 6.0% for "severe" (see Table 6.5,

November 21, 1995 submission).

HEMATOLOGIC: In paragraph 3, change the incidence of thrombocytopenia to 8.5% to be consistent with the table on page 18.

HYPERSENSITIVITY REACTIONS: Change the second sentence to read, "Severe hypersensitivity reactions have been observed in only 1% of patients receiving the recommended premedication regimen."

FLUID RETENTION: Change "severe fluid retention was observed in 5%" to "severe fluid retention was observed in 6%". Also change "median cumulative dose to onset of fluid retention was 705 mg/m^2" to "median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m^2" (see Table 6.5, November 21, 1995 submission). Change the last sentence to "Fluid retention was slowly reversible, lasting a median of 26 weeks (0.1-46+ weeks) from the onset of any fluid retention (see page 28, November 21, 1995 submission).

CUTANEOUS: Change the last sentence to read, "These reactions were characterized by hypo- or hyperpigmentation, and occassionally by onycholysis (in 0.8% of patients) and pain.

NEUROLOGIC: The term "dysthenia" is not listed in Dorland's Medical Dictionary, 27th edition. The term "dysesthesia" may be appropriate.

GASTROINTESTINAL: In the first sentence, specify which reactions are being referred to (nausea, vomiting and/or diarrhea?). Add a second sentence on stomatitis here.

HEPATIC: Change the last sentence to read, "Increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 3.9% of patients during study." (Note, 42/1070 = 3.9%, not 3.3%)

ONGOING EVALUATION: In line 2, insert a comma and space between "syndrome" and "anorexia".

DOSAGE AND ADMINISTRATION

PREMEDICATION REGIMEN: In line 1, delete "an" prior to "oral corticosteroids".

REFERENCES

A complete listing of the handling and disposal references should be provided.

B. The following information given in the draft product labeling has not been previously reported to the NDA. Supporting documents for each of these statements should be submitted as soon as possible.

1. The incidence of hypersensitivity reactions in patients who received the recommended premedication (mentioned in BOXED WARNINGS, WARNINGS, ADVERSE EVENT table on page 18, and section on HYPERSENSITIVITY REACTIONS on page 20). Table 11 of the October 17, 1995 ODAC Briefing Document (footnote #21, page 11) does not contain this information.

2. The incidence of fluid retention in anthracycline-resistant patients who received the recommended premedication (table, page 10)

3. The statement that patients with severe peripheral neurotoxicity "had their symptoms spontaneously reverse within 3 months" (page 15)

4. The statements that "Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 time ULN were observed in approximately 6% and 15.7% of patients, respectively. Bilirubin values greater than the ULN occurred in 5.6% of the patients." Table 79 of the ISS (original NDA, 7/27/95) reports the following incidence of laboratory abnormalities NCI grade 1 or higher: SGOT, 36%; SGPT, 25%; alkaline phosphatase, 33%; and bilirubin, 11%.

5. Information has not been provided as requested under point #4, page 3 of the October 27, 1995 Approvable Letter: "We would like to be able to describe in the labeling the fraction of patients who had infection complicated by the need for hospitalization or IV antibiotics. Please provide the incidence of infection requiring hospitalization or IV antibiotics by grade of neutropenia for anthracycline-resistant patients."

C. Draft Patient Package Insert: Upon review of the patient package insert, the following changes are recommended.

What is the most important information about Taxotere?
Insert a bullet item stating: Certain patients with liver dysfunction should not receive Taxotere. Your doctor will monitor your liver function tests carefully during Taxotere treatment.

What are the possible side effects of Taxotere?

Low Blood Cell Count: This section should be revised to alert patients to the possibility of developing serious infections. The current wording appears to minimize the risk of a low bloo cell count. Revise the second paragraph to read (in bold typeface), "Fever is often one of the most common signs of infection. Your doctor will recommend that you take your temperatur frequently, especially during the days following your treatment with Taxotere. If you develop fever, tell your doctor or nurse immediately.

Nail Changes: Change "changes to you finger or toenails" to "changes to your finger or toe

10. Physician Education Program

In response to MEDICAL Request #7 of the Approvable Letter, RPR has planned to implement speaker programs for physicians, nurses, and pharmacists. The speakers' slide kit, along with other "launch materials" will be submitted to DDMAC for pre-clearance. RPR will employ oncology representatives, as well as a separate group of oncology nurses to provide nursing in-services to hospitals and community-based practices. A Drug Information Department, manned by physicians, nurses, and pharmacists and accessed by an 800 number, will answer clinical and safety questions.

11. Post-Approval Commitments

RPR is planning to incorporate a population pharmacokinetic component into the TAX313 trial, evaluating docetaxel doses of 100 vs 75 mg/m^2 in metastatic breast cancer. In addition, activity of cytochrome P450 3A4, as estimated by the erythromycin breath analyzer test, will be correlated with docetaxel clearance for patients on the docetaxel arm of the TAX311 trial (proposal by

Julie Beitz, MD 2/23/96
Julie Beitz, MD Date

Robert Justice, MD 2/23/96
Robert Justice, MD Date

cc:
NDA # 20-449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

Request for Information: May 14, 1996

NDA # 20,449 TAXOTERE® (docetaxel) for Injection Concentrate

Sponsor: Rhone-Poulenc Rorer

Please convey the following to the sponsor:

During our labeling meeting with Dr. Temple yesterday evening, these questions were raised regarding the package insert for docetaxel. Please clarify the following ASAP:

1. The definitions of normal and abnormal LFTs included in the footnotes of the tables on pp. 11, 12, 26 do not clearly address the status of patients' bilirubin at baseline. If patients with a normal bilirubin at baseline were included in the group with normal LFTs, the patients with elevated bilirubin included in the group with abnormal LFTs? If patients with an abnormal bilirubin at baseline are actually included in both groups, then the phrase "normal bilirubin" should be omitted from the definition of "normal LFTs".

2. On p. 19, first paragraph, next to last sentence: "Hypersensitivity reactions requiring discontinuation of the Taxotere infusion were reported in five patients ***out of how many ?*** who did not receive premedication.

3. On p. 22, first paragraph, add a description of neuromotor problems under the heading of NEUROLOGIC.

4. What criteria were used to determine which adverse events to report in the table on p. 25? For example, was there a % incidence used as a cut-off when creating the table?

5. Cardiovascular events (hypotension, dysrhythmia) and nail changes were mentioned in the text on pp. 28-29 but do not appear in the table on p.25. Please include cardiovascular events in the table on p. 25 and in the patient package insert. Please include nail changes in the table on p. 25.

6. Myalgias do not appear in either the table on p.25 of the package insert or in the text that follows, but are discussed in the patient package insert. Please include information on myalgias in the table on p. 25 and in the text of the package insert.

7. On p. 27, under HEMATOLOGIC, second paragraph, the definition of febrile neutropenia is given as "< 1000 cells/mm³". This definition differs from that given in the table on p. 11. Please clarify the definition that should be used in the text on p. 27, and include it as a footnote at the bottom of the table on p. 25.

8. On p. 27, under HEMATOLOGIC, third paragraph, please explain what is meant by "pre-existing conditions".

9. On p. 27, under HYPERSENSITIVITY REACTIONS, first paragraph, please state whether any premedicated patients discontinued treatment due to hypersensitivity reactions.

10. On p. 28, under CUTANEOUS, include a sentence on alopecia.

Julie Beitz MD 5/14/96
Julie Beitz, MD Date

cc:
NDA #20,449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ D. Pease

MAY 14 1996

MEDICAL OFFICER REVIEW OF AMENDMENT TO NDA # 20-449

TAXOTERE® (docetaxel) for Injection Concentrate

February 28, 1996 Submission

1. Description of Clinical Data Sources

Following receipt of RPR's November 1995 response to DODP's Approvable Letter (dated October 27, 1995), DODP made additional requests for information and documents in a FAX dated 12/26/95. RPR's first response to this FAX was made on 2/28/96 (19 volumes). This prompted a meeting with RPR, held on 3/8/96, to clarify some of the firm's responses; follow-up written responses were submitted on 3/15/96. Subsequently, RPR responded to FDA's faxed questions from 3/15 on 4/3/95, to questions from 3/21 on 4/8/96, and to questions from 4/5 on 4/12/96. Revised product labeling was submitted on 3/27, 4/9, 4/12, and 4/19/96 and formatted on diskettes in MSWord 6.0 and WordPerfect 6.0.

Response/Document	Date Submitted
Treatment-Related Deaths, including case report forms	2/28/96, 3/15/96, 4/3/96, 4/9/96
Non-Fatal Docetaxel-Related Serious Adverse Events	2/28/96, 4/8/96
Severe Asthenia	2/28/96
Docetaxel Tolerance in Patients with Baseline Fluid Retention	2/28/96, 4/8/96
Maximum Level of Degradate RPR-112248	2/28/96
Evolution of Performance Status	2/28/96
Japanese Clinical Experience	2/28/96, 3/15/95, 4/3/96, 4/12/96
Japanese case report forms, xrays	4/29/96
Revised Product Labeling	3/27/96, 4/9/96, 4/12/96, 4/18/96

At an internal meeting held on 4/12/96, the medical review team decided that the Japanese clinical experience with docetaxel administered at 60 mg/m² was important since available data indicated that it was efficacious and better tolerated than the 100 mg/m² dose. Specifically, it was agreed to offer approval of docetaxel for anthracycline-resistant breast cancer at a dose range of 60 - 100 mg/m².

At a telecon with RPR on 4/16/96, these impressions were conveyed and a revision of product labeling was requested to include safety and efficacy information for both the 60 and 100 mg/m² doses, and safety data for the 75 mg/m² dose (evaluated only as first-line therapy). RPR agreed to revise labeling accordingly and to provide CRFs and supporting documents for patients entered on Japanese trials. Revised labeling was submitted on 4/18 and Japanese source documents (CRFs and xrays) on 4/29/96.

2. Treatment-Related Deaths

- **Review of Appendix I, Volume 1**

Data derived from RPR's Pharmacovigilance Database (PVG, Appendix I) was used to generate toxic death rates in the November 1995 and February 1996 submissions. This database is a "real-time" tracking system for serious adverse events. The cut-off date for the current analysis is 10/31/95. Since the toxic death rate of docetaxel monotherapy at 100 mg/m² is in question, RPR contends that all patients treated on phase 1 dose escalation, combination or sequential studies should be omitted. However, 36 such deaths were inadvertently included by RPR in the November 1995 submission, so that there were a total of 145 deaths instead of 109. Sixteen of these occurred in the early period (10/2/90 - 6/30/94) and 20 in the later period (7/1/94 - 10/31/95). In addition, the number of patients at risk in the early period is now reported to be 1491, instead of 631, since a number of patients were alive and still on study in both the early and the late periods. Thus, RPR's corrected early toxic death rate is 2.8% (41/1491), not 9% (57/631) as suggested in November 1995. RPR's corrected overall toxic death rate is 2.1% (109/5136), not 2.8% (145/5083).

Reviewer Comment: RPR's November 1995 submission did not identify the 145 deaths by study or patient number. Nonetheless, FDA assumes that the 36 omissions are accurately reported as follows: 4 patients treated on phase 1 studies and, hence, at a lower dose, 11 patients treated in Japanese studies at 50 mg/m², 19 patients treated on docetaxel combination studies, and 2 patients whose causality of death was subsequently changed by the investigator (TAX281 TAX296 See Appendix for RPR's list of omissions.

- **Review of Safety Update Report, Volume 3**

The current Safety Update Report (cut-off date 11/17/95) summarizes the experience in 1495 patients from 37 studies, all of whom received docetaxel as monotherapy at an initial planned dose of 100 mg/m² q 3 weeks. Of these, 624 were breast cancer patients including 216 anthracycline-resistant patients. Overall, there were 40 toxic deaths among 1490 evaluable patients or 2.7% (5 patients omitted due to treatment discontinuation in cycle 1 because of ASHR).

The current Safety Update, the ISS from the original NDA (7/94) and the 4-month Safety Update (11/94) were prepared using RPR's Clinical Database which contains all clinical study information collected on case report forms. It is updated as data are received from the investigational sites, and is periodically frozen by database management personnel.

The following series of tables attempt to identify the patient deaths occurring on studies evaluating docetaxel monotherapy at 100 mg/m². The PVG and Clinical Databases are presented side-by-side. The Clinical Database lags far behind in terms of numbers of patients entered on studies and number of patient deaths reported, especially after 7/94. Note that RPR plans to use the 2.7% toxic death rate derived from the Clinical Database in product labeling.

Table 1. Studies Submitted in Original NDA ISS
Docetaxel Monotherapy at 100 mg/m², N=23.

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
TAX220	40	0	0
TAX221	39	2	1
TAX222	38	3	1
TAX223	42	3	3
TAX224	34	3	3
TAX225	33	0	0
TAX227	42	0	0
TAX228	35	study omitted	0
TAX230	18	0	0
TAX231	29	0	1
TAX232	41	2	1
TAX233	41	1	1
TAX236	40	1	0
TAX237	34	0	0
TAX245	30	1	1
TAX252	59/57*	1	1
TAX256	20	study omitted	0
TAX257	19	0	0
TAX266	37	1	1
TAX267	42	0	0
TAX269	48	4	2
TAX270	44	1	1
TAX271	44	1	1
Toxic Death Rate		24/794 or 3.0%	18/847 or 2.2%

* Accrual figures differ in PVG and Clinical Databases

Table 2. Studies with Accrual Completed Prior to 7/94, N=27

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
23 Studies in Table 1	794/847	24	18
TAX247	43	1	1
TAX249	25	0	Study omitted
TAX281	37	1	0
TAX286	51	2	2
Toxic Death Rate		28/950 or 3.0%	21/978 or 2.2%

Table 3. Addition of Studies with Accrual Completed After 7/94, N=34

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
27 Studies in Table 2	950/978	28	21
TAX029	24	0	0
TAX226	144	1	study omitted
TAX229	40	0	study omitted
TAX268	12	0	study omitted
TAX291	43	0	study omitted
TAX292	47**	study omitted	study omitted
TAX295	45/44*	3	2
Toxic Death Rate		32/1258 or 2.5%	23/1046 or 2.2%

* Accrual figures differ in the PVG and Clinical Databases

** Accrual taken from Annual Report to IND

Table 4. Addition of Ongoing Phase 2 Studies, as of 11/17/95, N=53

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
34 Studies in Table 3	1258/1046	32	23
TAX204	17	0	study omitted
TAX208	1	0	study omitted
TAX217	1	0	study omitted
TAX235	95/84*	2	1
TAX238	24/15*	2	2
TAX246	38/37*	0	1
TAX248	138	3	study omitted
TAX258	22	0	study omitted
TAX264	58	3	3
TAX288	9	0	study omitted
TAX296	39/27*	0	0
TAX297	77	1	study omitted
TXB-2S	52	0	study omitted
UK-201	8	1	study omitted
TXB-201	93	5	study omitted
SI001	249	6	study omitted
SI002	516/110*	15	6
IT018	10	0	study omitted
P194	10	0	study omitted
Toxic Death Rate		70/2715 or 2.6%	36/1377 or 2.6%

*Accrual figures differ in PVG and Clinical Databases

Table 5. Addition of Ongoing Phase 3 Studies, as of 11/17/95, N=65

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
53 Studies in Table 4	2715/1377	70	36
TAX303	91/68*	2	2
TAX304	102/43*	2	2
TAX308	3**	study omitted	study omitted
TAX311	40/7*	2	0
TAX313	2	0	study omitted
TAX317	14	1	study omitted
TAX319	15	0	study omitted
TAX320	9	0	study omitted
SI007	29	0	study omitted
SI008	16	0	study omitted
SI009	13	0	study omitted
TXB-301	25	0	study omitted
Total	359	77/3071 or 2.5%	40/1495 or 2.7%

* Acrrual figures differ in the PVG and Clinical Databases

** Accrual taken from Annual Report to IND

Table 6. Addition of Ongoing Open Label or Compassionate Use Protocols, as of 11/17/95

Study	# Treated	Toxic Deaths	
		Pharmacovigilance	Clinical
65 Studies in Table 5	3071/1495	77	40
TAX301	853	13	study omitted
TAXCompa	818	12	study omitted
TAX-ATU (France)	615*	study omitted	study omitted
TAX-EAP (UK)	220	4	study omitted
Individual Patients (US)	4*	omitted	study omitted
TAX-401	1	0	study omitted
Toxic Death Rate		106/4963 or 2.1%	40/1495 or 2.7%

* Accrual taken from Annual Report to IND

Table 7. Studies Not Included in Tables 1-6

Reason	Studies
RPR Omitted - No reason given	NCI studies (N=10)
Docetaxel not given as monotherapy at an initial planned dose of 100 mg/m^2 q 3 weeks*	All Phase 1 Studies All Combination or Sequential Treatment Studies All Japanese Studies
Reviewer Omitted - Insufficient Information (also omitted by RPR)	216, 234

* For this reason, reviewer omitted TAX009, TAX207, TAX244, TAX253, TAX265, and TAX299 from Tables 1-6. This accounts for a total of 173 patients entered and 3 toxic deaths. RPR had included these patients in its PVG database to obtain 109 deaths out of 5136 patients as reported in volume 1 of this submission.

Reviewer Comments on the Pharmacovigilance Database:

1. The Pharmacovigilance Database lists 697 additional patients enrolled on 19 studies in the early period as compared to the number of patients listed in the Integrated Safety Summary of the original NDA (N = 847, Table 29, 7/94) and omits 55 patients on 2 Canadian studies, TAX228 and TAX256. The additional patients come from a variety of phase 2 and 3 studies that were apparently open to accrual in the early period but not included in the ISS. Focusing only on the 21 phase 2 studies that are common to both the PVG Database and the ISS, there was a net of 6 additional deaths reported in the PVG Database (24 vs. 18, Table 1). There were 7 additional deaths (reported on TAX221, TAX222, TAX232, TAX236, and TAX269) minus one patient death (TAX231 that was reclassified in the PVG Database as not related to docetaxel per the investigator. In addition, the PVG Database listed TAX 271 while the Clinical Database listed TAX271 as treatment-related deaths. **Using RPR's PVG Database, the toxic death rate for these 21 NDA studies is 3% rather than 2.2% (Clinical Database).**

2. Review of the 19 additional early studies in the PVG Database revealed a total of 697 patients and 17 deaths reported in the early period. RPR stated in its 3/15/96 response that the reasons these studies were not included in the original NDA are: a) different cut-off dates: 12/93 for the original NDA vs 6/94 for the early period of the PVG Database, and b) 8 studies (TAX009, 226, 229, 248, 249, 258, 268, and Compa) were "considered to be of lower priority" and "not encoded and mapped on time" for submission in the original NDA, nor the current Safety Update Report. (The 8 studies enrolled 375 patients and account for 5 toxic deaths; accrual on 6 of these began in 1992 and is complete in 4 of them.) **Using RPR's PVG Database, the toxic death rate for the early period (40 studies) is calculated to be 24 + 17/ 794 + 697 or 41/1491 (2.8%), not 9% (November 1995 submission).**

   The 19 additional studies in the PVG Database listed as early are:

   i. TAX009, a phase 1 trial of weekly escalating doses of docetaxel (4 patients, no toxic deaths), and TAX265, a trial evaluating docetaxel 50 mg/m² on a day 1, day 8 schedule (83 patients, 2 early toxic deaths); both should have been omitted using RPR's criteria (i.e., docetaxel monotherapy at 100 mg/m² q 3 wks);

   ii. Four phase 2 studies with accrual completed in the early period had 4 toxic deaths among 156 patients (3.2%) in the early period;

   iii. Five phase 2 studies with accrual completed in the late period had 3 toxic deaths among 241 (1.2%) reported in the early period;

   iv. Seven phase 2 studies ongoing as of 11/17/95 had a total of 7 toxic deaths among 210 patients (3.8%) reported in the early period; and

v. Three patients treated on TaxCompa, accounting for 1 toxic death.

Reviewer Comments on the Clinical Database (Safety Update Report):

1. The Safety Update Report does not include as many patients as the PVG Database for 8 ongoing studies (235, 238, 246, 296, SI002A, 303, 304, 311). If the patients in the PVG Database were included in the Safety Update Report, the total number of patients would be increased from 1495 to 2054.

2. The Safety Update Report also does not include the same studies at the PVG Database did for the early period (10/2/90 - 6/30/94). Recall that the PVG Database contained 19 additional early studies besides those in the original NDA. Of these 19 studies, only 10 appear in the Safety Update Report (029, 235, 238, 246, 247, 264, 281, 286, 295, and 296). The remaining 9 studies include those of "lower priority" listed above that RPR has not included in the Clinical Database as yet, plus TAX265, omitted presumably because it evaluated a different dose/schedule of docetaxel. Note that 4 studies not listed as early in the PVG Database are included in the Safety Update Report: TAX303, 304, 311, and SI002A.

3. Among the toxic deaths reported by RPR, assessment of treatment-relatedness for cause of death has been altered in the following cases. At a meeting held with RPR on 3/8/96, we were informed that the PVG Database would have the most up-to-date information submitted by individual investigators, while the Clinical Database would lag behind as is periodically frozen. See Appendix for RPR's explanatory table.

   TAX281 death possibly related to docetaxel (dyspnea noted in PVG Database) changed to not related following receipt of an autopsy report in 8/94; RPR has omitted this patient death from Appendix I and the Safety Update Report.

   TAX296 listed as death probably related to docetaxel (nausea, vomiting and diarrhea as well as disease progression noted in PVG Database); RPR has omitted this patient death from Appendix I and the Safety Update Report.

   TAX231 death was not related (pneumonia noted in Annual Report to IND and PVG Database) and possibly related (line listing, Clinical Database); Clinical Database was frozen before investigator's follow-up report was received two years later and could not be updated. This patient death was included among the toxic deaths in the SUR (2/28) but later omitted by RPR (4/3/96 submission).

   TAX271 death was not related (pneumonia noted in PVG Database) and possibly/probably related (line listing, Clinical Database). Clinical Database was frozen with a follow-up autopsy report pending. This patient death was included among the

toxic deaths in the SUR (2/28) but later omitted by RPR (4/3/96 submission).

TAXSI002A .... death was remotely related (line listing, Annual Report to IND) and not related (weakness and dyspnea noted in PVG Database) and probably related (pneumonia noted in Clinical Database). This patient death **was included** among the toxic deaths in the SUR (2/28) but later omitted by RPR (4/3/96 submission).

Source documents for these 5 patients were requested on 4/1/96. Upon review of these documents, FDA determined that TAX281 #0013 and TAX231 were not treatment-related deaths, but that the other three were (see Section 2.1 of this review).

4. TAXSI002A and TAX246 were counted in the Clinical Database but are listed as remotely related in both the Clinical and PVG Databases. In its 4/3 submission, RPR states that these patients were erroneously included in the Clinical Database and so removed them from the SUR. **Thus, in its 4/3 communication, RPR has removed 5 patients from its calculation of the toxic death rate in the SUR, reporting 35/1490 or 2.3%.** Case report forms for these 2 patients were requested on 4/1/96. Upon review of these documents, FDA determined that these were treatment-related deaths (see Section 2.1 of this review).

The next section describes FDA's independent assessment of toxic deaths, undertaken upon review of source documents provided by RPR. It is an attempt to classify the causality of patient deaths based on clinical information, regardless of how patients were classified by RPR in its two databases. The purpose of this activity is to reach agreement on which patients, in fact, died a treatment-related death on docetaxel monotherapy at 100 mg/m^2.

2.1 FDA Assessment of Toxic Deaths Using Source Documents

RPR has provided the following source documents: case report forms (for all non-septic deaths in the PVG Database) and CIOMS forms (for all septic deaths reported to the PVG Database between 7/1/94 and 10/31/96). These documents were submitted 2/28/96 in volumes 2, 4-10. In some instances, annotated case report forms (submitted 7/94, volumes 1.359 - 1.362), narrative summaries from study reports or data listings were the only records available.

- **Safety Update Report**

A total of 40 toxic deaths were reported in RPR's Safety Update Report (2/28 submission). **Overall assessment of these 40 patient deaths by FDA revealed agreement in 36 cases that deaths were treatment-related, and disagreement in 4 cases.** The table below summarizes these findings. Narrative summaries are provided in the Appendix. The majority of deaths were due to sepsis (26/36 or 72%). Of the 10 non-septic deaths, hepatic failure/GI hemorrage was the primary cause of death for 7 patients, fluid retention for 2, and pneumonia for 1.

Table 8. FDA Review of Toxic Deaths Reported in Safety Update Report

Study#	Patient#	Is Death Tx-Related?	Remarks
221		Yes	Sepsis
222		No	Probable CVA
223		Yes	Sepsis
223		Yes	Sepsis
223		Yes	Fluid retention
224		Yes	Sepsis
224		Yes	Sepsis
224		Yes	Sepsis
231		No	Pneumonia
232		Yes	Sepsis
233		Yes	Sepsis
235		Yes	Neutropenia; stomatitis; DIC; GI hemorrhage; Acute fluid retention
238		Yes	Sepsis

Study#	Patient#	Is Death Tx-Related?	Remarks
238		Yes	Sepsis
245		Yes	Sepsis
246		Yes	Neutropenia; hyperbilirubinemia; GI hemorrhage
247		Yes	Hematemesis; respiratory failure
252		Yes	Sepsis
264		Yes	Sepsis
264		Yes	Sepsis
264		Yes	GI hemorrhage
266		Yes	Coagulopathy; hemorrhage
269		Yes	Sepsis
269		Yes	Sepsis
270		Yes	Sepsis
271		Yes*	Pneumonia
286		Yes	Febrile neutropenia; stomatitis; GI hemorrhage
286		Yes	Sepsis; acute fluid retention
295		Yes	Sepsis
295		Yes	Pneumonia
303		Yes	Sepsis
303		Yes	Acute hepatic failure
304		Yes	Sepsis
304		Yes	Sepsis
SI002A		Yes**	Pneumonia
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Acute fluid retention
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis

*FDA assessment changed to not drug related after additional data was presented by RPR on 5/8/96

**Assessment of secondary reviewer: death was probably not related to docetaxel

- **Deaths Not Incorporated in Toxic Death Rate in Safety Update Report - Completed Studies**

Besides the 40 deaths noted above, 11 additional deaths have been evaluated. These patients were identified by FDA from either the PVG Database or the Annual Report to IND as having died of sepsis or a cause related to docetaxel. Since these patients were enrolled on completed phase 2 studies included in the Safety Update Report, they would be included in the 1490 patient denominator used by RPR. **Overall assessment of these 11 patient deaths by FDA revealed that 4 deaths were treatment-related, and 7 deaths were not.** The table below summarizes these findings. Narrative summaries are provided in the Appendix.

Table 9. FDA Review of Additional Toxic Deaths - Completed Studies

Study#	Patient#	Is Death Tx-Related?	Remarks
221		Yes*	Fluid retention/post-operative cardiogenic shock
222		Yes	? Cause, death in cycle 1
222		Yes*	Lung toxicity/disease progression
232		Yes*	Cardiac arrhythmia
235		Yes	Neutropenic sepsis, death in cycle 1
236		Yes*	? Cause - drug toxicities resolved prior to death
269		Yes*	Fluid retention/cardiovascular collapse
269		Yes	Acute fluid retention, death in cycle 1
271		Yes	Neutropenic sepsis, death in cycle 1
281		No	Disease progression
295		No	Disease progression

*FDA assessment changed to not drug related after additional data was presented by RPR on 5/8/96

Case report forms and CIOMS forms for patients listed in Tables 8 and 9 have been reviewed independently by a second reviewer, Dr. Robert Justice, who concurs with the findings above. His assessments are included in the narrative summaries.

- **Deaths Not Incorporated in Toxic Death Rate in Safety Update Report - Ongoing Studies**

Besides the 51 deaths noted above, 14 additional deaths have been evaluated. These patients were identified by FDA from either the PVG Database or the Annual Report to IND as having died of sepsis or a cause related to docetaxel. Since these patients were enrolled on ongoing phase 2 or 3 studies included in the Safety Update Report, it is not known whether any or all of these patients have been entered in the Clinical Database as of 11/17/95. All deaths occurred in 1995 through the month of October (see Appendix). It is not known when the Clinical Database may have been frozen in 1995. **Overall assessment of these 14 patient deaths by FDA revealed that all deaths were treatment-related.** The table below summarizes these findings. Narrative summaries are provided in the Appendix.

Table 10. FDA Review of Additional Toxic Deaths - Ongoing Studies

Study#	Patient#	Is Death Tx-Related?	Remarks
296		Yes	Acute fluid retention
311		Yes	Sepsis
311		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	Sepsis
SI002A		Yes	GI bleed, ? related to corticosteroids
SI002A		Yes	Cardiac failure, ? ischemia
SI002A		Yes	Sepsis
SI002A		Yes	Neutropenia, hyperbilirubinemia, cardiac ischemia
SI002A		Yes	Sepsis

- **Summary**

The table below summarizes the findings after review of source documents for patients who were reported to have sepsis or a treatment-related cause of death at least once - either in the PVG Database or the Clinical Database. All patients included here received docetaxel monotherapy at 100 mg/m² on studies that are included in the SUR. Recall that these patients represent a subset of the overall population of 4963 patients who received such therapy and who experienced a total of 106 toxic deaths as of 10/31/95 (see Table 6 above).

Table 11. Global Overview - All Toxic Deaths Identified by FDA

Category	# Deaths Confirmed	% Deaths in Cycle 1	Toxic Death Rate
Toxic Deaths in SUR	36	45% (15/33)*	2.4% (36/ 1490)
+ Deaths Not in SUR- Completed Studies	40	51% (19/37)*	2.7% (40/ 1490)
+ Deaths Not in SUR - Ongoing Studies	54	57% (28/49)*	2.6% (54/ 2054)

* Cycle at which death occurred was unknown a some cases

1. **If the additional toxic deaths from completed studies are added to those already included in the Safety Update Report, the toxic death rate is 2.7% (40/1490).** The estimate in the final row is meant to show what the toxic death rate would be if the Clinical Database had kept pace with patient accrual as noted in the PVG Database.

2. Sepsis accounts for the majority of treatment-related deaths (70% or 28/40).

3. There were a total of 6 patients with abnormal LFTs at baseline (combined transaminase and alkaline phosphatase elevations): TAX224 , TAX233 , TAX235 , TAX247 TAX266 and TAX286 The first two patients listed here died of sepsis, the remainder died of complications related to coagulopathy and GI hemorrhage in the setting of hepatic failure.

4. **An acute fluid retention syndrome** following a single dose of docetaxel has been reported; four cases above have been fatal, one life-threatening. Three patients developed acute fluid retention in association with abnormal hepatic function (TAX235 TAX281 and TAXSI002A , one in association with a pre-existing pericardial effusion (TAX269 and one with the development of sepsis (TAX286 In addition, two recent IND Safety Reports have been the subject of similar events: a report of ARDS on day 35 of cycle 1 was reported on 4/8/96; and, a case of worsened ascites, pleural effusion, and weight gain in the setting of abnormal hepatic function on day 2 of cycle 1 was reported on 3/29/96. These reports are included in the Appendix. Product labeling should advise close monitoring of patients with effusions at baseline for potential exacerbations on docetaxel therapy.

3. Specific Safety Issues Related to Docetaxel Monotherapy

- **Serious Adverse Events (Excluding Toxic Deaths)**

Patients are followed until death on all RPR-sponsored trials and all SAEs are reported to Pharmacovigilance within 48 hours of receipt. Similar to the problem with treatment-related deaths in Section 2, RPR inadvertently included non-fatal SAEs from 417 patients treated with doses and schedules other than docetaxel monotherapy at 100 mg/m² in its November 1995 submission. Thus, the correct number of patients at risk for SAEs in the update period is 4,035.

Table 12. Serious Adverse Events Related to Docetaxel Monotherapy at 100 mg/m²

Serious Adverse Event	Pharmacovigilance Database 7/1/94 - 10/31/95		ISS, Original NDA Submitted 7/94	
	1267 Events N (% of Events)	4035 Patients N (% of Patients)	660 Events N (% of Events)	912 Patients* N (% of Patients)
Leukopenia	14 (1%)	14 (0.4%)	50 (8%)	50 (6%)
Neutropenia	98 (8%)	98 (2%)	53 (8%)	53 (6%)
Febrile Neutropenia**	355 (28%)	355 (9%)	158 (24%)	158 (17%)
Thrombocytopenia	6 (0.5%)	6 (0.2%)	-	-
Infection	31 (3%)	31 (1%)	62 (9%)	62 (7%)
Pneumonia	31 (3%)	31 (1%)	8 (1%)	8 (1%)
Pyelonephritis/UTI	10 (0.8%)	10 (0.3%)	6 (0.8%)	6 (0.6%)
Sepsis	56 (4.4%)	56 (1.4%)	5 (0.8%)	5 (0.6%)
Allergy	17 (1%)	17 (0.4%)	34 (5%)	34 (4%)
Skin	10 (0.8%)	10 (0.3%)	15 (2%)	15 (2%)
Stomatitis/MMD	40 (3%)	40 (1%)	15 (2%)	15 (2%)
Diarrhea	50 (4%)	50 (1%)	20 (3%)	20 (2%)
Nausea	33 (3%)	33 (1%)	11 (2%)	11 (1%)
Vomiting	39 (3%)	39 (1%)	17 (3%)	17 (2%)
Asthenia/Malaise	34 (3%)	34 (1%)	21 (3%)	21 (2%)
Fluid Retention	42 (3%)	42 (1%)	40 (6%)	40 (4%)
Neurotoxicity	26 (2%)	26 (0.6%)	22 (3%)	22 (2%)

* Includes 75 patients treated at an initial docetaxel dose of 75 mg/m²

** Includes 7 patients with febrile leukopenia

The table above summarizes the reports of SAEs given in the current update vs those listed in the ISS of the original NDA. In its 4/3 and 4/8 responses, RPR clarified that the data shown for the ISS and in its November 1995 submission was "hand tabulated from Pharmacovigilance data listings by what is designated as the "pharmacovigilance term on the listing - the term by which the investigator identifies the adverse event". Tables of SAEs in the February 1996 submission, however, are derived programmatically by COSTART terms, a practice that began in 1/96. Thus, the data in the current submission are not strictly comparable to any prior SAE report submitted.

Direct comparison of the November and February submissions shows a reduction in reports of febrile neutropenia from 490 to 348, and of sepsis from 80 to 56. In its 4/8/96, RPR provided the SAEs for the 417 patients that had been removed to produce the February report. They accounted for 120 cases of febrile neutropenia and 16 cases of sepsis. This leaves 22 cases of febrile neutropenia and 8 cases of sepsis that are not accounted for and presumably the casualties of the change to a different reporting system.

Nevertheless, serious adverse events as submitted to the Agency are shown in the table above in two ways: as the % of all reported events for the given period, and as the % of patients at risk for the given period. Not all patients experienced SAEs (e.g., in the ISS, only 449 patients out of a potential of 912 experienced SAEs). In addition, some patients had more than one SAE. For example, 39 patients in the PVG Database had reports of sepsis and either neutropenia (27 cases), leukopenia (1 case), or febrile neutropenia (11 cases).

In response to FDA's question regarding the apparent increased reporting of sepsis during the update period, RPR states that a sepsis rate of 1.4% (56 reports among 4035 patients) is "not markedly different" from the incidence of sepsis in the ISS (0.6%, 5 reports among 912 patients). In its 4/3/95 response, RPR states that of the 56 cases of sepsis, only 2 occurred in patients with elevated LFTs.

One major difference in the patient populations at risk in the ISS vs the update period is the 1888 patients enrolled in compassionate use protocols (TAXEAP, TAXCompa, and TAX301) in the latter period, a group of patients that may have been more heavily pretreated. Review of Appendix II, volume 1, revealed that of the 56 reports of sepsis, 29 occurred in patients treated on the compassionate protocols. Of these 29, 22 patients also experienced neutropenia, leukopenia or febrile neutropenia. The 2147 patients (out of 4035) at risk on the remaining trials experienced 27 cases of sepsis, 17 of which were complicated by neutropenia, leukopenia, or febrile neutropenia. Thus, the infectious outcomes of patients treated on a compassionate basis and of those who were not do not appear very different.

Reviewer Comment: RPR's presentation of SAEs in the current submission is not consistent with earlier presentations in previous NDA documents. Thus, it is not possible to verify whether the incidence of a particular SAE has changed over time. In product labeling, the incidence of sepsis will be reflected in the infection rate derived from the Clinical Database (per RPR 4/8/96). The overall infection rate has remained stable over time at 21%.

- **Treatment Discontinuations due to Docetaxel Toxicity**

The Safety Update Report, volume 3, reports 240 patients out of 1490 (16%) have discontinued treatment prematurely due to docetaxel-related adverse events. RPR states this information is based on investigator assessments written in case report forms. **Fluid retention was the reason for treatment discontinuation in 116 patients, neurotoxicity in 58.** Asthenia accounted for treatment discontinuation in 32 patients, skin toxicity in 26 patients, and allergy in 16 patients (+ 5 who discontinued due to AHSR before completion of their first infusion). "Other" was the reason given in 40 patients. A single patient could have more than one reason. The previous Safety Update submitted in 11/94 reported 201 out of 1010 patients or 20% discontinued due to docetaxel-related adverse events. **In its 4/8/96 response, RPR's Table LUS.01 differed slightly with regard to the number of patients discontinuing treatment for these reasons: fluid retention 112, neurotoxicity 55, asthenia 40, skin 27, allergy 16, and other 39.**

In contrast, the Pharmacovigilance Database reports 62 patients have discontinued treatment prematurely due to docetaxel-related adverse events **during the update period thus far** (7/1/94 - 10/31/95). **This represents 1.5% of the 4035 patients at risk.** The most common reasons for treatment discontinuation were neurotoxicity (23 patients), fluid retention (13 patients), allergy or infection (6 patients each), asthenia (3 patients), diarrhea or skin toxicity (2 patients each), and other (7 patients). Source documents, including case report forms and CIOMS forms for these 62 patients were submitted (volumes 11-19). These patients are briefly summarized below:

TAX029: This phase 1/2 trial evaluated the pathophysiology of edema in patients with advanced breast or ovarian cancer treated with docetaxel 100 mg/m² every 3 weeks. Patients received no premedication, diuretics or calcium antagonists. Flavonoids were permitted for treatment of severe fluid retention. Twenty patients were entered on this study in 1994. All eight of the patients discontinuing treatment did so because of fluid retention after 4 or 5 cycles. When this study was first reported to the Agency (Specific Safety Analysis, 1/18/95), 12 of 15 patients or 80% had developed fluid retention, roughly twice the expected incidence, and 5 patients had discontinued treatment. See MOR 10/95 for additional details.

TAX235: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks in patients with metastatic breast cancer, both anthracycline- and non-anthracycline-resistant. Premedication with methylprednisolone (3 days) and cetirizine was given to all patients. As of 10/31/95, 95 patients were entered on this study and 10 had discontinued treatment due to toxicity after a median of 5 cycles (range 2-10 cycles). Fluid retention was the primary reason for discontinuation in 4; fluid retention and muscular weakness or asthenia or nail disorder in 3; paresthesias and asthenia in 1; severe infectious diarrhea due to Clostridia in 1; and neuromotor dysfunction of the hands in 1.

TAX238: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks in patients with metastatic or unresectable head and neck cancer. Patients were previously untreated with chemotherapy for advanced disease. Premedication with methylprednisolone (2 days) and cetirizine was given to all patients. As of 10/31/95, 24 patients were entered on this study and 2

had discontinued treatment after the first infusion. One patient experienced grade 4 skin toxicity (necrosis), febrile neutropenia and grade 3 mucositis. The other developed severe infection and renal insufficiency. Note that there are also two septic deaths reported thus far on this trial.

TAX246: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks in previously untreated patients with metastatic pancreatic cancer. As of 10/31/95, 38 patients were entered on this study and 1 had discontinued treatment after the second infusion due to grade 3 myalgias and fatigue.

TAX247: This trial evaluated docetaxel 100 mg/m² every 3 weeks in previously untreated patients with metastatic pancreatic cancer. Of 43 patients entered on this study, 4 discontinued treatment after 4, 6 or 8 cycles. Three patients discontinued due to fluid retention and one to skin toxicity.

TAX264: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks in previously treated patients with metastatic breast cancer. Patients are premedicated with 5 days of dexamethasone. As of 10/31/95, 58 patients were entered on this study and 9 had discontinued treatment after a median of 6 cycles (range 5-8 cycles). Eight patients discontinued due to neurosensory or neuromotor toxicities and one to severe fatigue.

TAX295: This trial evaluated docetaxel 100 mg/m² every 3 weeks in previously untreated patients with metastatic NSCLC. Of 45 patients entered on this study, 5 discontinued treatment after 1, 2, or 3 cycles. Each patient discontinued for a different reason: progressive pleural effusion and empyema; hypersensitivity reaction; severe edema and electrolyte imbalance due to severe diarrhea; asthenia; and severe dehydration due to dysphagia and diarrhea.

TAX296: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks in paclitaxel-resistant patients with metastatic breast cancer. Patients are premedicated with 5 days of dexamethasone. As of 10/31/95, 39 patients were entered on this study and 1 had discontinued treatment after 4 cycles due to neurosensory toxicity.

TAXSI002A: This ongoing trial evaluates docetaxel 100 mg/m² every 3 weeks as first- or second-line treatment of patients with metastatic NSCLC. As of 10/31/95, 516 patients were entered on this study and 14 had discontinued treatment after a median of 2 cycles (range 1-8 cycles). The reason for treatment discontinuation was infection in 3 (including death in 1); infection complicated by severe nausea and asthenia and CVA; acute hypersensitivity reaction in 4; neurosensory toxicity in 4; congestive heart failure in 1; and complications of diabetes mellitus in 1. In addition to the death noted above, there have been 14 additional treatment-related deaths reported thus far on this study.

TAX303: This ongoing phase 3 trial compares docetaxel with doxorubicin in patients with metastatic breast cancer who have failed alkylator therapy. As of 10/31/95, 91 patients were entered on this study on the docetaxel arm and 5 have discontinued treatment after 1, 2, or 5

cycles. The reason for treatment discontinuation was acute hypersensitivity reaction in 1; stomatitis in 1; acute hypersensitivity and stomatitis in 1; severe neurotoxicity and pleural effusion in 1; and severe neurotoxicity in 1.

TAX304: This ongoing phase 3 trial compares docetaxel with mitomycin C/velban in patients with metastatic breast cancer who have failed anthracycline. As of 10/31/95, 102 patients were entered on this study on the docetaxel arm and 3 have discontinued treatment after 1, 6, or 8 cycles. The reason for treatment discontinuation was infection in 1; fluid retention in 1; and fluid retention and neurosensory toxicity in 1.

Reviewer Comment: The highest treatment discontinuation rates occurred on trials in advanced breast cancer: 16% on TAX264, and 11% on TAX235 and TAX296. Among trials conducted in patients with other cancers, TAX247 in pancreatic cancer had the highest rate of treatment discontinuation (9%).

- **Severe Asthenia on Docetaxel Therapy**

At the ODAC Meeting in October 1995, investigators stated that the duration of severe asthenia "was usually a few days, therefore, the overall performance status reported for the cycle was not adversely affected." FDA's review of case report forms showed that performance scores were generally recorded at the start of a treatment cycle. Thus, the effect of asthenia occurring in mid-cycle on performance status was not recorded. Review of 31 case report forms (submitted for other safety issues) revealed: 1) examples of patients who experienced severe fatigue/weakness lasting several weeks, and 2) examples of severe fatigue/weakness associated with PS >2, especially when drug-related toxicities developed concurrently with disease progression (see MOR, pp 15-18, 2/96). In the 12/26/95 fax, RPR was requested to clarify for the labeling, the median duration (and range) of severe fatigue/weakness for anthracycline-resistant patients.

RPR has responded by agreeing that patients had asthenia or fatigue lasting more than one week in duration. RPR states that the case report forms were designed to collect the worse grade of asthenia over the entire cycle and do not allow determination of the duration of any individual grade of asthenia. Thus, the median duration of severe asthenia cannot be derived.

Reviewer Comments: The concern is the duration of severe asthenia that would appear in labeling, given the discrepancy in RPR's statements at the ODAC Meeting and what was subsequently noted in case report forms. Since investigators did identify the dates of onset and resolution of adverse events in the case report forms, why could the median duration and ranges be calculated for other adverse events, and not for asthenia? For example, RPR study reports routinely gave the median duration and ranges for grade 3 or 4 neutropenia in evaluable cycles. In addition, for labeling, RPR has calculated the median duration of fluid retention and neurotoxicity.

As a compromise on this issue, product labeling could include the following statement under PRECAUTIONS (under the heading for ASTHENIA): "Symptoms of severe fatigue and

weakness may last a few days up to several weeks, and may be associated with deterioration of performance status."

- **Fluid Retention**

At the October 1995 ODAC Meeting, RPR's slide 36 stated that 49% of patients with baseline edema and 59% of patients with baseline effusion were "improved on treatment". At FDA's request, RPR submitted 56 case report forms of patients with baseline fluid retention in support of its contention in November 1995. Review of CRFs revealed that only two patients clearly improved and two had mixed responses (see MOR pp 23-27, 2/96). In the 12/26/95 fax, FDA asked RPR to explain how the information on slide 36 was derived and to clarify what criteria were used to determine whether patients "improved" or not.

RPR responded that the results presented at ODAC were derived from a statistical program that included only adverse events on treatment that were possibly or probably related to treatment. If their original analysis is redone without taking into account the relationship of the fluid retention to study drug, then the proportion of patients improved is reduced to 6% for patients with baseline edema and 7% for patients with baseline effusions (see Table 13 below). RPR states that the majority of the remaining patients that were improved would now be reclassified as stable and that the proportion that worsened did not change much. They conclude that "patients with baseline fluid retention may receive docetaxel therapy without undue safety concern".

Table 13. Status of Fluid Retention on Docetaxel Treatment

Baseline Characteristic	RPR's ODAC Presentation	RPR's Re-Analysis
Edema (N = 85)	Improved - 49% Stable - 20% Worsened - 31%	Improved - 6% Stable - 56% Worsened - 38%
Pleural Effusion (N = 29)	Improved - 59% Stable - 24% Worsened - 17%	Improved - 7% Stable - 69% Worsened - 24%

Reviewer Comments: Note that assignment of the treatment-relatedness of fluid retention developing on docetaxel treatment is problematic for many patients. RPR's ODAC Briefing Document (10/17/95, Table 12) states that 6% (28/455) of breast cancer patients had moderate/severe fluid retention at baseline. Following a median of 5 cycles of docetaxel, the proportion with moderate/severe fluid retention increased to 40% (182/455). Of these, only a handful of patients had pleural/ascitic fluid cytologies performed (the presumption being that a negative cytology for an enlarging effusion is consistent with docetaxel-induced toxicity rather than disease progression). And, there is no objective test to document the treatment-relatedness or disease-relatedness of peripheral edema.

In FDA's review of case report forms, 21 of the 27 patients with worsening fluid retention were

assigned partial responses or stable disease. This suggests that worsening of fluid retention did not often enter into investigators' assessment of response and was generally considered docetaxel-related. This is also borne out in Table 7 included in RPR's study report for the TAX281 trial and provided in the Appendix. Among 16 patients withdrawn for fluid retention on that study, none were considered to have disease progression. This table also shows that assignment of WHO PS in these patients had little bearing on the severity of fluid retention that was experienced.

The table below summarizes the outcomes of the 56 second-line breast cancer patients whose case report forms were reviewed previously (see MOR's Table 10, p. 24 of the 2/96 review). Worsening of fluid retention is based on the development of new moderate or severe symptoms, progression of baseline symptoms to moderate or severe, and/or specific actions required, particularly drainage procedures. The two patients who developed thrombotic events treated solely with anticoagulants were considered stable rather than worsened (TAX 264 and TAX264 for the purpose of this analysis.

Table 14. Outcomes in 56 Patients with Baseline Fluid Retention

Outcome	Study/Patient
Improved N=2 (3.5%)	
Mixed Response N=2 (3.5%)	
Stable N=25 (45%)	
Worsened N=27 (48%)	

Agreement in the classification of 34 of these 56 patients with RPR (using their re-analysis) is apparent now that individual patients have been identified by fluid retention outcome (FDA request 3/21; see RPR response, 4/8/96, included in the Appendix).

FDA's concern is the discrepancy in RPR's slide shown at the ODAC Meeting regarding the improvement of patients with baseline fluid retention who received docetaxel vs. what was subsequently noted in case report forms. **RPR's slide 36 may have left the impression that one-half of patients with baseline fluid retention improved.** RPR's statement that patients with baseline fluid retention may receive docetaxel therapy without undue safety concern is probably valid, although comparable data have not been presented on patients without baseline

fluid retention.

Recommendation is made to include a statement in the product labeling under ADVERSE EVENTS to the effect that patients with baseline fluid retention who receive docetaxel generally do not have improvement in fluid retention and may experience worsening. Further study of this issue is warranted.

4. Evolution of Performance Status

Upon review of RPR's November 1995 submission, FDA concluded that end-of-study performance status scores (generally recorded within 30 days of the last docetaxel infusion) were not incorporated in the graphs shown at the October ODAC Meeting (slides 61-65). Taking these scores into account, assuming that the end-of-study PS was 4 for the three patients who suffered toxic deaths, and assuming that the PS recorded for patients on the TAX286 trial may not accurately reflect the impact of the toxicities these patients experienced, perhaps as many as 18 out of 134 anthracycline-resistant patients in pivotal trials experienced a deterioration in performance status concurrent with treatment-related adverse events. Thus, among 55 responders, PS improved in 4, remained stable in 28, and worsened in 23.

RPR responded that they acknowledge FDA's alternative analysis. Recommendation is made to include a statement in the product labeling under PRECAUTIONS (under the heading of GENERAL) to the effect that responding patients generally do not have improvement in performance status and may experience worsening.

5. Safety Update Report

5.1 Program Overview

Volumes 3-19, submitted on February 28, 1996, contain a summary of safety results on docetaxel monotherapy as of November 17, 1995. Results are presented for 28 completed phase 2 studies and 9 ongoing phase 2 and 3 studies with docetaxel at an initial planned dose of 100 mg/m² for various tumor types, including metastatic breast cancer. Altogether, 5136 patients were evaluable for safety (presented in the Pharmacovigilance Database, Appendix I). Of these, 1490 patients were included in this report. Five patients were excluded since they discontinued study drug due to AHSRs before completion of their first docetaxel infusion.

5.2 Patient Characteristics

The median age of the 1490 patients was 56 years (range 19-80). The male:female ratio was 0.6, and 83% had a WHO performance status of 0 or 1. The most common tumor types were breast (42%) and lung (27%). Seventy-five percent of patients had either 0 or 1 prior chemotherapy regimens. A median of 4 treatment cycles were delivered (range 1-29). Out of a total of 6830 cycles, 25% were given at a reduced dose. A treatment delay of 4-7 days occurred in 510 cycles, and of > 7 days in 298 cycles. There were 40 toxic deaths on study, 29 related to sepsis and 11 to other events.

5.3 Safety Profile - Docetaxel Monotherapy at 100 mg/m²

Toxic deaths, serious adverse events and adverse events leading to treatment discontinuation were discussed in Sections 2 and 3 of this review. RPR's Statistical Tables 7-12 provided listings of adverse events possibly or probably related to docetaxel. Specifically, Table 8 (adverse events by NCI terms) listed the incidence of all non-hematologic adverse events in the SUR, except for asthenia, myalgias, and nail disorder (which were listed by COSTART terms in Table 10), and for fluid retention (listed by ONCLASS and COSTART terms in Table 12).

The incidence of docetaxel-related hematologic toxicities in the Safety Update Report was similar to that reported at the October 1995 ODAC Meeting (see Table 15 below).

Reviewer Comment: For hematologic toxicities, RPR has submitted summary statistical tables of the incidence of key parameters, as well as of febrile neutropenia (defined as fever > 38°C, with IV antibiotics and/or fever serious). **It is not possible to extrapolate from listings of fever, granulocytopenia, or infection as given in NCI terms in Table 8 to RPR's summary data on febrile neutropenia.** On 3/21, FDA requested documentation of hematologic adverse events and on 4/8 received a second copy of tables 6.01, 7.01a and b, plus summary tables of neutropenic infection and febrile neutropenia by patient and by cycle (Attachments III and IV).

Table 15. Hematologic Toxicity - Overall Patient Population

Toxicity	All Patients - ODAC 10/95 N=1070	All Patients - SUR 2/96 N=1490
Neutropenia	97%	96%
Neutropenia grade 4	80%	76%
Febrile Neutropenia	13%	13%
Infections - severe	20% 6%	21% 6%
Thrombocytopenia	9%	8%
Septic Deaths	1.6%	1.9%

The incidence of docetaxel-related non-hematologic toxicities in the Safety Update Report was similar to that reported at the October 1995 ODAC Meeting.

Table 16. Non-Hematologic Toxicity - Overall Patient Population

Toxicity	All Patients - ODAC 10/95 N=1070	All Patients - SUR 2/96 N=1490
Stomatitis	44% (6%)	42% (6%)
Skin Toxicity	61% (7%)	55% (6%)
Fluid Retention	52% (9%)	48% (8%)
Neurosensory	51% (4%)	49% (4%)
Asthenia	69% (12%)	61% (12%)
Non-septic Deaths	0.6%	0.7%

Of 823 patients with neurotoxicity, duration of toxicity was evaluable in 290 patients (381 patients had ongoing symptoms and 152 had missing information). The median duration of neurotoxicity was 60 days (range 0 - 741 days).

On 3/21/96, RPR was asked to clarify why some adverse events listed under COSTART terms appear to be underreported when compared to listings by NCI terms. For example, there were 17 infections reported by COSTART term in RPR's Statistical Table 10 vs. 314 by NCI term in Table 8. In its 4/8/96 response, RPR states that the COSTART tables represent only those events that were non-NCI gradeable or not NCI graded by the investigator in the CRF (i.e., NCI term missing). "The most conservative approach can be taken by adding the by patient incidences of adverse events reported in each classification." These incidences have been

tabulated and included in the Appendix.

Reviewer Comments: The incidence of adverse events listed by NCI term do not substantially differ from the sum of the NCI AEs + COSTART AEs, with the exception of skin toxicity and neurosensory toxicity. Addition of the COSTART AEs contributes an additional 4% (62 or 65 patients, respectively) to the overall incidence of these adverse events. These combined incidence figures currently do not appear in RPR's proposed product labeling.

- **Safety Profile by Baseline Hepatic Function**

In its 4/8/96 submission, RPR has provided the incidence of adverse events for the overall patient population (1490 patients) by baseline hepatic function. There were 55 patients with elevated liver enzymes (defined as the combination of SGOT or SGPT > 1.5 x ULN and AP > 2.5 x ULN) and 54 with one or two parameters missing. RPR has chosen to include the patients with missing enzymes in the "normal" group. An overview of the incidence of hematologic and non-hematologic toxicities has been provided for the 1435 patients with "normal" liver function and is included in the Appendix. Incidences previously reported for 1028 patients at the October 1995 ODAC are also shown. There are no major differences between the two reports.

Reviewer Comment: In its 4/8/96 response, RPR's Table LUS.08 indicates that overall, there are a total of 94 patients with elevated hepatic enzymes at baseline: 51 with elevations of transaminases +AP (bilirubin normal); 2 with elevations of transaminases +AP (bilirubin missing); and 41 with elevations of transaminases + AP +bilirubin. Given previous discussions of the adverse sequelae of docetaxel treatment in patients with elevated bilirubin levels in MORs and at ODAC meetings, suggestion is made include the group of 94 patients in the "abnormal" liver function group.

5. . Fluid Retention

As of 10/31/95, a total of 3,036 patients had received 5-day dexamethasone premedication to ameliorate fluid retention. However, only 235 of these patients have been entered in the Clinical Database, and hence, are included in the Safety Update Report. Information on the remaining patients is limited to SAEs in the Pharmacovigilance Database. In addition, RPR states that information collected on patients on compassionate use protocols is limited and will not allow for a comprehensive analysis of all fluid retention parameters.

Appendix IV, volume 1, contains adverse events (regardless of relationship to docetaxel) for 60 breast cancer patients treated with docetaxel without premedication and for 235 breast cancer patients premedicated with 5-day steroids. The previously reported 104 breast cancer patients (Specific Safety Analysis, 3/9/95) are included in the 235. At FDA's request, RPR submitted tabulations of those events that were possibly or probably related to docetaxel (Attachment II,

4/8/96). These events are summarized here (a patient may have more than one event).

Table 17. Incidence of Fluid Retention - Effect of Steroid Premedication

Adverse Event	No Premedication N = 60	5-day Dexamethasone N = 235
Fluid Retention, Any	45 (75%)	114 (49%)
Fluid Retention, Moderate/Severe	31 (52%)	55 (23%)
Weight Gain	27 (45%)	11 (5%)
Peripheral Edema	13 (22%)	89 (38%)
Generalized Edema	2 (3%)	13 (6%)
Pleural Effusion	20 (33%)	17 (7%)
Pericardial Effusion	2 (3%)	2 (1%)
Ascites	0	4 (2%)

Reviewer Comments: The incidence of fluid retention among the 235 patients is consistent with that reported previously for 104 patients: 49% incidence overall, 20% moderate or severe cases. Docetaxel-related fluid retention, both overall and moderate/severe events, weight gain, and pleural effusions occur less frequently with premedication. Peripheral edema or generalized edema, however, remain a problem (possibly exacerbated) even with premedication. Other adverse events, possibly or probably related to docetaxel are:

Table 18. Other Adverse Events (NCI Terms) - Effect of Steroid Premedication

Adverse Event	No Premedication N = 60	5-day Dexamethasone N = 235
Allergy	4 (7%)	36 (15%)
Neurosensory	31 (52%)	116 (49%)
Myalgias*	10 (17%)	48 (20%)
Vomiting	18 (30%)	49 (21%)
Infection	14 (23%)	63 (27%)
Skin Toxicity	44 (73%)	107 (46%)
Stomatitis	22 (37%)	142 (60%)

* COSTART term

This data suggest a positive impact of steriod premedication on the incidence of skin toxicity.

The incidence of allergy and stomatitis appears worsened with premedication. Infection rates were comparable in both groups.

Additional information on fluid retention parameters observed for these two cohorts has been provided in Table 12 of the Safety Update Report, along with data from 85 breast cancer patients premedicated with a 3-day corticosteroid regimen (84 patients on TAX235 received methylprednisolone for 3 days + cetirizine pre-docetaxel, and 1 patient from TAX267 received an unknown corticosteroid for 3 days). This data is summarized below:

For 235 patients premedicated with a 5-day steroid regimen, the median number of treatment cycles was 4 (range 1-14), the median cumulative dose to onset of fluid retention was 397 mg/m², and the median cumulative dose to onset of moderate/severe fluid retention was 705 mg/m². Only four patients (1.7%) withdrew from treatment due to fluid retention. The median duration of fluid retention from the last docetaxel infusion was 29 weeks (range 0 - 42+weeks).

For 85 patients premedicated with a 3-day steroid regimen, the median number of treatment cycles was 6 (range 1-10), the median cumulative dose to onset of fluid retention was 399 mg/m², and the median cumulative dose to onset of moderate/severe fluid retention was 799 mg/m². Seven patients (8%) withdrew from treatment due to fluid retention. The median duration of fluid retention from the last docetaxel infusion was 14 weeks (0 - 40+weeks).

For 60 patients who were not premedicated, the median number of treatment cycles was 5 (range 1-13), the median cumulative dose to onset of fluid retention was 322 mg/m², and the median cumulative dose to onset of moderate/severe fluid retention was 490 mg/m². Nineteen patients (32%) withdrew from treatment due to fluid retention. The median duration of fluid retention from the last docetaxel infusion was 25 weeks (3 - 100+weeks).

5.5 Safety Profile in Anthracycline-Resistant Breast Cancer

A subset of 216 patients with anthracycline-resistant breast cancer is evaluable for safety. The median age of these patients was 50 years (range 27-80) and 84% had a WHO performance status of 0 or 1. Eighty-four percent of patients had either 0 or 1 prior chemotherapy regimens. A median of 5 treatment cycles was delivered (range 1-18). Out of a total of 1165 cycles, 29% were given at a reduced dose. A treatment delay of 4-7 days occurred in 122 cycles, and of > 7 days in 57 cycles. There were 5 toxic deaths on study, 4 related to sepsis and 1 to other events. Narrative summaries of these cases appear in the Appendix.

Serious adverse events for the subset of anthracycline-resistant patients have not been provided. Adverse events lead to treatment discontinuation in 18% (38/216) of patients. Twenty patients discontinued to due to fluid retention, 16 due to neurotoxicity and 2 due to asthenia. Neurotoxicity accounted for 42% of anthracycline-resistant patients withdrawn as compared to 24% of patients in the overall population withdrawn for toxicity.

The 216 patients in this report include 134 patients treated on the three pivotal trials (TAX233, TAX267, and TAX286). At the October 1995 ODAC Meeting, the safety profile of these patients was discussed in terms of baseline liver function, since patients with liver dysfunction had a higher incidence of febrile neutropenia, infections, thrombocytopenia, stomatitis, and toxic deaths. Thus, among the 216 anthracycline-resistant patients, 9 had liver dysfunction defined as the combination of SGOT or SGPT > 1.5 x ULN and AP > 2.5 x ULN. The remaining 207 patients were considered to have "normal" liver function. Baseline patient characteristics of patients with and without "normal" liver function were similar. However, the liver dysfunction patients tolerated treatment less well: a median of 4 cycles (range 1-8) was delivered, with a median cumulative dose of only 284 mg/m². Sixty per cent of treatment cycles in these patients were dose-reduced and 30% of cycles delayed 4 days or more.

The table below shows that anthracycline-resistant patients with "normal" liver function have a > 5% incidence of the following severe toxicities: grade 4 neutropenia, infection, stomatitis, skin toxicity, fluid retention, neurosensory toxicity, and asthenia.

Table 19. Safety Profile - Anthracycline-Resistant Patients with "Normal" Liver Function

Toxicity	ODAC Meeting N=127	Safety Update 2/96 N=207
Neutropenia	99%	99%
Neutropenia, grade 4	95%	89%
Febrile Neutropenia	22%	16%
Infections	25% (7%)	23% (8%)
Thrombocytopenia	12%	13%
Septic Deaths	0.8%	1.4%
Stomatitis	56% (9%)	56% (9%)
Skin Toxicity	62% (10%)	53% (8%)
Fluid Retention	57% (9%)	56% (10%)
Neurosensory	66% (7%)	62% (7%)
Asthenia	80% (23%)	70% (17%)
Non-septic Deaths	0	0

Figures in parentheses refer to grades 3+4 or severe toxicities

Of the 207 patients with "normal" LFTs at baseline, 23 patients experienced serious infections with grade 3/4 neutropenia and/or requiring IV antibiotic usage (Table LUS.07b, pp.17-18).

The nine patients with liver dysfunction fared less well: two patients suffered toxic deaths, 3 experienced febrile neutropenia, 4 had grade 3/4 infection, and 4 had grade 3/4 stomatitis.

Note that anthracycline-resistant patients with abnormal liver function have a > 5% incidence of the following severe toxicities: grade 4 neutropenia, thrombocyopenia, infection, stomatitis, skin toxicity, fluid retention, and asthenia. The incidence of febrile neutropenia is double that of patients with "normal" liver function (33% vs. 16%).

Recall that at the October meeting, ODAC recommended that **patients with liver dysfunction defined in this manner be excluded from treatment with docetaxel.** This recommendation has been incorporated into product labeling. In addition, product labeling currently states that patients with bilirubin levels > ULN should not receive docetaxel.

Table 20. Safety Profile - Anthracycline-Resistant Patients with Abnormal Liver Function

Toxicity	ODAC Meeting N=7	Safety Update 2/96 N=9
Neutropenia	100%	100%
Neutropenia, grade 4	100%	86%
Febrile Neutropenia	43%	33%
Infections	71% (57%)	56% (44%)
Thrombocytopenia	71% (14%)	67% (11%)
Septic Deaths	14.3%	11%
Stomatitis	71% (57%)	78% (44%)
Skin Toxicity	57% (14%)	44% (11%)
Fluid Retention	57% (14%)	44% (11%)
Neurosensory	43% (0)	56% (0)
Asthenia	43% (29%)	44% (33%)
Non-septic Deaths	14.3%	11%

Figures in parentheses refer to grades 3+4 or severe toxicities

6. Japanese Clinical Experience with Docetaxel 60 mg/m²

RPR has submitted an updated analysis of the efficacy data in 174 breast cancer patients previously treated with chemotherapy as presented in the November 21, 1995 submission. **RPR reports that the Japanese Ministry of Health and Welfare has reviewed the conduct of the docetaxel breast cancer trials and has found the trials to be in compliance with GCP.** Clinical data was assessed by a committee of Japanese investigators in accordance with the "Criteria for Assessment of Direct Efficacy of Chemotherapy for Solid Tumors" proposed by the Japanese Society for Chemotherapy, and with "Rules on Dealing with Breast Cancer" proposed by the Society for the Study of Breast Cancer. According to GCP guidelines, audits of investigator sites in Japan are not routinely performed by sponsors. However, a medical oncologist, Dr. Alex Zukiwsky, from the US Research and Development Oncology clinical team has reviewed data from breast cancer trials at RPR-Japan in Tokyo. His findings form the basis of RPR's reports submitted to the Agency. This data has not been "reviewed by an independent panel as were the pivotal US and European breast cancer clinical trials".

The major new findings in this report as compared to the 11/95 report are:

1) RPR's review of case report forms revealed that 14% of patients entered on Japanese trials had received > 3 prior chemotherapy regimens rather than 5%; and the response rate to docetaxel among these patients was 40% (10/25) instead of 25% (2/8);

2) clarification of prior response to anthracycline among patients enrolled and their subsequent response to docetaxel (submitted in part on 2/28 and 4/3/96 at FDA's request); and

3) calculation of response duration (submitted on 2/28 and 3/15/96, at FDA's request).

Table 21 below compares the baseline characteristics of all patients entered on Japanese breast cancer trials and on pivotal US/EORTC trials. Table 22 shows the baseline characteristics for the subgroup of patients in each trial who had PD as the best response to prior anthracycline.

Comments on Baseline Characteristics - All Patients with Prior Anthracycline:

1. In its 4/3/96 response, RPR indicated that among the subset of 127 Japanese patients who had received prior anthracycline, the intent of prior **anthracycline** therapy was: adjuvant/neoadjuvant only in 23%, advanced only in 66%, and adjuvant/neoadjuvant + advanced in 10%. In its 4/12/96 response, the intent of prior chemotherapy (± anthracyclines) for these patients was: 15%, 42%, and 43%, respectively. This breakdown is comparable to that observed in the pivotal studies. **It is not known whether the 19 adjuvant patients ever received additional chemotherapy for advanced disease; thus, some of these patients may have received docetaxel as first-line therapy and are not strictly comparable to patients on the pivotal US/EORTC trials.**

2. RPR has provided information on the number of prior chemotherapy regimens received for the

subset of 127 patients who had prior anthracycline (4/12/96 submission). More patients in Japanese trials had received > 3 prior chemotherapy regimens.

Table 21. Baseline Patient Characteristics in Japanese and US/EORTC Trials: All Patients with Prior Anthracycline

Characteristic	Japanese 60 mg/m² N=127	TAX233[a] 100 mg/m² N=41	TAX267[b] 100 mg/m² N=42	TAX286[c] 100 mg/m² N=51
Intent /Prior Chemo				
Adj/neoadj only	19 (15%)	4 (10%)	2 (5%)	6 (12%)
Adv only	53 (42%)	22 (54%)	14 (33%)	20 (39%)
Adj/neoadj + Adv	55 (43%)	15 (36%)	26 (62%)	25 (49%)
# of Prior Regimens				
1	41 (32%)	15 (37%)	9 (21%)	21 (41%)
2	41 (32%)	19 (46%)	20 (48%)	24 (47%)
3	23 (18%)	7 (17%)	12 (29%)	6 (12%)
> 3	22 (18%)	0	1 (2%)	0
Duration of prior anthracycline				
Median (mos)	4.3	5	4.4	3
Range (mos)				
Time since last anthracycline				
Median (mos)	8	2[d]	1.8[d]	1.5[d]
Range (mos)				

[a] Table 13, 8-38-70 [b] Table 13, 8-44-71 [c] Table 18, 9-12-203
[d] Derived from Table 9 of Data Listings

3. The median duration of prior anthracycline therapy is similar across trials. In Japan, however, there were 3 patients with prior anthracycline therapy lasting ≥ 2 years. One patient was treated adjuvantly, one for advanced disease, and one was treated both adjuvantly and for advanced disease. Note that when patients received only one cycle of anthracycline, the duration of therapy was coded as 1 day rather than 21 or 28 days.

4. The median time since last anthracycline administration was provided for patients on Japanese breast cancer trials. There were 23 patients (18%) who received anthracycline ≥ 2 years previously: 11 had received anthracycline adjuvantly, 9 had responded to or stabilized on prior anthracycline given for metastatic disease, and 3 had unknown responses to prior anthracycline. No information on subsequent treatment was provided. On TAX233, 3 patients received anthracycline ≥ 2 years previously in the adjuvant setting. On the TAX267, 4 patients had received anthracycline ≥ 2 years previously: 3 as adjuvant therapy and 1 in the adjuvant and advanced settings. All seven patients also received chemotherapy subsequently for advanced

disease before docetaxel.

5. While most patients received docetaxel immediately after anthracycline, several did receive additional chemotherapy after anthracycline and prior to docetaxel: 12/41 patients on TAX233, 12/42 patients on TAX267, 2/51 patients on TAX286, and 4/174 patients on Japanese trials.

Table 22. Subgroup of Patients with PD as Best Response to Prior Anthracycline

Characteristic	Japanese 60 mg/m² N=26	TAX233* 100 mg/m² N=13	TAX267* 100 mg/m² N=15	TAX286* 100 mg/m² N=25
Intent /Prior Chemo				
Adj/neoadj only	0	2 (15%)	0	0
Adv only	10 (38%)	7 (54%)	5 (33%)	10 (40%)
Adj/neoadj + Adv	16 (62%)	4 (31%)	10 (67%)	15 (60%)
# of Prior Regimens				
1	5 (19%)	6 (46%)	4 (27%)	10 (40%)
2	10 (38%)	5 (38%)	8 (53%)	11 (44%)
3	4 (15%)	2 (15%)	3 (20%)	4 (16%)
>3	7 (27%)	0	0	0
Duration of prior anthracycline				
Median (mos)	4.2	1.6	4.4 mos	2.1 mos
Range (mos)				
Time since last anthracycline				
Median (mos)	2.3	1.8	1.3	1.5
Range (mos)				

*Table 9, Data Listings for each study report

Comments on Baseline Characteristics - Patients with PD as Best Response to Prior Anthracycline:

1. Among the 127 patients who had received prior anthracycline on Japanese trials, there were 26 patients with PD as the best response to anthracycline. RPR's 4/3/96 submission revealed that 88% of these patients had received anthracycline for advanced disease. Confirmation of this was requested on 4/5, since the 2/28 submission indicated that only 29% of Japanese patients with PD as best response received chemotherapy for advanced disease only. Table 22 shows the intent of prior chemotherapy (± anthracyclines) as presented in RPR's 4/12/96 submission. These figures are comparable to those for patients on the TAX267 and TAX286 trials.

2. Note the minority of worse prognosis patients enrolled on Japanese trials: among 127 patients

with prior anthracycline, only 20% (N=26) had PD as best response to prior anthracycline vs 40% (53/134) for the US/EORTC trials.

3. The proportion of patients who had 3 or more prior regimens was greatest in the Japanese experience.

4. The median duration of prior anthracycline therapy in the Japanese studies was most comparable to that observed for the TAX267 trial. In the US/EORTC trials, two factors contributed to a longer duration of anthracycline treatment: a long course of adjuvant therapy or use of anthracyclines in both the adjuvant and advanced settings. In Japanese trials, the longest median duration was noted for patients who received anthracycline in both adjuvant and metastatic settings.

5. The median time elapsed between the last dose of prior anthracycline and docetaxel is comparable across all studies. The upper end of the range in Japanese trials, 30 months, represents one outlier. Note that for the US/EORTC trials, time since last anthracycline and time since last chemotherapy are identical for this patient subgroup.

6. The anthracyclines administered to this subgroup of patients varied from study to study. Among the 21 unresponsive patients in late phase 2 studies in Japan, 13 patients received doxorubicin, 2 epirubicin, 3 terarubicin, and 1 an investigational anthracycline. Four patients received two different anthracyclines. In TAX233, 11 patients received doxorubicin, 1 patient received doxorubicin, mitoxantrone and epirubicin, and 1 patient liposomal doxorubicin. In TAX267, all 15 patients received doxorubicin; two of these also received mitoxantrone. In TAX286, 15 patients received epirubicin, 8 farmorubicin, 4 doxorubicin, and 2 mitoxantrone. Four patients received two different agents. **Recall that for drug approval and product labeling no distinction has been made by the agency regarding the activity of different prior anthracyclines. At the 3/8/96 meeting, [redacted]R stated that Japanese patients were not comparable to patients on US/EORTC patients because of the different anthracyclines administered to them. One could make the same argument for patients entered on the pivotal EORTC trial TAX286.**

Comments on Response Rates to Docetaxel:

1. Table 3.2 of this submission (page A20) lists objective response rates in Japanese trials (N=174) related to the number of prior chemotherapy regimens received. These were: 47% for 1 prior regimen, 45% for 2 prior regimens, 48% for 3 prior regimens, and 40% (10/25) for more than 3 regimens. **The response rate in this last category is improved from 25% (2/8) reported in November 1995.** Comparable response rates were noted for patients on the TAX233, TAX 267 and TAX286 trials (N=134): a 40% response rate for patients with 1 prior regimen, 38% for 2 prior regimens, and 52% for 3 prior regimens. Only 1 patient had 4 prior regimens and did not respond to docetaxel.

2. Early phase 2 Japanese trials included 35 patients who had received prior anthracycline therapy. **There were a total of 15 responses (1 CR, 14 PRs) among them for an overall response rate of 43%.** Two PRs were reported among the subset of 5 patients who had PD as the best response to prior anthracycline.

Table 23. Comparison of Docetaxel Efficacy in Patients with PD as Best Response to Prior Anthracycline

Efficacy Endpoint	Japanese 60 mg/m² N=26	TAX233 100 mg/m² N=13	TAX267 100 mg/m² N=15	TAX286 100 mg/m² N=25
Overall Response Rate	2/5 (40%) early 7/21 (33%) late	4/13 (31%)	5/15 (33%)	9/25 (36%)

3. Late phase 2 Japanese trials included 92 patients with prior anthracycline exposure. **There were a total of 44 responses among them for an overall objective response rate of 48%.** One CR and six PRs were reported among the subset of 21 patients who had PD as the best response to prior anthracycline. Three PRs were reported when docetaxel was administered as second-line therapy, and 1 CR and 3 PRs were reported in patients receiving third-line therapy.

4. **Thus, the overall response rate for the 26 patients in the Japanese experience with PD as best response to prior anthracycline was 35% (95% CI: 15-54%).** Similar response rates have been noted with 3- and 24-hour infusions of paclitaxel for the subgroup of patients having PD as best response to prior anthracycline. A response rate of 27% (8/30; 95% CI: 10-44%) for paclitaxel 175 mg/m² over 3 hours (Bristol-Myers Squibb randomized phase 3 trial) was confirmed by this Division, and a response rate of 22% (21/94; 95% CI: 14-31%) for paclitaxel 175 mg/m² over 24 hours (Treatment Referral Center Trial, Abrams et al., JCO:13, 1995. In addition, a response rate of 32% (10/31, 95% CI: 15-50%) has been reported for paclitaxel 250 mg/m² over 24 hours (Seidman et al., JCO:13, 1995). See Appendix for graphical presentation.

5. Response rates for other patient subsets (response to prior anthracycline, no change to prior anthracycline) are comparable for both the 100 and 60 mg/m² dose levels. Due to the large confidence intervals, no statistically significant difference can be demonstrated among patients subsetted by prior response to anthracycline. See summary table below (Table 24) and graphical representation of response rates and 95% confidence intervals appended below.

6. The 37 patients in Japanese trials with an unknown response to prior anthracycline is due, in part, to the inclusion of patients who received anthracycline in the adjuvant setting when, in fact, no response would have been expected.

7. The ORR at the 100 mg/m² dose (N=106 evaluable patients) was 40% (95%CI: 30-49%). The ORR at the 60 mg/m² dose (N=127 evaluable patients) was 46% (95%CI: 38-55%).

Table 24. Summary of Efficacy Parameters: 100 mg/m² versus 60 mg/m²
Patients Evaluable by Prior Response to Anthracycline

Response to Prior Anthracycline	60 mg/m² Japanese Early & Late Phase 2		100 mg/m² US/EORTC Pivotal Trials	
	Response Rate	Response Duration	Response Rate	Response Duration
Response (CR/PR)	36% (13/36)	3.3 mos (1 - 10.5 mos)	56% (5/9)	4 mos (3 - 6 mos)
No Change	50% (14/28)	5 mos (1.5 - 8.8+ mos)	44% (14/32)	7 mos (2.8 - 11.8+ mos)
PD as Best Response	35% (9/26)	3.8 mos (1.5 - 8.3+ mos)	34% (18/53)	6 mos (3 - 16.5+ mos)
Unknown Response/ Adjuvant Anthracycline	62% (23/37)	2.5 mos (1 - 6.3 mos)	42% (5/12)	8.5 mos (3.5 - 10 mos)
All Evaluable Patients	46% (59/127)	3.8 mos* (1 - 10.5 mos)	40% (42/106)	6.3 mos (2.8 - 16.5+ mos)

* RPR reported a median response duration for the 59 responders of 4 mos (range 0.3 - 11+ mos) (7/20/95)

Comments on Duration of Response to Docetaxel:

1. Overall, the median response duration at 100 mg/m² appears to exceed that observed at 60 mg/m² by approximately 2.5 months. Censoring information has been provided (4/12/96 submission) for only 4 patients treated at 60 mg/m² who were still responding at the cut-off date of 1/27/94. Censoring information has not been provided for the early phase 2 patients (RPR's 7/95 report indicated an 11+ month response duration which likely corresponds to patient who was enrolled in an early trial). Note that characterization of even a handful of patients as censored at the cut-off date instead of not censored could lengthen the median response duration. Thus, differences in the median for this endpoint for patients treated at these two dose levels could diminish.

Comments on Appendices VII, VIII, and IX:

1. Appendix VII is a copy of "Good Clinical Practice for Trials on Drugs" as set forth by the Japanese Ministry of Health and Welfare and the Japanese "Guideline of Clinical Evaluation for Cancer Chemotherapy".

2. Appendix VIII entitled "Overall Response" is a revision of Appendix I from 11/21/95, that now includes whether patients have had prior anthracycline chemotherapy (yes or no). At FDA's request, Appendix VIII was further revised (submitted 3/15/96) to include assignment of patients' prior response to anthracycline (CR, PR, NC, or PD) and response duration for patients responding to docetaxel. Overall responses and lesion responses are re-iterated here along with

site(s) of indicator lesions. Appendix VIII was revised yet again (submitted 4/3/96) to include the intent of prior anthracycline therapy, duration of prior anthracycline, dates of last anthracycline administration and of first taxotere administration.

3. Appendix IX entitled "Tumor Measurements" is a revision of Appendix II from 11/21/95, that is "cleaner" in terms of clerical errors, and designates baseline tumor measurements as "Cycle 0". However, tumor measurements have not been modified. These were recorded by the investigators in case report forms, however, individual investigators have not been audited nor independently reviewed apart from the Judgment Committee's deliberations. Thus, the same criticisms apply now as before: discrepancies in the descriptions of indicator lesions as listed in Appendices VIII and IX; "lesion" responses can be confirmed in 48 instead of 79 patients. Thirty-five of these responses occurred in patients with prior exposure to anthracycline and in all instances, "lesion" responses corroborated the determination of overall response.

4. The methodology used to determine these responses has not been provided, however, a copy (untranslated) of the minutes of the Judgment Committee's meetings was submitted on 3/15/96 at FDA's request. This document was reviewed by Dr. Masahiro Takeuchi of the Division of Biometrics. He reports that patient eligibility criteria, tumor assessments and response duration for each patient were carefully reviewed at three separate meetings, two of which were attended by RPR staff. In particular, no response was considered true if it was not documented 4 weeks later. This is reassuring since response duration could not be confirmed at 4 weeks for 16 responders using sponsor's Appendix II or IX (see Table 3 of MOR 2/96). On 5/1/96, RPR submitted an untranslated copy of "Guidelines of Clinical Evaluation for Cancer Chemotherapy" and stated that they were in the process of obtaining "Criteria for Assessment of Direct Efficacy of Chemotherapy for Solid Tumors" and "Rules on Dealing with Breast Cancer". The latter two documents, requested by FDA on 4/26/96, formed the basis for the Judgment Committee's actions.

Population Pharmacokinetics of the 60 mg/m² dose:

An abstract entitled, "Population Pharmacokinetics of Docetaxel in Japanese Patients", by Tanigawara, et al., appeared in Proc ASCO 15:479, 1996. Analysis of 662 plasma concentration samples from 102 patients revealed that the disposition of docetaxel was described by a 3-compartment linear model at a dose range of 10-90 mg/m². Patients having hepatic dysfunction (defined as SGOT or SGPT > 60 IU/l) showed a 12% reduction in clearance. The mean clearance for the Japanese patients was 20.3 L/hr/m², similar to that of European/American populations (20.6 L/hr/m², Bruno et al., Proc ASCO 1995) suggesting no racial difference in the elimination of docetaxel. A copy of this abstract appears in the Appendix.

Safety Profile of 60 vs 100 mg/m² dose levels:

RPR's 7/20/95 submission provided the safety profile for the total cohort of 174 previously treated patients entered on Japanese breast cancer trials. Of these, 167 had "normal" liver function at baseline. Since this group may include patients who received docetaxel as first- or second-line therapy as well as anthracyline-resistant patients, the following comparisons are made with 100 mg/m² in 130 first-line, 282 second-line, and 207 anthracycline-resistant patients with "normal" liver function at baseline.

Table 25. Hematologic Toxicity of Docetaxel - 60 vs 100 mg/m²

Toxicity	60 mg/m² N = 174	1st Line - 100 N = 130	2nd Line - 100 N = 282	A-Resistant -100 N = 207
Neutropenia	96%	99%	97%	99%
Neutropenia, grade 4	76 %	92%	92%	89%
Febrile Neutropenia	10%	20%	16%	16%
Infections (severe)	-	22% (4%)	23% (6%)	23% (8%)
Thrombocytopenia	14%	4%	14%	13%

RPR's Table LUS.10 (4/8/96 submission, Attachment IV) indicates the following rates of febrile neutropenia by cycle. In the setting of normal LFTs, the febrile neutropenia rate is 3.2% for cycles dosed at 100 mg/m² vs 1.7% for those dosed at 55 mg/m²; in the setting of abnormal LFTs, the febrile neutropenia rate is 13% for cycles dosed at 100 mg/m² vs 7% for those dosed at 55 mg/m². Recall that patients on US/EORTC trials were dosed at 55 mg/m² if they had not tolerated a dose reduction from 100 to 75 mg/m².

Table 26. Non-Hematologic Toxicity of Docetaxel - 60 vs 100 mg/m²

Toxicity	60 mg/m² N = 174	1st Line - 100 N = 130	2nd Line - 100 N = 282	A-Resistant -100 N = 207
Stomatitis	19% (0.6%)	43% (5%)	57% (9%)	56% (9%)
Skin Toxicity	31% (0)	62% (10%)	57% (8%)	53% (8%)
Fluid Retention	13% (0)	77% (17%)	59% (10%)	56% (10%)
Neurosensory	20% (0)	66% (3%)	53% (4%)	62% (7%)
Asthenia	66% (0)	72% (5%)	71% (19%)	70% (17%)

Figures in parentheses refer to grades 3+4 or severe toxicities

In addition, at the 60 mg/m² dose, there were two toxic deaths, and three patients discontinued due to toxicity according to the 7/20/95 submission. **Reviewer Comment:** Per FDA translation of Judgment Committee minutes, there was one treatment-related death (due to combined respiratory and GI complications).

At the 3/8/96 meeting with RPR, the firm stated that due to cultural differences between Japan and the US/Europe, it is expected that patients would under-report symptoms to their physicians. Note, however, that the 60 mg/m² is myelosuppressive and that most of the non-hematologic toxicities noted above (stomatitis, skin toxicity, edema, etc.) should be readily detectable on physical exam. Possible exceptions to this could be neurosensory toxicity and severe asthenia.

- **Toxic Deaths**

Among patients dosed at 60 mg/m², mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function at baseline. All deaths occurred in cycles 1 or 2. Sepsis was the primary cause of death in all cases. In one patient (TAX289 , grade 4 neutropenia was noted on day 8 of cycle 1, followed by increased pleural effusion on day 9 and death from ARDS on day 10.

Overall Conclusions Regarding Docetaxel Therapy at 60 mg/m²:

1. Not all patients entered on Japanese breast cancer trials are strictly comparable in baseline characteristics to patients entered in pivotal phase 2 trials in the US/EORTC. However, the subgroup of patients with PD as best response to prior anthracycline appears to be a more homogeneous group, especially in terms of the duration and timing of prior anthracycline received. Baseline characteristics of this subgroup appear comparable across trials and cultures.

2. Docetaxel administered at an initial planned dose of 60 mg/m² appears to be active in advanced breast cancer patients who have been previously treated with anthracycline (objective responses in 46%, including 9 CRs).

3. Data available suggest that the response duration may be inferior for the 60 mg/m². However, complete information regarding which patients were censored for this endpoint is required before any definitive statements can be made regarding response duration at this dose level.

4. The 60 mg/m² dose appears to be as myelosuppressive as the 100 mg/m² dose, but results in less non-hematologic toxicity, particularly those of a severe nature.

6.1 FDA Assessment of Japanese Source Documents

On 4/29/96, RPR submitted case repo.. forms and source materials (xrays, CT scans) for the 59 responding patients among the 127 breast cancer patients who had received prior anthracycline. The case report forms from Japan were actually written, in part, in English. All dates, tumor measurements and laboratory values were given in arabic numerals. Indicator lesions were drawn and numbered on an anatomical chart for easy reference. Some of the films submitted identified these lesions by number as well. For each tumor measurement, the per cent reduction from the baseline measurement was given. At every assessment, the investigator circled his/her determination of response as either CR, PR, MR, NC, or PD.

Previously, responses in indicator lesions had been reviewed, but confirmation in 19 of the 59 responders was not possible due to missing data and/or erroneous transcription from CRFs (see review of Appendices I and II in Table 3, MOR 12/26/95). The tables below summarize the responses to docetaxel observed, according to the patients' prior response to anthracycline.

Table 27. Response to Docetaxel 60 mg/m²
Responders who had PD as Best Response to Prior Anthracycline (N=9)

Patient	Indicator Lesion(s)	Evaluation Method(s)	Remarks
	Lymph node (1)	Physical exam	PR
	Liver metastases (1)	USG	PR; > 50% reduction in CEA, TPA, CA 15-3
	Lung metastases (4)	CXR	PR confirmed at 4 wks
	Liver metastases (4)	CT	PR
	Lung metastases (3)	CXR, lung tomos	PR confirmed at 4 wks normalization of CEA, CA 15-3
	Lymph node (1)	Physical exam	CR
	Skin nodule (1) Evaluable skin, bone lesions	Physical exam Skeletal films (cervical & lumbar spine, pelvis, hips)	CR in measurable skin lesion PR in evaluable skin lesions NC in bone lesions > 50% reduction in CA 15-3
	Lung atelectasis/ ?mass Liver (2) Pelvic bone (3) Evaluable skin lesions	CXR CT abdomen Pelvis films Physical exam	Atelectasis improved NC in liver on 1 exam NC in bone lesions on 1 exam PR in skin at 4 wks Overall Response per CRF = MR
	Lymph nodes (2)	Physical exam	PR in both lesions > 50% reduction in CA 15-3

FDA agrees with the investigator's assessment of MR in patient All other responses are

confirmed. The overall RR is 31% (8/26) for this subgroup.

Table 28. Response to Docetaxel 60 mg/m² Responders who had NC to Prior Anthracycline (N=14)

Patient	Indicator Lesion(s)	Evaluation Method(s)	Remarks
	Lymph node (1) Evaluable skin lesion (1)	Physical exam	PR in lymph node CR in skin lesion
	Lymph node (1) Liver metastases (3)	Physical exam CT of abdomen	CR in lymph node and 1 liver lesion PR in other liver lesions Normalization inCEA > 50% reduction in CA 15-3
	Lymph nodes (3) Skin nodule (1)	Physical exam	CR in all lesions for 28 days
	Liver metastases (4)	CT of abd/pelvis	PR in all lesions confirmed
	Skin nodules (2)	Physical exam	PR > 50% reduction in CEA, CA 15-3
	Skin nodule Blastic lesion L2	Physical exam Lumbar spine films	CR in skin Stable lesion at L2
	Skin nodules (5)	Physical exam; photos CT of chest, abd	CR in skin; NC in chest/abd CTs
	Skin nodules (2) Eval lumbar spine mets	Physical exam	PR MR in bone disease
	Lymph node (1) Liver metastases (2)	Physical exam Liver USG	CR in lymph node PR in one liver lesion, MR in other > 50% reduction in CA 15-3
	Liver metastases (5) L1, pelvic bone mets	CT of abd Skeletal films	PR Stable bone disease Normalization of CEA, CA 15-3
	Skin nodules (4)	Physical exam	CR
	Evaluable disease in lung and bone	CT of chest Skeletal films	No tumor measurements
	Lymph nodes (3) Skin nodule (1) Liver metastasis (1)	Physical exam CT of chest, abd Liver USG	CR in liver, skin, 1 lymph node PR in other nodes
	Liver metastases (diffuse)	CT of chest/abd	NC

FDA dose not agree with the PR reported for patients

Table 29. Response to Docetaxel 60 mg/m² Responders who had CR/PR to Prior Anthracycline (N=13)

Patient	Indicator Lesion(s)	Evaluation Method(s)	Remarks
	Mult lung metastases Lymph node (1)	CXR Physical exam	1 cycle given only MR in one lung lesion NC in mult other lung lesions PR in LN not confirmed at 4 wks
	Lymph node (1) Breast nodule (1)	Physical exam	PR
	Lymph node (1) Lung metastases (3)	Physical exam CXR	CR in lymph node PR in lung lesions > 50% reduction in CEA, CA 15-3
	Lymph node (1)	Physical exam	CR Normalization of CEA, CA 15-3
	Lymph node (1) Skin nodule (1)	Physical exam	PR Normalization of CEA, CA 15-3
	Liver metastases (5)	USG CT abd/pelvis	PR in all lesions by CT Normalization of CEA, CA 15-3
	Lung metastases (4)	CXR	PR in all lesions
	Liver metastases (4)	CT of abd/pelvis	PR confirmed for 21 days only
	Skin nodule (1)	Physical exam	PR confirmed for 4 wks
	Liver metastases (2)	Liver USG	CR confirmed for 4 wks
	Liver metastasis (1) Skin nodule (1)	Liver USG Physical exam; photos	PR in liver lesion; MR in skin > 50% reduction in CEA
	Skin nodule (1) Lymph node (1)	Physical exam Chest CT (f/up CTs not available)	PR in skin NC in lymph node per CRF PR per Judgment Committee
	Lung nodules (2)	CXR, Chest CT	PR in one lesion confirmed for 4 wks

FDA disagrees with the investigator's assessment of PR in patient and with the duration of PR in patient

Table 30. Response to Docetaxel 60 mg/m²
Responders who had an Unknown Response to Prior Anthracycline (N=23)*

Patient	Indicator Lesion(s)	Evaluation Method(s)	Remarks
	Skin (chest wall) Skin (back)	Physical exam	PR in chest wall for 28 days MR in back lesion PR per Judgment Committee
	Liver metastasis (1) Skin nodule (1) Pleural effusion	CT abd/pelvis Physical exam CT chest	PR in liver and skin; pleural effusion stable NC in CEA, CA 15-3
	Skin nodules (3)	Physical exam	PR confirmed at 4 wks
	Lymph nodes (4)	Physical exam	PR in all lesions Normalization in CEA
	Skin nodules (2)	Physical exam	PR Normalization of CA 15-3
	Skin nodules (2)	Physical exam	PR
	Periclavicular lymph node mass	CT of neck	PR confirmed for 28 days
	Skin nodules (5)	Physical exam	PR confirmed
	Skin nodule (1)	Physical exam	CR
	Rt. hilar mass Pleural effusion	CXR	PR in hilar mass; effusion resolved > 50% reduction in CEA, CA 15-3
	Lymph nodes (2)	Physical exam	PR confirmed for 4 wks
	Lymph nodes (5)	Physical exam	PR > 50% reduction in CEA
	Liver metastases (3) Pleural effusions	CT of abd CT of chest	PR confirmed for 4 wks Effusions stable Normalization of CEA >50% reduction in CA 15-3
	Chest wall mass	CT of chest	PR confirmed for 4 wks
	Evaluable skin lesions	Physical exam	No tumor measurements
	Liver metastases (3) Skull, pelvic bone mets Evaluable lung disease	CT of abd Skeletal films CT of chest	PR in liver for 4 weeks NC in bone or lung lesions Normalization of CEA, CA 15-3
	Lymph node (1) Liver metastasis (1)	Physical exam Liver USG	PR in both lesions for 4 wks
	Substernal mass	CT of chest	PR confirmed for 4 wks

	Lymph nodes (2)	Physical exam	PR confirmed for 4 wks
	Liver metastases (4) Lymph node (1) Pulm metastases (2) Eval bone metastases	CT of abd Physical exam CXR Bone scan, skeletal films	PR in liver CR in lymph node, lung NC in bone disease Normalization of CEA, CA 15-3
	Lymph node (1) Mult lung metastases	Physical exam CT of chest	CR in lymph node Chest CT improved
	Lymph node (1) Skin nodule (1)	Physical exam	PR
	Lymph nodes (4)	Physcial exam	CR in one, PR in other nodes

*Includes prior anthracycline as adjuvant therapy

FDA cannot accept the PR reported for patient due to lack of tumor measurements.

Excluding the 6 patients identified above (due to lack of confirmation of objective response), the summary of efficacy parameters for the 60 mg/m² dose is recalculated below.

Table 31. Summary of Efficacy Parameters: 100 mg/m² versus 60 mg/m² (Confirmed) Patients Evaluable by Prior Response to Anthracycline

Response to Prior Anthracycline	60 mg/m² Japanese Early & Late Phase 2		100 mg/m² US/EORTC Pivotal Trials	
	Response Rate	Response Duration	Response Rate	Response Duration
Response (CR/PR)	31% (11/36)	3.8 mos (1.8 - 10.5 mos)	56% (5/9)	4 mos (3 - 6 mos)
No Change	43% (12/28)	5 mos (2 - 8.8+ mos)	44% (14/32)	7 mos (2.8 - 11.8+ mos)
PD as Best Response	31% (8/26)	5.8 mos (1.5 - 8.3+ mos)	34% (18/53)	6 mos (3 - 16.5+ mos)
Unknown Response/ Adjuvant Anthracycline	59% (22/37)	2.6 mos (1 - 6.3 mos)	42% (5/12)	8.5 mos (3.5 - 10 mos)
All Evaluable Patients	42% (53/127)	4 mos* (1 - 10.5 mos)	40% (42/106)	6.3 mos (2.8 - 16.5+ mos)

* RPR reported a median response duration for the 59 responders of 4 mos (range 0.3 - 11+ mos) (7/20/95)

The ORR at the 60 mg/m² dose (confirmed) was 42% (95% CI: 33-51%). Thus, removal of the six patients does not appreciable change the efficacy of the 60 mg/m² dose (compare to Table 24 above and refer to graphical representations appended below). The ORR confirmed for the subset of patients with PD as best response to anthracycline was 31% (95% CI: 12-50%).

7. Maximum Level of Degradate RPR-112248

In its 12/26/95 communication to RPR, FDA stated that "the clinical experience with exposure to levels > 0.8% of degradate RPR-112248 is insufficient to rule out the possibility for the development of severe neurotoxicity. If additional clinical data is not available to clarify this point, then further toxicologic evaluation in mice (as previously described by the Pharm/Tox review) may be required."

RPR's response (2/28/96) was that RPR-112248 is at least 370-fold less cytotoxic than docetaxel against the P388 cell line. A mouse neurotoxicity study will be initiated early March 1996 and submitted to the Agency in May 1996. A protocol outline for this study was submitted and has been reviewed by the Pharm/Tox reviewer.

8. Recommended Regulatory Action

1. TAXOTERE® (docetaxel) for Injection Concentrate is approved under the "accelerated approval" regulations based on its objective response rate in phase 2 trials evaluating patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy (21 CFR 314.510).

Phase 3 studies are underway to assess docetaxel's clinical benefit in advanced breast cancer. Reports of these studies must be submitted and reviewed to satisfy the requirements of the "accelerated approval" regulations. Three studies compare docetaxel at 100 mg/m² with paclitaxel (TAX311), with doxorubicin (TAX303), and with mitomycin C/velban (TAX304). In addition to response rate and toxicity, these trials will assess time to progression (the primary endpoint in TAX303 and TAX304; the secondary endpoint in TAX311). In addition, all three trials will assess survival and quality of life. A fourth trial, TAX313, will compare docetaxel 100 with 75 mg/m². Time to progression, survival, and quality of life are secondary endpoints in this trial. Eligible patients with advanced breast cancer will receive docetaxel as first or second line therapy (TAX303, TAX304 and TAX311), or as second line therapy only (TAX313). Over 50% of patients enrolled to date on TAX304 have anthracycline-resistant disease.

2. TAXOTERE® is approved at a dose range of 60 - 100 mg/m² administered over 1 hour every three weeks. This decision is based on a) a higher than expected treatment-related mortality at the 100 mg/m² dose of 2.7%, and b) recent confirmation that the 60 mg/m² dose is efficacious and better tolerated than the 100 mg/m² dose, particularly with respect to severe non-hematologic toxicities, including fluid retention, neurosensory toxicity, stomatitis, skin toxicity, and asthenia.

Docetaxel monotherapy at 100 mg/m² in 134 anthracycline-resistant patients (defined above) produced a 41% overall response rate, a 2% CR rate and a 5.9 month response duration. Docetaxel monotherapy at 60 mg/m² in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast carcinoma breast carcinoma produced an overall response rate of 45%, a CR rate of 5% and a 4 month response duration. Docetaxel monotherapy in the subset of 26 patients who had progression of disease as best response to prior anthracycline treatment produced an overall response rate of 35%, a CR rate of 4%, and a 4 month response duration.

9. Post-Marketing Commitments

- **Status of Prior Commitments**

The Agency's October 27, 1995 Approvable Letter specified the following post-marketing commitments. RPR's response to each (November 21, 1995) is given below in highlighted text.

a) Ongoing phase 3 studies evaluating docetaxel single agent activity at 100 mg/m² versus paclitaxel (TAX311), versus doxorubicin (TAX303), and versus mitomycin C/vinblastine (TAX304). For the TAX311 and TAX304 studies, sufficient numbers of anthracycline-resistant patients should be accrued to confirm the risk:benefit ratio of docetaxel in the patient population for which approval is based.

Accrual of patients to TAX303, TAX304 and TAX311 will be maintained as planned. Currently, over 50% of patients enrolled in TAX304 were actually anthracycline-resistant. The most current versions of each study protocol were submitted.

b) Ongoing phase 3 study in second line breast cancer evaluating docetaxel 100 versus 75 mg/m². Serious consideration should be given to the evaluation of the 60 mg/m² dose (patients progressing after 2 cycles on the low dose could be retreated at a higher dose, assuming the higher dose can be tolerated).

At the TAX313 investigators' meeting held November 4, 1995, consensus was reached that they willing to accept testing of the 75 mg/m² dose in the context of a randomized trial. However, they were unwilling to treat their patients at a dose that was 60% of the approvable dose due to their concerns that they would be sacrificing efficacy. Therefore, currently, RPR does not see a 60 mg/m² arm as a viable option for TAX313. However, if results of TAX313 show that the efficacy of 75 mg/m² is similar to that of 100 mg/m², then it would be appropriate to test an even lower dose aiming to further improve the risk-benefit ratio.

c) Ongoing phase 3 comparison of different corticosteroid premedications for the amelioration of fluid retention; please submit the study protocol to the NDA.

As per the recommendation of the FDA at the end-of-phase 2 meeting on June 6, 1995, RPR is not performing a randomized trial comparing corticosteroid regimens. RPR will obtain more data on the 5-day corticosteroid program from the ongoing studies TAX264, 297, 303, 304, 311, and 317. In response to the FDA's request at the end-of-phase 2 meeting RPR is evaluating the efficacy of a shorter (2.5-day) corticosteroid premedication regimen in two recently initiated US phase 3 trials, TAX313 and TAX320. The current versions of these study protocols were submitted. In addition, the TAX235 study explored a 3-day regimen of methylprednisolone (+ pre-infusion cetirizine). Results of this trial will be made available.

Reviewer Comment: In its February 28, 1996 response, RPR submitted updated information on

235 patients who received a 5-day dexamethasone premedication regimen and on 84 patients on TAX235 who received a 3-day methylprednisolone regimen. Results were fairly comparable for the two programs, however, the rate of treatment discontinuation due to fluid retention was higher for patients on the 3-day regimen (8% vs 1.7%; see Section 5.4 above). It is expected that future study reports of ongoing trials will provide further documentation of the utility of corticosteroid premedication.

d) Ongoing phase 2 study evaluating the benefit of G-CSF with respect to myelotoxicity endpoints (febrile neutropenia, infection, duration of neutropenia, septic deaths); please submit the study protocol to the NDA.

In the TAX313 and TAX320 trials, the efficacy of G-CSF in preventing febrile neutropenia will be evaluated. If a patient receiving docetaxel 100 mg/m² on these trials develops febrile neutropenia or prolonged neutropenia, the patient is retreated at the same dose with the addition of G-CSF. Therefore, each patient serves as his/her own control comparing the cycle prior to G-CSF with the cycle(s) post-G-CSF. Current versions of these protocols were submitted.

e) Ongoing and future studies evaluating docetaxel dosing in patients with elevated bilirubin or patients with combined elevations of transaminase and alkaline phosphatase; such studies should include pharmacokinetic evaluation in addition to assessment of efficacy and safety. Please submit all relevant protocols to the NDA.

TAX008 is a US phase 1 study defining the MTD in patients with an abnormal bilirubin and in patients with combined abnormalities of SGOT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN with a normal bilirubin. Pharmacokinetic studies are included in this protocol. Further data on patients requiring dose reductions on ongoing phase 3 trials should also provide data on the safety of docetaxel in patients with mild hepatic impairment. In Europe, the TAX210 phase 2 trial is being initiated to study docetaxel 75 mg/m² in advanced breast cancer patients previously treated with anthracyclines and who have impaired liver function (normal bilirubin and SGOT > 1.5 and ≤ 3.5 x ULN and AP > 2.5 and ≤ 6 x ULN).

f) Please submit a full report of the safety registration study required by the regulatory authorities in Europe to the NDA.

The post-marketing study which is being planned in Europe will be forwarded to the FDA when it is complete, sometime in 1997.

g) Further exploration of pharmacokinetics/pharmacodynamic relationships, specifically toxicity and response.

A population pharmacokinetic component is going to be implemented in the TAX313 phase 3 trial comparing docetaxel doses of 100 versus 75 mg/m². Hopefully, this study will allow a

better assessment of correlation between docetaxel exposure and response rate. In addition, a study evaluating the correlation between the activity of cytochrome P450 3A4 as estimated by the erythromycin breath analyzer test and docetaxel clearance is planned as part of the docetaxel arm of the TAX311 trial.

- **Post-Marketing Commitments to be Conveyed to the Sponsor**

1. Reference should be made to the post-marketing commitments (c) - (g) described in the Agency's Approvable Letter (October 27, 1995) and in RPR's response of 11/21/95. RPR has agreed to complete and submit results of the studies noted above.

2. Studies described in (a) and (b), namely, TAX303, TAX304, TAX311, and TAX313, must be completed and reports submitted for review to satisfy the requirements under "accelerated approval" regulations. As in 10/27/95, the Agency will recommend that the sponsor give serious consideration to the evaluation of the 60 mg/m² dose in patients with advanced breast cancer receiving docetaxel as second line therapy.

10. Comments on Product Labeling/Patient Package Insert

Clinical comments have been inserted in RPR's draft product labeling and patient package insert below and are highlighted in ***bold and italic*** text.

Julie Beitz 5/13/96
Julie Beitz, MD Date

Robert E. Justice, MD 5/14/96
Robert Justice, MD Date

cc:
NDA #20-449
HFD-150/Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

(4)

DRUG USAGE IN PEDIATRIC PATIENTS

NDA # 20-449 Trade (generic) names Taxotere (docetaxel) Inj.

Check any of the following that apply and explain, as necessary, on a separate sheet:

___ 1. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children (e.g., drugs for angina or Alzheimer's disease).

✓ 2. Pediatric studies should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (i.e., there are several similar alternative drugs, for example, contrast agents).

___ a. The applicant has committed to doing such studies as will be required to include a pediatric claim in the labeling.

___ (1) We have approved the protocol(s).
___ (2) The protocol(s) has/have been submitted and is/are under review.
___ (3) Protocol design is under discussion with the applicant.
___ (4) The applicant has not yet submitted a protocol.

✓ b. The applicant has not committed to doing such studies.

___ 4. Pediatric studies designed to provide the information needed to include a pediatric claim are ongoing.

___ 5. Some information on pediatric dosing and safety are included in the draft labeling but without a specific pediatric claim.

(Check the appropriate blanks under #2 to indicate whether further data on effectiveness in pediatric patients will be obtained in Phase 4 studies.)

___ 6. The proposed claim in the draft labeling is specifically directed toward a pediatric illness, e.g., petit mal seizures, otis media, JRA, patent ductus.

___ 7. The dosage form is expected to be used primarily in the pediatric population.

___ a. A specific pediatric claim is included in the labeling.

___ b. The labeling does not include a specific pediatric claim. Check the appropriate blanks under #2 to indicate whether further data on effectiveness in pediatric patients will be obtained in Phase 4 studies.)

LRipper/4-12-90/0247r

cc: Orig NDA
D: ✓ File
HFD-510/G. Trundle

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

D W Rose
Signature of Preparer

5-6-96
Date

cc: Orig NDA
HFD-150/Div File
NDA Action Package
HFD-510/G. Troendle

D. Beale

Request for Information: March 21, 1996

TAXOTERE® (docetaxel) for Injection Concentrate

NDA #20-449 Submission dated February 26, 1996

Sponsor: Rhone-Poulenc Rorer

Please convey the following to the sponsor:

1. Serious adverse events among 4452 patients were presented in Table 6.1 of the November 1995 submission. In Appendix II, volume 1, of the current submission, 417 patients have been removed. This has resulted in reduced reporting of SAEs, for example, 142 fewer reports of febrile neutropenia, 44 fewer reports of infection, and 24 fewer reports of sepsis. Please provide a complete tabulation of all SAEs in the 417 patients removed for direct comparison with SAEs reported in November 1995 and February 1996.

2. Please identify which patients with baseline fluid retention were included in each of the on-study categories (improved, stable, or worsened) as presented in ODAC slide 36 and in your February response, p. 15.

3. Your update of steroid premedication for fluid retention in 235 patients (Appendix IV, volume 1) includes adverse events regardless of relationship to study drug. Please provide listings of adverse events possibly or probably related to docetaxel.

4. The Safety Update Report does not routinely list sepsis as a drug-related adverse event. Please explain where sepsis is recorded in the SUR - is it rolled into infection, febrile neutropenia or some other category?

5. In the SUR (Statistical Tables 7-12) and in your update of steroid premedication for fluid retention (Appendix IV, volume 1) adverse events are listed by NCI terms and by COSTART terms. Many adverse events listed under COSTART terms appear underreported when compared to the comparable listing using NCI terms. For example, 17 infections are reported in Table 10 vs. 314 in Table 8. Please explain.

6. Statistical Tables 7-12 document the incidence of non-hematologic adverse events that are given in the SUR. Please provide documentation for the hematologic adverse events in Table 6 of the SUR.

7. In the December 1995 version of product labeling, a tabulation of adverse events in 1028 patients with normal liver function tests is given. Please submit a comparable updated table for the SUR - the current submission for 1490 patients does not provide the safety profile for the subset of patients with normal liver function.

Julie Beitz MD 3/2/06

Julie Beitz, MD Date

cc:
NDA #20-449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ D. Pease

Request for Information: March 7, 1996

TAXOTERE® (docetaxel) for Injection Concentrate

NDA #20-449 Submission dated February 26, 1996

Sponsor: Rhone-Poulenc Rorer

Please convey the following to the sponsor:

1. For patients on Japanese breast cancer trials, please provide information on prior anthracyclines received, including indication, doses, schedules and duration of treatment.

2. There were 40 treatment related deaths reported in the Safety Update, volume 3. Please explain why the following patient deaths were not included: TAX222 and TAX271 Please explain why the following patient deaths were included: TAX246 and TAXSI002A

3. Please provide documentation of the investigators' changes for the relationship of drug treatment to death for TAX231 , TAX271 and TAXSI002A

4. In the Integrated Safety Summary of the original NDA, Table 38 lists non-fatal serious adverse events for 912 patients. Was this table derived from the Pharmacovigilance database and is it comparable to the listings given in Appendix II, volume 1, of the current submission? Of the 56 cases of sepsis reported in Appendix II, how many occurred in patients with elevated liver function tests?

5. Please identify and describe in narrative the five deaths that occurred among anthracycline-resistant breast cancer patients.

Julie Beitz 3/15/96

Julie Beitz, MD Date

cc:
NDA #20-449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ D. Pease

Request for Information: March 7, 1996

TAXOTERE® (docetaxel) for Injection Concentrate

NDA #20-449 Submission dated February 26, 1996

Sponsor: Rhone-Poulenc Rorer

Please convey the following to the sponsor:

1. Please clarify what is meant by "different characteristics of the prior anthracycline treatment" (Appendix VII, page A23, last paragraph of the "Anthracycline Resistance" Section). Are the patients who had PD on prior anthracycline in Japanese trials different from those who had PD on prior anthracycline on the TAX233, TAX267 or TAX286 trials?

2. In Appendix VIII, please identify the patients for whom a prior response to anthracycline is now known and whether it was CR/PR, NC, PD or unknown.

3. Please submit the response duration for each responder on the Japanese breast cancer trials. Please identify each responder by her response to prior anthracycline therapy, if this is known.

4. Please submit the untranslated minutes of the Judgment Committee's meetings (page 20).

Julie Beitz MD 3/7/96
Julie Beitz, MD Date

Robert Justice MD 3/7/96
Robert Justice, MD Date

cc:
NDA #20-449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ D. Pease

Request for Information: December 26, 1995

TAXOTERE® (docetaxel) for Injection Concentrate

NDA # 20,449 Submissions of November 3, 6, 21, and December 1, 1995

Sponsor: Rhone-Poulenc Rorer

Information to be conveyed to the sponsor:

Treatment-Related Deaths:
1. Please explain the apparent treatment-related death rate of 9% (57/631) among patients treated prior to 7/1/94 as described on page 26 of the November 21, 1995 submission. This figure is in serious disagreement with the 1.9% toxic death rate reported among 912 patients in the original NDA, and the 2% toxic death rate reported among 1327 patients at the ODAC Meeting in October 1995. The number of treatment-related deaths occurring on study (within 30 days of docetaxel infusion) and beyond 30 days should be enumerated for the "infection" and "other" categories for the early (N= 631) and later (N= 4,452) cohorts of patients.

2. Assuming that the majority of infectious deaths likely occurred on study, this data raise the concern of late-occurring "other" treatment-related deaths not previously reported to the Agency. Please submit your assessment of the 57 "other" treatment-related deaths occurring among the total cohort of 5,083 patients, along with case report forms for each of these patients.

Non-Fatal Docetaxel-Related Serious Adverse Events:
1. Please clarify the methods used in the follow-up of the 4,452 patients noted on page 25 of the November 21, 1995 submission, including the duration of follow-up, and your assessment of the increased incidence of sepsis events (1.8% vs 0.8% in the original NDA, N= 912).

2. Given the large number of patients treated with docetaxel at the proposed dose and schedule since submission of the original NDA, and the time elapsed since the last formal safety update (4-month safety update, November 1994, on 1010 patients), a more comprehensive safety update is warranted at this time. This update should include data available on the 3,036 patients who received the 5-day dexamethasone premedication, especially with respect to amelioration of fluid retention, and side effects of corticosteroids. Please also provide annotated case report forms for patients withdrawn from treatment for adverse events and for patients dying on study (excluding the 57 patients above whose full case report forms are being requested).

Severe Asthenia:
At the ODAC Meeting in October, investigators stated that the duration of severe asthenia "was usually a few days, therefore, the overall performance status reported for the cycle was not adversely affected. Among the 43 cycles with severe asthenia, no PS > 2 was reported". In the

case report forms, however, performance scores were generally recorded at the start of a treatment cycle. Thus, it would be fair to say that the effect of asthenia or other adverse events occurring in mid-cycle on performance status was generally not recorded. Preliminary review of 31 case report forms (submitted for evaluation of other safety issues) revealed examples of patients who experienced severe fatigue/weakness lasting several weeks (TAX233, TAX221, and TAX267, . In addition, there were examples of severe fatigue/weakness associated with PS > 2, especially when drug-related toxicities developed concurrently with disease progression (TAX233 TAX221, TAX235, and TAX264, Please clarify for the labeling, the median duration (and range) of severe fatigue/weakness for anthracycline-resistant patients.

Docetaxel Tolerance in Patients with Baseline Fluid Retention:
At the October 1995 ODAC Meeting, you reported that 49% of patients with baseline edema and 59% of patients with baseline effusions improved on docetaxel (slide 36). Preliminary review of 21 case report forms (TAX029, ; TAX233, TAX267, TAX286, TAX296 TAX221, ; TAX235, , revealed that improvement or resolution of baseline fluid retention occurred in only two patients (TAX233, . TAX267. Please explain in detail how the information on slide 36 was derived. In particular, please clarify what criteria were used to determine whether patients "improved" or not.

Taxotere Degradate:
The clinical experience with exposure to levels > 0.8% of degradate RPR112248 is insufficient to rule out the possibility for the development of severe neurotoxicity. If additional clinical data is not available to clarify this point, then further toxicologic evaluation in mice (as previously described by the Pharm/Tox review) may be required.

Japanese Clinical Experience:
For some patients, doses below the recommended 100 mg/m^2 will undoubtedly be used. To the extent possible, the proposed label should advise practicing physicians of the risks and benefits of administering doses below 100 mg/m^2. To this end, the sponsor is strongly urged to audit its Japanese sites, if it has not already done so.

Specific concerns regarding the data submitted are:

1. Only 9 of the 59 responders among patients previously treated with anthracycline in Japanese trials were discussed. To completely describe the responses seen in Japan, so that a fair comparison to responses in the three pivotal trials can be carried out, please provide the number of responses that occurred in patients in the following groups: a) those with an initial CR or PR on anthracycline, then PD, b) those with an initial response of NC on anthracycline, then PD, c) those with progression on anthracycline therapy for advanced disease, and d) those with progression on adjuvant anthracycline.

2. Appendices I and II listed different indicator lesions for the same patient. Other difficulties encountered were: responses in lesions described in Appendix II were not confirmed 4 weeks later (16 patients), tumor measurements were either missing on study, or disease was not measurable (7 patients), and measurements were unidimensional (4 patients). Thus, confirmation of patients' overall responses as given in Appendix I could not be carried out in a rigorous manner. Is a "cleaner", more complete listing of tumor measurements and response assessments forthcoming? Notation of which patients received prior anthracycline and which did not would also be helpful.

Comments on Assessment of the Evolution of Performance Status on Study:
End-of-study performance scores (PS), generally recorded within 30 days of the last docetaxel infusion, were not incorporated in the graphs shown at the October ODAC Meeting (slides 61-65). Taking these scores into account, assuming that the end-of-study PS was 4 for the three patients who suffered toxic deaths, and assuming that the PS recorded for patients on the TAX286 trial may not accurately reflect the impact of the toxicities these patients experienced, perhaps as many as 18 out of 134 anthracycline-resistant patients in pivotal trials experienced a deterioration of performance status concurrent with treatment-related adverse events. Thus, among the 55 responders, PS improved in 4, remained stable in 28, and worsened in 23.

Draft Product Labeling (December 1, 1995):

A. Upon review of the most recent version of the draft product labeling (dated December 1, 1995), the following changes are recommended.

CLINICAL STUDIES

A footnote below the tables on pages 9 and 10 should be added, stating that "Normal Liver Function includes patients with SGOT and/or SGPT $\leq$ 1.5 times ULN or with alkaline phosphatase $\leq$ 2.5 times ULN".

WARNINGS

The heading "HEMATOLOGIC EFFECTS", page 12, line 2, should be moved to the next line.

PRECAUTIONS

FLUID RETENTION: In the second paragraph, change "severe fluid retention was 5%" to "severe fluid retention was 6%". Also change "median cumulative dose to onset of fluid retention was 705 mg/m^2" to "median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m^2" (see Table 6.5, November 21, 1995 submission).

NEUROLOGIC: Change "Severe peripheral neurotoxicity is infrequent" to "Severe peripheral neurotoxicity was observed among 7% of 134 patients with anthracycline-resistant breast cancer".

ASTHENIA: Change the second sentence to read, "Severe asthenia was reported in 23% of 134 patients with anthracycline-resistant breast cancer and in 5.5% of 786 cycles received." Note that Valero et al., JCO 13:2886-2894, 1995, state that there were 19 patients with severe asthenia on the TAX233 trial vs 16 in RPR's study report (Table 43, original NDA, 7/27/94). If this is the case, then the number of anthracycline-resistant patients with severe asthenia is 34 or 25%.

DRUG INTERACTIONS: In line 6, place a period following "enzyme" and begin the next sentence with "Caution".

ADVERSE REACTIONS

In the first paragraph and in the footnote below the table on page 18, change "Abnormal liver function: SGOT and/or SGPT $\geq$ 1.5 times ULN concomitant with alkaline phosphatase $\geq$ 2.5 times ULN" to "Normal liver function includes patients with SGOT and/or SGPT $\leq$ 1.5 times ULN or with alkaline phosphatase $\leq$ 2.5 times ULN".

In the ADVERSE EVENT table on page 18, the incidence of fluid retention with recommended premedication (n=201) should be 49.8% for "any" and 6.0% for "severe" (see Table 6.5, November 21, 1995 submission).

HEMATOLOGIC: In paragraph 3, change the incidence of thrombocytopenia to 8.5% to be consistent with the table on page 18.

HYPERSENSITIVITY REACTIONS: Change the second sentence to read, "Severe hypersensitivity reactions have been observed in only 1% of patients receiving the recommended premedication regimen."

FLUID RETENTION: Change "severe fluid retention was observed in 5%" to "severe fluid retention was observed in 6%". Also change "median cumulative dose to onset of fluid retention was 705 mg/m^2" to "median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m^2" (see Table 6.5, November 21, 1995 submission). Change the last sentence to "Fluid retention was slowly reversible, lasting a median of 26 weeks (0.1-46+ weeks) from the onset of any fluid retention (see page 28, November 21, 1995 submission).

CUTANEOUS: Change the last sentence to read, "These reactions were characterized by hypo- or hyperpigmentation, and occassionally by onycholysis (in 0.8% of patients) and pain.

NEUROLOGIC: The term "dysthenia" is not listed in Dorland's Medical Dictionary, 27th edition. The term "dysesthesia" may be appropriate.

GASTROINTESTINAL: In the first sentence, specify which reactions are being referred to (nausea, vomiting and/or diarrhea?). Add a second sentence on stomatitis here.

HEPATIC: Change the last sentence to read, "Increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 3.9% of patients during study." (Note, 42/1070 = 3.9%, not 3.3%)

ONGOING EVALUATION: In line 2, insert a comma and space between "syndrome" and "anorexia".

DOSAGE AND ADMINISTRATION

PREMEDICATION REGIMEN: In line 1, delete "an" prior to "oral corticosteroids".

REFERENCES

A complete listing of references should be provided.

B. The current version of the draft product labeling includes information not stated in the previous version. Please indicate where in the NDA each of the following statements has been discussed, or submit supporting documents as soon as possible.

1. The incidence of hypersensitivity reactions in patients who received the recommended premedication (mentioned in BOXED WARNINGS, WARNINGS, ADVERSE EVENT table on page 18, and section on HYPERSENSITIVITY REACTIONS on page 20). Table 11 of the October 17, 1995 ODAC Briefing Document (footnote #21, page 11) does not contain this information.

2. The incidence of fluid retention in anthracycline-resistant patients who received the recommended premedication (table, page 10)

3. The statement that patients with severe peripheral neurotoxicity "had their symptoms spontaneously reverse within 3 months" (page 15)

4. The statements that "Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 time ULN were observed in approximately 6% and 15.7% of patients, respectively. Bilirubin values greater than the ULN occurred in 5.6% of the patients." Table 79 of the ISS (original NDA, 7/27/95) reports the following incidence of laboratory abnormalities NCI grade 1 or higher: SGOT, 36%; SGPT, 25%; alkaline phosphatase, 33%; and bilirubin, 11%.

C. The current version of the draft product labeling does not provide the information requested under point #4, page 3 of the October 27, 1995 Approvable Letter:
"We would like to be able to describe in the labeling the fraction of patients who had infection complicated by the need for hospitalization or IV antibiotics. Please provide the incidence of infection requiring hospitalization or IV antibiotics by grade of neutropenia for anthracycline-resistant patients."

D. Draft Patient Package Insert: Upon review of the patient package insert, the following changes are recommended.

What is the most important information about Taxotere?
Insert a bullet item stating: Certain patients with liver dysfunction should not receive Taxotere. Your doctor will monitor your liver function tests carefully during Taxotere treatment.

What are the possible side effects of Taxotere?

Low Blood Cell Count: Revise the second paragraph to read (in bold typeface), "Fever is often one of the most common signs of infection. Your doctor will recommend that you take your temperature frequently, especially during the days following your treatment with Taxotere. If you develop a fever, tell your doctor or nurse immediately.

Nail Changes: Change "changes to you finger or toenails" to "changes to your finger or toenails".

The content of this document was discussed with Dr. Robert Justice on 12/26/95 and faxed to the sponsor (Ms. Anne-Margaret Martin, Regulatory Affairs, RPR) on 12/26/95.

Julie Beitz MD 12/26/95

Julie Beitz, MD Date

cc:
NDA #20-449
HFD-150/Division File
HFD-150/J. Beitz
HFD-150/ R. Justice
HFD-150/D. Pease

Request for Information

Amendment to NDA # 20,449

TAXOTERE® (Docetaxel) for Injection Concentrate

From: Division of Oncology and Pulmonary Drug Products, HFD-150

To: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Date: May 17, 1995

Information to be Conveyed to the Sponsor:

The purpose of the End-of-Phase 2 Meetings on June 6, 1995, will be to determine whether the proposed clinical plans are adequate for submission for the indications in breast (first line) or lung cancer (first or second line). **This meeting is not intended to deal with specific safety, pharmacology/toxicology or chemistry issues.**

Please provide the following materials on or before June 1, 1995.

Breast Cancer: First Line

1. Updated versions of the protocols for each of the ongoing phase 3 trials: TAX303, TAX304, and TAX311

2. A list of questions to be discussed at the meeting

Non-Small Cell Lung Cancer: First and Second Line

1. A list of questions to be discussed at the meeting

Julie Beitz 5/17/95
Julie Beitz, MD Date

Robert L Justice 5/17/95
Robert Justice, MD Date

cc:

HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ L. McCollum
HFD-150/ D. Pease

Request for Information

Amendment to NDA #20,449

TAXOTERE® (Docetaxel) for Injection Concentrate

From: Division of Oncology and Pulmonary Drug Products, HFD-150

To: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Date: May 5, 1995

Information to be Conveyed to the Sponsor:

The following analysis (see table below) was undertaken to determine the impact of elevated hepatic enzymes on breast cancer patients treated on two of the pivotal trials in the original NDA. Data was derived from tables 14, 15, and 21 of the Data Listings for the TAX233 and TAX267 trials conducted in anthracycline-resistant breast cancer patients.

1. In order to interpret the effect of dose reductions in these patients, it would be necessary to know when these occurred in relation to the onset of infections and stomatitis in each patient.

2. It would be difficult to show that dose reductions affected the incidence of grade 4 neutropenia in these trials, since this toxicity was universal among patients and occurred in roughly 70-90% of evaluable cycles (i.e., cycles with at least one WBC report on days 6-10 of each cycle). It was not possible to determine the incidence of febrile neutropenia grade 4 from the data listings, however. This is perhaps, a more relevant endpoint and should be correlated with baseline hepatic enzyme status and timing of dose reductions.

3. Data listings were not provided for the third pivotal trial in anthracycline-resistant breast cancer, the EORTC TAX286 trial. Evaluation of these patients by hepatic enzyme status at baseline would also be helpful.

Outcomes in Anthracycline-Resistant Breast Cancer Patients
Initial Docetaxel Dose at 100 mg/m²:
Effect of LFTs at Baseline

Feature/Endpoint	Patient Subset w/ Elevated LFTs[a] N=95	Patient Subset w/ Normal LFTs[a] N=800	TAX233 + TAX267[b] Baseline LFTs Elevated N=27	Normal N=51
Pts w/ Liver Mets	83%	29%	56%	33%
Pts w/ Dose Red'ns	-	-	56%	57%
Response Rate				
-all patients	-	-	41%	55%
-dose-reduced pts	-	-	47%	72%
Median #Cycles				
-all patients	4 (1-19)	4 (1-25)	5 (1-12)	5 (1-15)
-dose-reduced pts	-	-	9 (4-12)	7 (3-15)
Pts w/ Neutropenia				
-grade 3+4	95%	92%	-	-
-grade 4	-	-	96%	96%
-dose-reduced pts			100%	97%
Pts w/ Infections	26%	20%	56%	47%
-dose-reduced pts	-	-	67%	48%
Pts w/ Stomatitis	16%	7%	81%	65%
-dose-reduced pts	-	-	93%	76%
Deaths				
-Toxic	5 (5.3%)	8 (1.0%)	0	0
-Septic	0	5 (0.6%)	1 (3.7%)	0

[a] From Updated Safety Analysis, Appendix V, 3/10/95
[b] Compiled from Tables 14, 15, 21 of Data Listings in TAX233 and TAX267 Study Reports, 7/27/94

Julie Beitz 5/5/95
Julie Beitz, MD Date

Robert Justice M.D. 5/5/95
Robert Justice, MD Date

cc:
NDA #20,449
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-426/ L. Kaus
HFD-150/ D. Pease

Request for Information

Amendment to NDA # 20,449

TAXOTERE® (Docetaxel) for Injection Concentrate

From: Division of Oncology and Pulmonary Drug Products, HFD-150

To: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Date: April 24, 1995

Information to be Conveyed to the Sponsor:

The amendment to NDA # 20,449 (submitted 1/23/95 and 3/10/95) contains insufficient safety data to conclude that docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks has an acceptable therapeutic index for the treatment of patients with locally advanced or metastatic breast cancer. The following information should be submitted for review no later than May 8, 1995.

Fluid Retention:

1. For the 104 breast cancer patients receiving the 5-day dexamethasone regimen and for the 60 breast cancer patients in the comparator group that received no premedication, the sponsor should provide: the study on which each patient was enrolled, a detailed comparison of patient baseline characterisitics, drug delivery including median cumulative dose given, treatment outcomes, and evolution of performance status on and off study, as well as, the median cumulative dose to onset of moderate or severe fluid retention, median cumulative dose to treatment discontinuation, and all supportive measures required including concomitant medications, drainage procedures, and hospitalizations on and off study.

2. For the 26 patients that developed fluid retention on the TAX237 trial, the sponsor should provide additional information on the clinical course of patients after treatment discontinuation, including evolution of performance status, duration of moderate and severe symptoms, supportive measures required (concomitant medications, drainage procedures, hospitalizations) and disease status at last follow-up (alive on new treatment, death, etc.).

3. For the 89 patients that were included in the regression analysis (Updated Safety Analysis, page 10), the sponsor should provide detailed background information both on and off study as described in paragraphs (1) and (2). In addition, the sponsor should attempt to reconcile the 16 week median duration of fluid retention after treatment discontinuation in this group with the 25 week observation in the TAX237 trial.

4. For all patients receiving steroid premedication in ongoing and proposed phase II and III studies, the information requested in paragraghs (1) and (2) should be collected prospectively, (ideally until disappearance of fluid retention in symptomatic patients), and reported in future safety updates to the Agency.

Tolerance in Patients with Elevated Hepatic Enzymes:

1. For the 95 patients identified with elevated hepatic enzymes in Appendix V, please specify the numbers of patients in each grade according to NCI Common Toxicity Criteria.

2. Please provide a safety analysis of patients with baseline elevated alkaline phosphatase levels.

3. The sponsor should provide a safety analysis (as in Appendix V) for all evaluable patients with baseline elevations of hepatic enzymes who received reduced doses of docetaxel. Please also provide an efficacy analysis for all breast cancer patients with baseline elevations of hepatic enzymes who were dose-reduced to confirm that the dose reductions were adequate and that efficacy was not compromised.

4. Up to one-third of patients developed elevations of SGOT, over 40% developed elevations of alkaline phosphatase, and 11% of bilirubin while on docetaxel treatment. The sponsor should provide a safety analysis, as in Appendix V, for all evaluable patients who developed elevations of hepatic enzymes while on docetaxel therapy.

5. For all evaluable patients with hepatic enzyme elevations at baseline or subsequently, treated at full or reduced doses, and enrolled in ongoing and proposed phase II and III studies, safety analyses, as in Appendix V, should be reported in future safety updates to the Agency.

Julie Beitz MD 4/24/95
Julie Beitz, MD Date

Robert C. Justice M.D. 4/21/95
Robert Justice, MD Date

cc:
NDA # 20,449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

D Draft
OCT 2 3 1995

MEDICAL OFFICER REVIEW OF NDA # 20-449

TAXOTERE® (Docetaxel) for Injection Concentrate

Table of Contents

1. General Information and Timeline

Drug Name:	Taxotere® (Docetaxel) for Injection Concentrate
Applicant:	Rhone-Poulenc Rorer, Collegeville, PA
NDA Submission Date:	July 27, 1994
Pharmacologic Category:	Antineoplastic Agent
Proposed Indications:	Breast Cancer, Metastatic, Second-line Non-Small Cell Lung Cancer, Metastatic, Second-line
30-Day Meeting with Sponsor:	August 26, 1994
Electronic Data Files Installed (Original NDA):	October 28, 1994, Paradox 5.0 for Windows
90-Day Meeting with Sponsor:	November 1, 1994
Updated Safety Report:	November 7, 1994
Electronic Data Files Installed (Updated Safety Report):	November 18, 1994, Paradox 5.0 for Windows
ODAC Meeting	December 13, 1994

2. Description of Clinical Data Sources

Volume 1.1 of the July 27, 1994 submission contains the index, proposed text of labeling, and overall synopses for the following: CMC, nonclinical pharmacology and toxicology, human pharmacology and bioavailability, and clinical data.

The relevant volumes for this clinical review are listed below. For each trial, the study report, study protocol and amendments, list of investigators, sample case report form, IRB approval, statistical tables, data listings, and publications were provided. Case report form summaries were provided for all patients who either died on study or withdrew due to adverse events.

Pivotal Phase I Studies: TAX001, TAX006:	8.3 to 8.10
Breast Cancer Pivotal Phase II Studies: TAX233 TAX267 TAX221	 8.38 to 8.43 8.44 to 8.49 8.50 to 8.55
NSCLC Pivotal Phase II Studies: TAX270 TAX271 TAX231 TAX232 TAX269 TAX223	 8.75 to 8.80 8.81 to 8.86 8.87 to 8.94 8.95 to 8.100 8.101 to 8.108 8.109 to 8.114
Integrated Summary of Safety	8.117
Integrated Summary of Efficacy Breast Cancer, NSCLC	 8.118, 8.119
Updated Safety Report	9.1 to 9.12
Case Report Form Tabulations	12.1 to 12.5

The overall synopses and the integrated summaries of efficacy and safety were submitted on diskette in WordPerfect 6.0 for Windows on September 6, 1994. On October 28, 1994, electronic data files on all pivotal studies were installed using Paradox 5.0 for Windows. An Updated Safety Report was submitted on November 7, 1994, which included: 1) an updated safety summary, including preliminary results on the pathophysiology of fluid retention (TAX029 and TAX265), and analysis of the 5-day dexamethasone premedication regimen versus no premedication (for fluid retention), as requested by FDA at the 30-day post-submission teleconference (August 26, 1994), 2) updated analyses of the duration of response, time to progression, and survival for patients in the pivotal trials, and 3) comprehensive study reports for two new trials in metastatic breast cancer, TAX286

(anthracycline-resistant patients) and TAX281 (previously untreated patients). Electronic data files for the Updated Safety Report were installed on November 18, 1994.

3. Introduction

Rhone-Poulenc Rorer proposes that docetaxel, given at a dose of 100 mg/m² IV over 1 hour every three weeks, be approved for the treatment of:

> "patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed; prior therapy should have included an anthracycline unless clinically contraindicated"
>
> "patients with locally advanced or metastatic non-small cell lung cancer even after failure of platinum-based chemotherapy."

On November 7, 1994, RPR amended its claim relative to non-small cell lung cancer by deleting the word "even".

The clinical data in the original NDA submission were derived from 1601 patients, including 430 from Japan, 560 from Europe, and 611 from the US and Canada. A total of 38 studies were presented: eight phase I studies, ten phase II studies in breast cancer, nine phase II studies in NSCLC, and eleven phase II studies in other solid tumors intended to confirm the safety profile of docetaxel. At the May 13, 1993 meeting with the Division of Oncology and Pulmonary Drug Products, RPR indicated that randomized phase III trials would be ongoing at the time of FDA's review of this NDA. At present, there are two phase III trials in breast cancer open to accrual in Europe (TAX303 and TAX304), and one in the US (TAX311). A phase III trial in NSCLC (TAX317) was initiated in the US in November, 1994.

Two phase I studies are considered pivotal in defining the dose and schedule of docetaxel for RPR's phase II program (TAX001 and TAX006), that is, 100 mg/m² IV over one hour every three weeks. In Japan, studies were conducted in accordance with the Guidelines of the Japanese Society of Cancer Therapy and a lower dose was selected for phase II studies (60 mg/m²). For this reason, the sponsor analyzed the 6 studies in breast and NSCLC (3 each) separately and did not pool data from the Japanese studies with the US/European studies.

In breast cancer, 111 second line patients have been treated with the proposed dose and schedule of docetaxel in the three pivotal phase II trials (2 in US, 1 in Europe). This figure includes 60 anthracycline-resistant patients. Four supportive trials in patients with no prior chemotherapy for metastatic disease were also conducted (1 in US, 1 in Canada, 2 in Europe). The sample size in these trials ranged from 34 to 51 patients, according to the 2-step statistical design of Fleming or Gehan. The initial planned dose in all studies was 100 mg/m² except in two studies conducted at 75 mg/m² in order to measure the impact of dose on fluid retention.

In NSCLC, 88 second line and 160 first line patients have been treated in two pivotal and four supportive phase II trials, respectively (5 in US, 1 in Europe). Among second line patients, a subset of 37 cis-platin-resistant patients has been defined. The sample size in these trials ranged from 41 to 49 patients, according to the 2-step statistical design of Fleming or Gehan. These studies were conducted at 100 mg/m² except for one study conducted at 75 mg/m².

The primary efficacy endpoints for all phase II trials were tumor response rate and duration of response. Quality of life assessments were to be made in evaluable patients at baseline and at cycle 4 of treatment: performance status, analgesic use, and incidence/severity of tumor-related symptoms.

In breast cancer, phase II studies showed an overall response rate of 56% in the intent to treat population of untreated patients, and 49% in previously treated patients. The median duration of response was similar for both groups (30 and 28 weeks, respectively). There was significant activity of docetaxel in visceral metastatic sites, especially in the liver (52%). There was a slightly lower overall response rate in patients treated at 75 mg/m² (47%) than in patients treated at 100 mg/m² (56%); the median duration of response was similar in both groups (34 and 30 weeks in the 75 mg/m² and 100 mg/m², respectively).

In non-small cell lung cancer, phase II studies showed an overall response rate of 27% in the intent to treat population of untreated patients, 17% in previously treated patients, and 13.5% in cisplatin-refractory patients. The median duration of response was 25 weeks for previously untreated patients and 29 weeks for previously treated patients.

Overall, 833 patients were evaluable for safety at the proposed 100 mg/m² dose of docetaxel. Neutropenia was the dose limiting toxicity of docetaxel. Despite the high incidence of grade 4 neutropenia (in 75% of patients), the incidence of febrile neutropenia and infection was comparatively low (22% and 19% of patients, respectively). The short duration of grade 4 neutropenia (median of 7 days) for docetaxel is the presumed reason for this finding.

Acute non-hematologic toxicities occurring in >5% of patients were: hypersensitivity reactions, gastro-intestinal toxicities, stomatitis, fever, and reactions at the site of injection. Chronic toxicities occurring in >5% of patients were: fluid retention, skin toxicity often with associated nail disorders, neuro-sensory toxicity, alopecia, and asthenia.

The recommended premedication for docetaxel is dexamethasone 8 mg PO bid for 5 days, starting on the day prior to treatment. RPR states that this regimen will reduce the "incidence and severity" of drug-related fluid retention. This recommendation is based on the reduction in incidence and severity of fluid retention seen in 32 breast cancer patients who received this premedication as compared to 60 breast cancer patients who never received premedication (43% overall incidence and 6% severe reactions versus 77% overall incidence and 20% severe reactions).

4. Breast Cancer Pivotal Trials

4.1 TAX233

4.11 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Advanced Anthracycline Resistant Metastatic Breast Cancer (8.38.130 - 8.38.222)

Investigators: V Valero, MD, MD Anderson Cancer Center, Houston, TX
TW Dobbs, MD, East Tennessee Oncology/Hematology, Knoxville, TN
JA Strupp, MD, Dan Rudy Cancer Center, Nashville, TN

Study Dates: 6/23/92 - 7/29/93
Data Cut-off Date: 10/31/93
Database Frozen: 6/29/94

Review of Protocol Amendments:

A total of 5 protocol amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (5/12/92): For anaphylactoid reactions of grade 1, 2, 3 (by NCI Toxicity Criteria), treatment with dexamethasone 10 mg IV and diphenhydramine 50 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For grade 4 reactions, the patient will go off study.

Amendment 2 (9/18/92): All patients may be pre-treated with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion. If despite pre-treatment, the patient experiences an anaphylactoid reaction of grade 1, 2, 3, then treatment with dexamethasone 10 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For subsequent infusions, patients should receive dexamethasone 20 mg PO 12 hours prior and diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion.

Amendment 3 (2/19/93): Patient eligibility was tightened to include only metastatic disease patients who progressed on anthracycline-based chemotherapy. Previously, patients with less than a partial response to such therapy in metastatic disease were also eligible.

Amendment 4 (3/25/93): All patients must be pre-treated with dexamethasone 8 mg PO bid for 5 days starting the day before the docetaxel infusion, and with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion.

Amendment 5 (5/26/93): Patients who are already receiving steroids for treatment or prevention of side effects should continue receiving their current regimen.

Design:

This was a phase II multicenter trial in anthracycline-resistant patients with locally advanced or metastatic breast cancer. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Premedication with dexamethasone and diphenhydramine was mandated by amendment 4 to the original protocol.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in anthracycline-resistant patients with metastatic breast cancer.

Patient Population:

The inclusion, exclusion, and post-admission criteria are provided in the appendix. In summary, eligible patients were female, over 18 years, with histologic proof of metastatic breast cancer resistant to anthracycline therapy (defined as relapse while receiving such therapy in the adjuvant setting, or progressive disease after a minimum of one cycle of such therapy for advanced disease as first or second line treatment). They must have at least one bidimensionally measurable lesion, and have no clinical evidence of brain metastases. They should have a baseline Karnofsky PFS $\geq$ 60% and no current peripheral neuropathy > grade 2. They should have received no more than two prior chemotherapy regimens for advanced disease, and at least 30 days (48 days for mitomycin C or nitrosoureas) should have elapsed between the end of previous chemotherapy and protocol entry. Previous radiotherapy was permitted, but not to a site used to assess response. Non-evaluable lesions included: bone lesions, malignant effusions, pulmonary lymphangitic spread, abnormal LFTs, and abnormal tumor markers.

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. Just prior to use, the solution must be diluted with 6 ml of 5% dextrose or 0.9% saline. The appropriate amount of drug is further diluted in 250 ml of 5% dextrose or 0.9% saline and administered as a continuous IV infusion using a peristaltic pump.

No prophylactic use of antiemetics or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 4, however, pretreatment with dexamethasone and

diphenhydramine prior to infusions was mandated. No prophylactic use of colony-stimulating factors was permitted; G-CSF may be given to patients with febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or asymptomatic neutropenia grade 3 lasting > 14 days.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Patients experiencing febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or thrombocytopenia grade 4 were allowed a 25% dose reduction. Other conditions in which a 25% dose reduction was permitted were: grade 4 vomiting despite antiemetic prophylaxis, grade 3 or 4 diarrhea despite antidiarrheal treatment, and grade 2 peripheral neurotoxicity. Treatment was stopped in the case of grade 3 peripheral neurotoxicity and grade 4 HSRs.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray. Radionuclide scans and CT scans were to be repeated at the end of every 2 cycles.

Changes in performance status, analgesic use, and pre-existing symptoms would be followed as secondary endpoints.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not clearly define quality of life measures prospectively or stipulate the frequency with which such measures were to be monitored.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle. Cardiovascular toxicity was monitored by blood pressure and pulse recordings pre-infusion, at 0, 5, 10, 15, 30, 45 and 60 minutes

after the start of the infusion, and 30 minutes post-infusion. In addition pre- and post-treatment EKGs were taken.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

4.12 Study Conduct

The TAX233 trial was sponsored by RPR. Patients were accrued to 3 centers in the US. Of 41 patients registered, 35 were treated at MD Anderson Cancer Center, 5 were treated by Dr. Strupp, and 1 by Dr. Dobbs. The study was monitored by the Clinical Research Department of RPR or by the RPR-supervised CRO, Theradex (Princeton, NJ).

All case report forms were processed by RPR. The database was frozen on 6/29/94. All responses reported by investigators on CRFs were reviewed by an independent expert panel which included a radiologist and a medical oncologist and were recorded on response review forms (RRFs). If there were no discrepancies between the CRF and the RRF, the data in the CRF were considered valid for analysis. If the panel's decision differed from the investigator's and the investigator agreed with the panel, then the original information from the CRF was replaced by the RRF data. If the investigator did not agree with the panel's assessment, then both CRF and RRF data were retained, but the RRF assessment was considered valid for efficacy analysis.

4.13 Efficacy Results

Eligibility:

Forty-one patients with anthracycline- or anthracenedione-resistant disease were entered: 5 patients were ineligible and 8 nonevaluable for response; hence, 33 patients were evaluable for efficacy. All 41 patients were evaluable for toxicity.

Among the 5 patients who were deemed ineligible, 4 did not have bidimensionally measurable disease and 1 was not documented as being resistant to either doxorubicin or mitoxantrone. Three additional patients were nonevaluable: one did not have tumor assessments of all lesions, one had further chemotherapy while on study, and one died 6 days after cycle 1 due to gram negative sepsis.

Investigator/Site	No. of Patients Entered	No. of Responders
Valero/ MD Anderson CC	35	17
Strupp/ Dan Rudy CC	5	2
Dobbs/ Baptist Regional CC	1	0

Patient Withdrawals:

Twenty-eight patients withdrew for disease progression, three died (one due to toxicity, two due to disease progression), and two withdrew for toxicity. One patient was withdrawn due to receipt of other chemotherapy while on study and one due to an unrelated adverse event (thrombosis at cauda equina). Six patients were still on treatment as of 10/31/93. Among the patients withdrawn due to toxicity, one had severe dyspnea (sequelae of pneumonia) and one had severe rash, asthenia, and pleural effusion; both patients were partial responders.

Patient Characteristics:

The median age of the 41 patients was 51.0 years (range 27-80 years). The baseline Karnofsky performance status was $\geq$80% in 82.9%. All patients had infiltrating ductal carcinoma; 21 were estrogen and progesterone receptor negative. Thirty-nine patients had metastatic disease, 2 had locally advanced disease. Only 15% had one organ involved; the rest had two or more organs involved. Specifically, 48% of patients had liver involvement, 39% had bone, and 32% had breast, superficial lymph node, lung, pleural or skin disease. Twenty-seven had undergone surgery, 21 prior radiotherapy, and 19 prior hormonal therapy. All patients received prior chemotherapy for advanced disease, except for 3 patients who relapsed during adjuvant chemotherapy with doxorubicin. Fourteen patients had received 2 prior chemotherapy regimens for advanced disease. Thirty-five patients were resistant to doxorubicin, 5 to mitoxantrone. Seventeen (41.5%) had progressive disease as the best response to prior anthracycline or anthracenedione therapy. **Comments:** *Given the descriptions of disease extent and prior treatment histories, the patients entered on this trial appear to have far advanced disease despite a good performance status. While this constellation of clinical features would seem to make these patients ideal protocol candidates, the reviewer questions the likelihood of identifying such patients in the setting of a general practice. The original protocol and subsequent amendments did not specify mitoxantrone-resistance as an inclusion criterion. It seems reasonable, however, to include these patients in the overall efficacy and safety analyses.*

Drug Delivery:

A total of 228 cycles were administered: 122 (53.5%) at the initial planned dose of 100 mg/m^2, 86 (37.7%) at 75 mg/m^2 and 20 (8.8%) at 55 mg/m^2. The median number of cycles given was 4 (range 1-15). Treatment was delayed most commonly because of non-

hematologic toxicities (12 patients and 17 cycles) and non-drug-related reasons (11 patients and 16 cycles). Dose modification was due to hematologic toxicity in 12 patients and 16 cycles, following granulocytopenia, fever in the absence of infection, and leukopenia. Non-hematologic toxicities accounted for dose modifications in 11 patients and 12 cycles, following stomatitis, peripheral edema, skin rash, infection, pleural effusion, severe dyspnea, and atrial flutter. Most dose reductions occurred in the first 4 cycles, with 13 patients (35%) requiring a dose reduction after the first cycle. **Comment:** *Beyond cycle 2, no more than one-half of evaluable patients appear to tolerate therapy at the 100 mg/m² dose.*

The median cumulative dose administered was 398 mg/m² (range 99-1132 mg/m²); median dose intensity given was 29 mg/m²/week (range 19-35 mg/m²/week); and the median relative dose intensity was 0.87 (range 0.57-1.06). Thirty-five patients had an RDI > 0.7.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 41 patients included in the intent to treat analysis, there were no CRs and 19 PRs for an overall response rate of 46.3% (95% CI = 30.7; 62.6). Seven patients had stable disease, 12 had progressive disease, and three were not evaluable. Similar response rates were observed among patients resistant to doxorubicin (17/35 patients, 48.6%) or to mitoxantrone (2/5 patients, 40%). **Comment:** *The reviewer agrees with the overall response rates given.*

The highest response rate occurred in evaluable patients with lung lesions (6/7, 85.7%), followed by breast lesions (4/7, 57%), lymph node involvement (5/10, 50%), liver (6/13, 46%), or skin disease (3/9, 33%). A higher response rate was observed in patients $\leq$ 49 years (61%) than in patients $\geq$ 50 years (46.7%). Among 13 patients whose best response to prior chemotherapy was progression (the so-called anthracycline-refractory patients), there were 5 PRs to docetaxel.

Comments: *The table below summarizes the 19 partial responses noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.42.160 - 8.42.251. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All responders listed are doxorubicin-resistant except for patients (mitoxantrone-resistant). All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patients These patients had lesions that were slightly undersized. Since none of these patients were responders, the overall response rate in the intent to treat population would remain the same. Patients had a major response in a lesion $\geq$ 5 cm (in lung, liver, or breast) and patient had complete regressions in multiple sites.*

RESPONSES (ITT) - TAX233

Investigator/Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
Valero:	Liver, lung	38
	Chest wall (2), axillary mass	12
	Chest wall (4)	36
	Lung	12
	Lung*	27
	Breast (2), chest wall mass, liver (2)	27
	Breast*, liver*	47+
	Breast*, skin	22
	Breast*, lymph node, skin (2)	24
	Lymph node (2)	17
	Liver (3)*	34
	Skin	30+
	Liver	19
	Lymph node	30+
	Liver (2)*	27
	Lung, lymph node (2), skin	12
	Lung	16+
Strupp:	Breast	13
	Lung	16+

- **Response Duration**

The median duration of response in responding patients (intent to treat analysis) was reported as 27 weeks in the study report (range 12-47+ weeks, CI = 19; 36). **Five of 19 responders were censored due to no documentation of progression before the cut-off date.** Similar results were observed among the 17 evaluable responding patients resistant to doxorubicin (median 27 weeks, range 12-47+ weeks). **Comment:** *The reviewer agrees with RPR's response durations as recorded in Table 4.03 of the study report (8.39.128 - 8.39.129).*

- **Other Endpoints**

The median time to first response was 13 weeks (range 3-31+) for all treated patients (22/41 patients censored for this analysis). The median time to progression was 13 weeks (range 1-47+) among all treated patients (7/41 patients censored). The median survival time for all treated patients was 9 months (range 0.2-14+, 25/41 patients censored). The median follow-up time was 7.4 months (range 3-14 months). **Comment:** *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

There was no significant deterioration in performance status in patients in this study: the median Karnofsky PFS was 80% at baseline as well as at cycle 4 and 6. **Comment:** *The number of patients evaluable for PFS determinations dropped dramatically from 41 at baseline to 26 at cycle 4 and to 16 at cycle 6. Review of PFS values for all patients by cycle (Table 12, 8.40.115 - 8.40.193) revealed 5 patients who experienced a decline in PFS of 30% or more over baseline. In addition, patient began and ended the trial with a PFS of 50% which represents a protocol violation.*

Two of 13 patients who required pain medication had an improvement in analgesic requirement at cycle 4: patient Both were responders. The remaining 11 patients had no change in analgesic requirements (Table 6.29 of the Study Report, 8.39.300).

Among 11 patients who had tumor-related symptoms other than pain (such as cough, dyspnea) and were followed to cycle 4, improvement was observed in 2 patients:
(Table 6.30 of the Study Report, 8.39.302 - 8.39.303). Both were responders.

Comment: *The numbers of patients evaluable for analgesic requirement or tumor-related symptoms is fairly small making conclusions of clinical benefit from docetaxel difficult.*

4.14 Safety Results

Of the 41 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (36 patients), anemia (39 patients), asthenia (35 patients), stomatitis (33 patients), skin (32 patients), diarrhea (30 patients), nausea (25 patients), alopecia (24 patients), fever in the absence of infection (22 patients), and fluid retention (17 patients, severe in 7). The vast majority of patients with grade 4 AEs had granulocytopenia (31 patients). The most frequent grade 3 AEs were leukopenia (16 patients), stomatitis and infection (9 patients each). (See Table 29, 8.38.88, of the study report)

Overall, 26 patients experienced 51 serious AEs. Of these, the following events were deemed possibly or probably related to docetaxel. There was one toxic death due to gram negative sepsis. Infections occurred in 12 patients (15 events), including the one toxic death. The documented source of infection was urinary tract in 5, pneumonia in 2, central venous catheter in 2, and cellulitis in 2. Febrile neutropenia occurred in 11 patients (15 events) and resulted in four hospitalizations. Serious fluid retention developed in 5 patients who required 8 hospitalizations for diuretic therapy and/or thoracenteses. One patient developed atrial flutter requiring cardioversion. (See Table 31, 8.38.90, of the study report)

- **Acute Hematologic Toxicities**

Leukopenia and neutropenia were observed in 36/37 (97%) of patients evaluable for this analysis (4 patients were excluded due to treatment with G-CSF in every cycle); 31 (84%) of these had grade 4 neutropenia. Out of 185 evaluable cycles (with at least one blood count between days 6 and 15), 122 (66%) showed grade 4 neutropenia. There was no significant difference in the incidence of grade 3 and 4 neutropenia between cycles at 100 or 75 mg/m^2. There was no relationship between neutropenia and number of prior chemotherapies or time since last chemotherapy. The median neutrophil nadir was 0.1 x $10^3/mm^3$ (range 0-3.2) and the median day to nadir was 8 days (range 5-12). These values were unchanged across all dose levels. No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was 7 days; 4 cycles failed to show recovery of neutrophil count by day 22 ± 3.

Thrombocytopenia was observed in 11 patients, and was grade 3 in two. The median nadir of platelets by patient was 143 x $10^3/mm^3$ (range 27-479).

Anemia was observed in 39 of 41 patients, and was grade 3 in six patients. The median nadir of hemoglobin was 9.2 g/dl (range 6.9-12.0), with a median day to nadir of 10 (range 2-25).

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 13 patients and 15 cycles. Eight of 13 patients required IV antibiotics. Eleven of 15 events occurred with treatment at 100 mg/m^2. Infection occurred in 15 patients and 21 cycles. Grade 3 or 4 neutropenia was observed in 16/21 episodes of infection.

Comment: *The reviewer agrees with the sponsor's conclusion that the incidence of febrile neutropenia is lower than would be expected given the high frequency of grades 3 and 4 neutropenia, because of the short duration of neutropenia. There does not appear to be a cumulative effect of docetaxel on myelosuppression, allowing the potential for treament with several cycles. Despite the absence of a correlation between incidence, severity, and duration of neutropenia and docetaxel dose, febrile neutropenia was, in fact, more frequent at the higher 100 mg/m² dose. I cannot offer any explanation for this.*

- **Acute Non-Hematologic Toxicities**

Only the acute adverse events considered possibly or probably related to docetaxel are presented in Table 38 (8.38.102) of the study report.

Hypersensitivity reactions: One patient had a grade 2 HSR within the first five minutes of the infusion, manifested by flushing and dyspnea. This patient had received diphenhydramine premedication. **Comment:** *No conclusion can be drawn on the efficacy of different premedications for prophylaxis against HSRs in this trial.*

There were three patients with injection site reactions; one of these was grade 3, resolving in 20 days with local care.

Nausea was observed in 25 patients, and was grade 3 in one patient. Vomiting occurred in 20 patients, and was grade 4 in one patient. Diarrhea occurred in 30 patients, and was grade 4 in one patient. Stomatitis occurred in 33 patients, and was grade 3 in nine patients.

Cardiac dysrhythmia (atrial flutter) occurred in 1 patient. Pulmonary toxicity occurred in 6 patients: pleural effusions associated with dyspnea in 2 patients and pneumonia in a third.

- **Chronic Non-Hematologic Toxicities**

Table 43 (8.38.107) of the study report summarizes the chronic non-hematologic toxicities deemed possibly or probably related to docetaxel.

Fluid retention (defined as peripheral edema, facial edema, pleural effusion, ascites, or pericardial effusion with or without weight gain) was observed in 17 (41.5%) of patients. All 17 patients had peripheral edema, while 10 had pleural effusions. Seven patients were noted to have severe fluid retention (see below). The median cumulative dose to onset of fluid retention was 540 mg/m^2 (range 99-982). A trend in favor of diphenhydramine + steroid premedication or no premedication was observed with respect to the incidence and median cumulative dose to onset of fluid retention. **Comment:** *The table below summarizes premedications administered to the seven patients experiencing severe fluid retention as recorded in Table 31 of the data listings, 8.43.7 - 8.43.175. The reviewer has also included H2-blockers and steroids given for other reasons, as they may have influenced the clinical course in these patients.*

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN SEVEN PATIENTS EXPERIENCING SEVERE FLUID RETENTION

Patient	Medication	Cycle	Indication
	No premedication	1,2	
	Benadryl 50 mg IV	3 to 8, 12	Protocol
	+ Dexamethasone 16 mg PO x5d	9 to 11	Prophylaxis
	Prednisone 40mg/5mg PO	1 to 11	Radiation Pneumonitis
	Zantac 150 mg PO	1 to 11	GI Prophylaxis
	Benadryl 50 mg IV	1, 6, 7	Protocol
	+ Dexamethasone 16 mg PO x5d	8 to 11	Prophylaxis
	Benadryl 50 mg IV	1 to 10	Protocol
	+ Dexamethasone 16 mg PO x5d	6, 7, 8	Prophylaxis
	+ Zantac 150 mg PO	8, 9, 10	Nausea
	+ Dexamethasone 16 mg PO qd	9	Brain Metastases
	+ Dexamethasone 8 mg PO qd	10	Brain Metastases
	Benadryl 50 mg IV	1, 5	Protocol Prophylaxis
	+ Prednisone 80 mg PO x 5d	1	Skin Rash
	+ Dexamethasone 16 mg PO x5d	5	Protocol Prophylaxis
	Prednisone 40 mg PO x 5d	6, 7	Protocol
	+ Vistaril 25 mg IV	6, 7	Prophylaxis
	Prednisone 40 mg PO x 5d	8 to 14	Protocol Prophylaxis
	Benadryl 50 mg IV	1 to 9	Protocol Prophylaxis
	+ Prednisone 10 mg PO x 5d	1	Skin Reaction
	+ Dexamethasone 16 mg PO x5d	5 to 9	Protocol Prophylaxis
	Benadryl 50 mg IV	1 to 5	Protocol
	+ Dexamethasone 16 mg PO x5d	5	Prophylaxis
	Benadryl 50 mg IV	1 to 4	Protocol
	+ Dexamethasone 16 mg PO x5d	1 to 4	Prophylaxis

Comment: *All seven patients with severe fluid retention had both peripheral edema and pleural effusions. All were partial responders to therapy. Fluid retention was rated as severe beginning with cycle 4 in two cases, with cycle 6 in four cases, and with cycle 7 in one case. The median age of this group was 48 years (range 27-53 years). All had prior treatment with anthracycline (median dose 240 mg/m², range 120-450 mg/m²), two had prior radiotherapy. Four had pulmonary findings at entry: two had bilateral pulmonary metastases, one had radiation pneumonitis, one had lymphangitic spread of tumor. At least one thoracentesis was*

performed in three patients; the remaining patients were managed with diuretics. Serum albumin levels were noted to decline below normal levels in all but one patient. No significant abnormalities were noted in renal function. Six patients also experienced grade ≥ 2 skin toxicity. Two patients had a decline in PFS of 100 to 80% and two had a decline from 80 to 70% that corresponded with the onset of this toxicity. Fluid retention was the reason for dose reductions in two patients, and for treatment discontinuation in a third. The clinical benefit of any one premedication regimen is difficult to discern.

Skin toxicity occurred in 32 patients, and was grade 3 in five patients, and grade 4 in 1 patient. Signs included erythema, pruritis, burning, pain, exfoliation, desquamation, and ulceration, primarily of the trunk, hands and feet. The median cumulative dose to onset of chronic skin toxicity was 398 mg/m^2 (range 96-982). A trend in favor of diphenhydramine or no premedication could be demonstrated with respect to severity and median cumulative dose to onset of chronic skin rash. Nail disorder was observed in 14 patients, one case was severe (onycholysis and nail loss). Alopecia occurred in 25 patiens and was grade 2 in most.

Neurosensory toxicity was observed in 19 patients, none was higher than grade 2. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Three patients experienced neuromotor signs, one patient had grade 3 weakness. Asthenia was seen in 35 patients and was severe in 16, resulting in withdrawal of one patient from study.

- **Laboratory Tests**

In 37 evaluable patients, elevations of the following parameters were seen: SGPT (6 patients), SGOT (14 patients), total bilirubin (4 patients), alkaline phosphatase (14 patients). Hypoalbuminemia (≤ 3 g/dl) developed in 19/37 patients. Only 2 paients had albumin levels < 2 g/dl; hence, correlation between severe hypoalbuminemia and fluid retention was not carried out. Only 2 patients developed increased creatinine levels (grade 1 in both).

- **Deaths on Study**

Deaths ≤ 30 days from last infusion	Cause of Death
603	Malignant disease
647	Malignant disease
607	Gram negative sepsis

In addition, case report form summaries indicate that the following patients died due to disease progression >30 days from the last infusion:

4.15 Publications/ Abstracts

Valero V, Esparza L, Holmes F, et al. Phase II study of taxotere in refractory metastatic breast cancer. Proc ASCO: 12:96, 1993. Report of the first 13 patients treated. Reversible myelotoxicity was the principal toxicity.

Valero V, Esparza L, Theriault RL, et al. Phase II study of taxotere in refractory metastatic breast cancer. 18th International Congress of Chemotherapy, Stockholm: 95:693abs, 1993. Report of the first 16 patients treated. Reversible myelotoxicity, skin toxicity, and fluid retention of uncertain etiology were the principal toxicities.

Valero V, Walters R, Theriault RL, et al. Phase II study of taxotere in refractory metastatic breast cancer. Jerusalem, 11/93. Report of the first 18 patients treated.

Valero V, Theriault RL, Esparza L, et al. Phase II study of taxotere in patients with anthracycline-resistant metastatic breast cancer. Proc 18th International Congress of Chemotherapy, Stockholm: pp 844-845, 1993. Report of the first 31 patients treated. A partial response was noted in 45% of 24 evaluable patients.

Valero V, Walters R, Theriault RL, et al. Phase II study of docetaxel (taxotere) in patients with anthracycline-resistant metastatic breast cancer. Proc ASCO:13:470, 1994. Report on 35 patients treated. Eighteen PRs (55%) were noted. The use of steroids "probably delays the onset, and decreases the severity of" the fluid retention syndrome.

Valero V, Walters R, Theriault RL, et al. Phase II study of taxotere in patients with anthracycline-resistant metastatic breast cancer. Amsterdam, 3/94. Report on 35 patients.

4.16 Sponsor's Conclusions

The sponsor claims that the overall response rate, median duration of response, and median time to progression observed in this trial are superior to those usually observed for single agents or combination chemotherapy regimens utilized in patients refractory to and/or failing an anthracycline-based regimen. RPR's review of the literature indicates that the combination of mitomycin C/ vinblastine is probably the most effective in this setting, with reported response rates of 7-40%, median duration of response between 4.3-5.5 months, and median survival of 9 months. Single agent treatments with nitrosoureas (CCNU or BCNU), vinorelbine or platinum derivatives are associated with lower response rates (see Table 47, 8.38.118 of the study report). In a stratified, randomized phase III trial of paclitaxel in patients previously exposed to anthracycline, a response rate of 29% was observed in 152 evaluable patients treated at 175 mg/m^2 (over 3 hours) and 21% in 151 patients treated at 135 mg/m^2. Median time to progression was 3.7 months at the higher dose, 3.0 months at the lower dose of paclitaxel.

RPR notes that the actual dose given, the median dose intensity and the median relative dose intensity are slightly lower than planned, possibly related to the large percentage of patients who had been heavily pretreated (34% received two prior chemotherapy regimens for advanced disease).

The sponsor points out that the acute toxicities of nausea, vomiting, diarrhea, stomatitis were well tolerated and are common to most chemotherapy regimens. Despite the high incidence of grade 4 neutropenia (84% of patients), febrile episodes and infection occurred in 32% and 36.6% of patients, respectively. The sponsor concludes that this is probably related to the short duration of grade 4 neutropenia. HSRs were not treatment-limiting.

The most common chronic toxicities were fluid retention, skin toxicity, asthenia and alopecia. Fluid retention was cumulative. Premedication with diphenhydramine and steroids may delay the onset of fluid retention. The incidence of skin toxicity is not clearly affected by any of the premedication regimens tested. Neurosensory toxicity was mild.

The risk/benefit ratio for docetaxel therapy in patients with anthracycline/anthracenedione refractory metastatic breast cancer is favorable.

4.17 Reviewer's Conclusions

The TAX233 trial was a multicenter phase II study evaluating docetaxel in anthracycline-resistant patients with metastatic breast cancer. Docetaxel was found to have remarkable efficacy as a single agent in this clinical setting, with an overall response rate of nearly 50% (all partial responses) and a response duration of at least 6 months. The majority of patients experienced grade 3 and 4 neutropenia, but only one-third developed febrile neutropenia. This finding was not unexpected given a similar experience with the related drug, paclitaxel. In this trial HSRs were not a problem, however, unexpected chronic toxicities developed the

scope of which was not predicted by phase I studies. These toxicities included cumulative fluid retention, skin reactions, and asthenia. Clearly, the benefits of treatment with docetaxel must be weighed against its side effects.

Although this trial was conducted at three sites, the majority of patients entered and later found to respond to therapy were followed at only one of these sites (MD Anderson Cancer Center). The small sample size in a trial such as this may be offset by the remarkable reproducibility of drug dose intensity, objective response rates and response duration in the three pivotal trials. However, a drug's superior response rate in the phase II setting often does not hold up in subsequent randomized trials.

The investigators should be commended for their efforts in defining and demonstrating clinical activity for docetaxel in the thirty-five anthracycline-resistant patients. Effective treatment of such patients is sorely needed. Five mitoxantrone-resistant patients were included in this study although this entry criterion was not specified in the protocol; they experienced a similar clinical response to docetaxel.

A total of 41 heavily pre-treated advanced disease patients with good performance status were entered on this trial. While these patients may be excellent protocol candidates, they may not be truly representative of the typical advanced disease patient seen in clinical practice.

Previous experience with other cytotoxic agents, such as doxorubicin and cisplatin, has shown that many of the anticipated side effects of these agents can be prevented or controlled. For example, hematopoietic growth factors could be employed to ameliorate the myelosuppression of docetaxel, and potentially allow the delivery of more cycles at the planned dose of 100 mg/m^2. While the overall incidence of infections was relatively low, 76% of episodes of infection (16/21) were associated with grade 3 or 4 neutropenia.

Of greater concern is the prevention and/or management of the chronic non-hematologic toxicities, in particular, fluid retention and skin toxicity. The ability to prevent such reactions is hampered by a dearth of information regarding the mechanism by which they develop. Cytokine release has been proposed as a mechanism, however, premedications have not offered clearcut benefits in this trial. One is also hampered by the inability at the present time to discern which patients are at greater risk for the development of chronic toxicities.

When seven of nineteen partial responders experience severe fluid retention, one has to question what impact this toxicity has had on their quality of life. It is very difficult to get a feel for this, even with the sponsor's retrospective analysis of analgesic use and tumor-related symptoms since there were so few patients evaluable for or included in such analyses.

In summary, the reviewer agrees with the sponsor that treatment with docetaxel provided net clinical benefit for patients with anthracycline-resistant metastatic breast cancer, given that

they are of good performance status, relatively free of concomitant medical problems and pre-existing treatment-related toxicities, well informed of the results of the pivotal trials, and highly motivated.

The labeling should give a comprehensive report of the safety profile of docetaxel, enumerating both hematologic and non-hematologic toxicities. Guidelines for monitoring and managing neutropenia, fluid overload, and skin toxicity should be included. This trial alone does not support the sponsor's claim that premedication with dexamethasone for 5 days will reduce the "incidence and severity" of docetaxel-related fluid retention.

4.2 TAX267

4.21 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Advanced Anthracycline Resistant Metastatic Breast Cancer (8.44.128 - 8.44.238)

Investigators: WA Biermann, MD, Thomas Jefferson University Hospital, Philadelphia, PA
PD Eisenberg, MD, Marin Oncology Associates, Greenbrae, CA
MJ Kane, MD, The Medical Center at Princeton, Princeton, NJ
P Ravdin, MD, University of Texas Health Science Center, San Antonio, TX

Study Dates: 6/9/92 - 8/10/93
Data Cut-off Date: 10/31/93
Database Frozen: 6/15/94

Review of Protocol Amendments:

A total of 4 protocol amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (5/12/92): Same as TAX233

Amendment 2 (9/18/92): Same as TAX233

Amendment 3 (2/19/92): Same as TAX233

Amendment 4 (5/17/93): This amendment mandated that all patients must be pre-treated with dexamethasone 8 mg PO bid for 5 days starting the day before the docetaxel infusion, and with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion. Patients who are already receiving steroids for treatment or prevention of side effects should continue receiving their current regimen. (This amendment incorporated Amendments 4 and 5 to TAX233)

Design:

This was a phase II multicenter trial in anthracycline-resistant patients with locally advanced or metastatic breast cancer. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Premedication with dexamethasone and diphenhydramine was mandated by amendment 4 to the original protocol.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in anthracycline-resistant patients with metastatic breast cancer.

Patient Population:

The inclusion, exclusion, and post-admission criteria are identical to those for TAX233 and are provided in the appendix. Briefly, eligible patients were female, over 18 years, with histologic proof of metastatic breast cancer resistant to anthracycline therapy. They must have at least one bidimensionally measurable lesion, a baseline Karnofsky PFS $\geq$ 60%, and should have received no more than two prior chemotherapy regimens for advanced disease.

Procedure:

The procedures followed in this study are identical to those in TAX233. Briefly, patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Following the acceptance of amendment 4, however, pretreatment with dexamethasone and diphenhydramine prior to infusions was mandated. If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2).

Efficacy Definitions:

Efficacy endpoints were defined as in the TAX233 protocol. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray. Radionuclide scans and CT scans were to be repeated at the end of every 2 cycles.

Changes in performance status, analgesic use, and pre-existing symptoms would be followed as secondary endpoints.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not clearly define quality of life measures prospectively or stipulate the frequency with which such measures were to be monitored.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle. Cardiovascular toxicity was monitored by blood pressure and pulse recordings pre-infusion, at 0, 5, 10, 15, 30, 45 and 60 minutes after the start of the infusion, and 30 minutes post-infusion. In addition pre- and post-treatment EKGs were taken.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

4.22 Study Conduct

The TAX233 trial was sponsored by RPR. Patients were accrued to 4 centers in the US. Of 42 patients registered, 28 were treated at San Antonio, 9 were treated by Dr. Eisenberg, 3 by Dr. Biermann, and 2 by Dr. Kane. The study was monitored by the Clinical Research Department of RPR or by the RPR-supervised CRO, Theradex (Princeton, NJ).

All case report forms were processed by RPR. The database was frozen on 6/15/94. All responses reported by investigators on CRFs were reviewed by an independent expert panel which included a radiologist and a medical oncologist and were recorded on response review forms (RRFs). If there were no discrepancies between the CRF and the RRF, the data in the CRF were considered valid for analysis. If the panel's decision differed from the investigator's and the investigator agreed with the panel, then the original information from the CRF was replaced by the RRF data. If the investigator did not agree with the panel's assessment, then both CRF and RRF data were retained, but the RRF assessment was considered valid for efficacy analysis.

4.23 Efficacy Results

Forty-two patients with anthracycline or anthracenedione-resistant disease were entered: 5 patients were ineligible and 7 nonevaluable for response; hence, 35 patients were evaluable for efficacy. All 42 patients were evaluable for toxicity.

Among the 5 patients who were deemed ineligible, 3 did not have bidimensionally measurable disease, and 2 were not resistant to either doxorubicin or mitoxantrone. Two

additional patients were not evaluable for response: one had a mastectomy while on study, and one had no tumor measurements after baseline.

Investigator/Site	No. of Patients Entered	No. of Responders
Ravdin/San Antonio	28	3 CRs, 13 PRs
Eisenberg/Marin Onc Assoc	9	3 PRs
Biermann/Thomas Jefferson	3	0
Kane/Princeton	2	2 PRs

Patient Withdrawals:

Twenty patients withdrew for disease progression and 8 withdrew for toxicity. Two patients withdrew consent and one patient underwent bone marrow transplantation. Eleven patients were on study as of 10/31/93. Among the patients withdrawn due to toxicity, 3 discontinued due to neurotoxicity (1 partial responder), 2 due to fluid retention (both complete responders), 2 due to asthenia and 1 due to interstitial pneumonia. One of the patients who withdrew consent was a partial responder who "felt that mild side effects did not justify further therapy given her overall outlook".

Patient Characteristics:

The median age of the 42 patients was 53.5 years (range 29-70 years). The baseline Karnofsky performance status was $\geq$ 80% in 81%. The most common type of tumor was infiltrating ductal carcinoma; equal numbers of patients had negative and positive results for both types of receptors. Forty patients had metastatic disease, 2 had locally advanced disease. Only 26% had one organ involved, the rest had 2 or more organs involved. Specifically, 36% of patients had liver involvement, 43% had bone, 36% had superficial lymph node disease, and 33% had lung disease. Thirty-six patients had undergone surgery, 25 prior radiotherapy, and 27 prior hormonal therapy. All patients received prior chemotherapy for advanced disease, except for 2 patients who relapsed during adjuvant chemotherapy with doxorubicin. Seventeen patients had received 2 prior chemotherapy regimens for advanced disease. Twenty-five patients were resistant to doxorubicin, 15 to mitoxantrone. Twenty-seven (64.3%) had progressive disease as best response to prior anthracycline or anthracenedione therapy. **Comments:** *Given the descriptions of disease extent and prior treatment histories, the patients entered on this trial appear to have far advanced disease despite a good performance status. While this constellation of clinical features would seem to make these patients ideal protocol candidates, the reviewer questions the likelihood of identifying such patients in the setting of a general practice. The original protocol and subsequent amendments did not specify mitoxantrone-resistance as an inclusion criterion. It seems reasonable, however, to include these patients in the overall efficacy and safety analyses.*

Drug Delivery:

A total of 235 cycles were administered: 154 (65.5%) at the initial planned dose of 100 mg/m^2, 65 (27.7%) at 75 mg/m^2 and 16 (6.8%) at 55 mg/m^2. The median number of cycles given was 5 (range 2-12). Treatment delays were related most commonly to non-hematologic toxicities (16 patients, 30 cycles) or to non-drug-related reasons (15 patients, 31 cycles). Dose modification was due to hematologic toxicity in 14 patients and 19 cycles, following granulocytopenia, fever in the absence of infection, and leukopenia. Non-hematologic toxicities accounted for dose modifications in 10 patients and 10 cycles, following moderate peripheral edema, skin rash, moderate mucositis, severe fatigue, severe asthenia, mild neurotoxicity, mild weakness or anorexia. Most dose reductions occurred in the first 4 cycles, with 10 patients (24%) requiring a dose reduction after the first cycle.

The median cumulative dose administered was 476 mg/m^2 (range 176-1103 mg/m^2); median dose intensity given was 26.7 mg/m^2/week (range 19-34 mg/m^2/week); and the median relative dose intensity was 0.80 (range 0.58-1.02). Thirty-three patients had an RDI >0.7.

Efficacy End points:

- **Tumor Response Rate**

Among the 42 patients included in the intent to treat analysis, there were 3 CRs and 18 PRs for an overall response rate of 50.0% (95% CI = 34.2; 65.8). The 3 CRs in this study had either chest wall or superficial lymph node involvement. Thirteen patients had stable disease, 5 had progressive disease, and three were not evaluable. A similar response rate was observed among patients resistant to doxorubicin (12/25 patients, 48%) or to mitoxantrone (8/15 patients, 53.3%). **Comment:** *The reviewer agrees with the sponsor's determination of overall response rates.*

The highest response rate occurred in evaluable patients with skin involvement (2/2, 100%), followed by lymph node involvement (7/9, 78%), breast (2/4, 50%), lung (4/8, 50%), and liver lesions (4/12, 33%). There was no difference in response rates observed in patients $\leq$ 49 years as compared to patients $\geq$ 50 years.

Comments: *The table below summarizes the 3 complete and 18 partial responses noted in the intent to treat population in Table 28 of Data Listings, 8.48.174 - 8.48.280. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). CRs were noted in patients All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patients whose lesions were slightly undersized. Patient had bone only disease. As none of these were responders, the overall response rate in the intent to treat population would remain the same. Patients had a major response in a lesion $\geq$ 5 cm (in skin, chest wall, breast).*

RESPONSES (ITT) - TAX267

Investigator/Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
Ravdin:	Chest wall (3)	66+
	Skin*	28
	Lung (3), lymph node	20
	Chest wall (3)	40
	Liver*	21
	Chest wall	27
	Liver	32
	Chest wall, lymph node	34
	Chest wall	26+
	Lymph node (2), skin (2)	31
	Scalp (3)	11
	Liver (3), lung	24+
	Lung, lymph node	18+
	Lung (3)	22+
	Lung	16+
	Chest wall*	12+
Kane:	Breast*, lymph node	9
	Liver (3)	14+
Eisenberg:	Lymph node (2), axilla (2), chest wall	12
	Parotid gland, mass posterior to left ear	19
	Breast (2), nodule over sternum	18

- **Response Duration**

The median duration of response in responding patients was 28 weeks (range 9-66+ weeks, CI = 20; 34). **Eight of 21 responders were censored due to no documentation of PD before the cut-off date in 7 patients, and further chemotherapy before progression in one patient.** The durations of the complete responses were 23, 25, and 39+ weeks. The median duration of response among the 12 evaluable responding patients resistant to doxorubicin was 28 weeks, and 21 weeks among the 8 evaluable patients resistant to mitoxantrone. **Comment:** *The reviewer agrees with the sponsor's response durations in partial responders as recorded in Table 4.03 of the study report (8.45.171 - 8.45.172). However, RPR's response durations for the 3 CRs were calculated from the time of first docetaxel infusion to the time of progression: this is in violation of the protocol which stipulated that duration of CRs would be calculated from the time of first documentation of CR to the time of progression. Using the protocol definition of CR, the median duration of response in this trial drops to 25 weeks (95% CI = 20; 31). The reviewer accepts the dates of progression for patients and the start date of further chemotherapy in patient given in the Paradox 5.0 for Windows files.*

- **Other Endpoints**

The median time to first response was 13 weeks (range 3-29+) for all treated patients (21/42 patients were censored for this analysis).

The median time to progression was 20 weeks (range 5-66+) among all treated patients, 20 weeks among the evaluable patients resistant to mitoxantrone, and 22 weeks among patients resistant to doxorubicin. Seventeen patients were censored before progression was noted: 13 because of no documentation of progression before the cut-off date, 2 due to further chemotherapy, one due to further hormonal therapy, and one due to further surgery.

The median survival time for all treated patients was 12 months (range 2.5-15.2+). On the cut-off date (10/31/93), nine patients were dead and 33 alive.

Comment: *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

There was no significant deterioration in performance status in patients in this study: the median Karnofsky PFS was 90% at baseline and at cycle 4, 80% at cycle 6. Among responders at cycle 4, increases in PFS of 10% were noted in 5 patients and of 30% in 1 patient over baseline. At the same time, declines in PFS of 10, 20, and 30% were noted in 2 responding patients each. **Comment:** *Review of PFS values for all patients by cycle (Table 12, 8.46.124 - 8.46.203) revealed 2 patients who had a 30% increase in PFS but 7 patients who had a 30% or greater decrease in PFS over baseline while on study.*

Five of 13 patients who required pain medication had an improvement in analgesic requirement: patients One of these patients had a CR, and two had PRs. Seven patients had no change in analgesic requirements and one had a worsening in requirement (Table 6.29 of the Study Report, 8.45.366).

Among 16 patients who had baseline tumor-related symptoms other than pain and data through cycle 4, symptom improvement was noted in patients (Table 6.30 of the Study Report, 8.45.368 - 8.45.369). Three were responders. **Comment:** *Review of Table 23 (8.48.16 - 8.48.44) revealed only 14 patients with at least one tumor-related symptom recorded at baseline and at cycle 4. Seven of these had improvement as shown below.*

IMPROVEMENT IN TUMOR RELATED SYMPTOMS AT CYCLE 4

Patient Number	Tumor-Related Symptom	Change in Severity	Tumor Response
	Ascites	Moderate to mild	Non-responder
	Fatigue, shortness of breath	Moderate to mild	Non-responder
	Rt arm swelling	Moderate to mild	PR
	Breast & chest wall pain	Severe to mild	PR
	Pruritis/open chest wall lesions	Moderate to mild	PR
	Rt hand/wrist neuropathy	Moderate to mild	PR
	Cough	Moderate to mild	PR

No information was provided for patients
Incomplete data was provided for patients
, which did not include assessments beyond baseline, cycle 1 or 2.

Comment: *The number of patients evaluable for PFS determinations dropped from 42 at baseline to 33 at cycle 4 and to 17 at cycle 6. Similarly, the numbers of patients evaluable for analgesic requirement or tumor-related symptoms is fairly small making conclusions of clinical benefit from docetaxel difficult.*

4.24 Safety Results

Of the 42 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (41 patients; patient 297 was not evaluable due to treatment with G-CSF in every cycle), anemia (39 patients), neuro-sensory (33 patients), fever in the

absence of infection (31 patients), skin (31 patients), asthenia (30 patients, severe in 8), alopecia (29 patients), stomatitis (28 patients), fluid retention (25 patients), diarrhea and nausea (21 patients each). The vast majority of patients with grade 4 AEs had granulocytopenia (39 patients). The most frequent grade 3 AEs were leukopenia (16 patients) and neurosensory, neuromotor, skin, and stomatitis (total of 21 patients). (See Table 29, 8.4.89 of the study report)

Overall, 25 patients experienced 40 serious AEs resulting in hospitalization. There were no toxic deaths. Febrile neutropenia occurred in 15 patients (20 events), fluid retention in 3 patients (3 events), interstitial pneumonitis in one patient (1 event), atrial fibrillation in 1 patient (2 events), and congestive heart failure in one patient (1 event, patient received approximately 370 mg/m² doxorubicin previously). (see Table 31, 8.38.90)

- **Acute Hematologic Toxicities**

Leukopenia and neutropenia were observed in 41/41 (100%) of patients evaluable for this analysis (1 patient was excluded due to treatment with G-CSF in every cycle). Twenty-five (61%) of these had grade 4 neutropenia. Out of 195 evaluable cycles (with at least one blood count between days 6 and 15) 128 (66%) showed grade 4 neutropenia. Cycles administered at 100 mg/m² were associated with a higher incidence of grade 4 neutropenia than cycles at 75 mg/m². There was no relationship between incidence of neutropenia and number of prior chemotherapies or time since last chemotherapy. There was no cumulative myelotoxicity. The median neutrophil nadir was 0.1 x 10^3/mm^3 (range 0-1.1) and the median day to nadir was 7 days (range 6-13). There appeared to be a dose-related decrease in nadir neutrophil counts, but the median day to nadir and the median duration of grade 3 and 4 neytropenia was similar across all dose levels. The median duration of grade 4 neutropenia was 7 days; 2 cycles failed to show recovery of neutrophil count by day 22$\pm$3.

Thrombocytopenia was observed in 5 patients, and was grade 3 in one. The median nadir of platelets by patient was 171 x 10^3/mm^3 (range 43-262).

Anemia was observed in 39 of 42 patients, and was grade 3 in four patients. The median nadir of hemoglobin was 9.6 g/dl (range 7.0-13.2), with a median day to nadir of 10 (range 5-26).

Febrile neutropenia (defined as fever > 38°C with grade 3 or 4 neutropenia) occurred in 15 patients and 24 cycles. In addition, there were two episodes of grade 4 neutropenia with grade 1 fever that were rated as serious. Seven patients developed febrile neutropenia in cycle 1. Fourteen patients required IV antibiotics. There was no relationship between incidence of febrile neutropenia and dose. Infection occurred in 10 patients and 17 cycles. Grade 3 or 4 neutropenia was observed in 12/17 episodes of infection.

Comment: *The reviewer agrees with the sponsor's conclusion that the incidence of febrile neutropenia is lower than would be expected given the high frequency of grades 3 and 4*

neutropenia, because of the short duration of neutropenia. There does not appear to be a cumulative effect of docetaxel on myelosuppression, allowing the potential for treatment with several cycles. Despite the apparent dose-related increase in incidence of grade 4 neutropenia and decrease in neutrophil nadirs, febrile neutropenia was not, in fact, more frequent at the higher 100 mg/m² dose.

- **Acute Non-hematologic Toxicities**

Only the acute adverse events considered possibly or probably related to docetaxel are presented in Table 38 (8.44.102) of the study report.

Hypersensitivity reactions: Seven patients and 16 cycles showed an HSR; 5 patients had a grade 1 reaction and two had a grade 2. Ten episodes occurred during the infusion. Flushing was the most frequent symptom. The sample size is too small to determine if there was any benefit to premedication.

Nausea, vomiting, and diarrhea was observed in 21, 14, and 21 patients, respectively, and was grade 1 or 2. Stomatitis occurred in 28 patients, and was grade 3 in five patients.

Hematochezia, grade 1, occurred in one patient with normal platelet counts.

Cardiac dysrhythmia (sinus tachycardia) occurred in two patients.

Pulmonary toxicity occurred in 7 patients and was grade 4 in two patients; pleural effusion and interstitial pneumonia accounted for the grade 4 toxicities.

- **Chronic Non-hematologic Toxicities**

Table 43 (8.44.107) of the study report summarizes the chronic non-hematologic toxicities deemed possibly or probably related to docetaxel.

Fluid retention (defined as peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 25 (59.5%) of patients. Twenty-three patients had peripheral edema, 14 had pleural effusions, and 10 suffered weight gain. Two patients discontinued treatment due to moderate peripheral edema, both were complete responders. The median cumulative dose to onset of fluid retention was 400 mg/m² (range 99-875). A trend in favor of diphenhydramine + steroid premedication or no premedication was observed with respect to incidence and median cumulative dose to onset of fluid retention. **Comment:** *Patient received no premedication except for Prednisone 20 mg PO x 2 days in cycles 10-12, and Diphenhydramine 50 mg IV in cycle 11. Patient received premedication with Diphenhydramine IV in cycles 1, 2, 7, 10, and 11; with Prednisone 20 mg PO in cycle 7 only; and with Dexamethasone 16 mg PO x 5 days in cycle 11 only. No conclusion can be drawn on the benefit of premedication for fluid retention.*

Skin toxicity occurred in 31 patients, and was grade 3 in five patients. Signs included erythema, pruritis, dry skin, pain, and macular rash. The median cumulative dose to onset of chronic skin toxicity was 801 mg/m^2 (range 99-801). With respect to the incidence and median cumulative dose to onset of chronic skin toxicity, there was a trend in favor of no pretreatment or diphenhydramine + steroid pretreatment. Nail disorder was observed in 15 patients, one case was severe (onycholysis). Alopecia occurred in 29 patiens and was grade 2 in most.

Neurosensory toxicity was observed in 33 patients and was grade 3 in six patients. Three patients with grade 3 toxicities were discontinued from the study, one was a partial responder. All 3 had predisposing factors, such as a history of "ongoing alcohol abuse", diabetes mellitus, and prior vincristine. Frequent symptoms/signs were numbness/tingling, paresthesias, and decrease in deep tendon reflexes. Nine patients experienced neuromotor signs, five patient had grade 3 toxicities. **Note that seven of these patients were also COSTART coded as asthenia.** Asthenia was seen in 30 patients and was severe in 8. Asthenia resulted in withdrawal of two patients from study.

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: SGPT (10 patients), SGOT (15 patients), total bilirubin (6 patients), alkaline phosphatase (15 patients). Hypoalbuminemia ($\leq$ 3 g/dl) developed in 24/42 patients. Only 1 paient had albumin levels $<$ 2 g/dl; hence, correlation between severe hypoalbuminemia and fluid retention was not analyzed. Only 4 patients developed increased creatinine levels (grade 1 in all).

- **Deaths on Study**

There were no deaths on study.

4.25 Publications/ Abstracts

Burris HA, Ravdin PM, Fields SM, et al. Phase II evaluation of Taxotere (RP-56976) as chemotherapy for anthracycline refractory metastatic breast cancer. Breast Cancer Res Treat 27:132, 1993.

Ravdin PM, Burris HA, Cook G, et al. Phase II evaluation of Taxotere (RP-56976) as chemotherapy for anthracycline refractory metastatic breast cancer. Eighth NCI-EORTC Symposium on New Drugs in Cancer Therapy. 5(suppl 5):203, 1994.

Comment: *The abstracts were not included in the application.*

4.26 Sponsor's Conclusions

The sponsor claims that the overall response rate, median duration of response, and median time to progression observed in this trial are superior to those usually observed for single agents or combination chemotherapy regimens utilized in patients refractory to and/or failing an anthracycline-based regimen, including doxorubicin, paclitaxel, and mitomycin C + velban.

RPR notes that the actual dose given, the median dose intensity and the median relative dose intensity are slightly lower than planned, possibly related to the large percentage of patients who had been heavily pretreated (40% received two prior chemotherapy regimens for advanced disease).

The sponsor points out that the acute toxicities of nausea, vomiting, diarrhea, stomatitis were well tolerated and are common to most chemotherapy regimens. Despite the high incidence of grade 4 neutropenia (95% of patients), febrile episodes occurred in 36% of patients (10% of cycles). Only one grade 4 infection was noted. There were no toxic deaths. The sponsor concludes that this low complication rate is probably related to the short duration of docetaxel-related grade 4 neutropenia.

HSRs were not treatment-limiting. Premedication did not appear to offer any benefit.

The most common chronic toxicities were fluid retention, skin toxicity, asthenia and alopecia. Fluid retention was cumulative, but caused treatment discontinuation in only 2 patients. Premedication with diphenhydramine and steroids may delay the onset of fluid retention. The incidence of skin toxicity is not clearly affected by any of the premedication regimens tested. Neurosensory toxicity was observed in 33 patients and resulted in treatment discontinuation in 3 patients with predisposing factors for the development of neurotoxicity.

The risk/benefit ratio for docetaxel therapy in patients with anthracycline/anthracenedione refractory metastatic breast cancer is favorable.

4.27 Reviewer's Conclusions

The TAX267 trial was a multicenter phase II study evaluating docetaxel in anthracycline-resistant patients with metastatic breast cancer. Docetaxel was found to have remarkable efficacy as a single agent in this clinical setting, with an overall response rate of 50% (3 CRs) and a response duration of at least 5 months. The majority of patients experienced grade 3 and 4 neutropenia, but only one-third developed febrile neutropenia. This finding was not unexpected given a similar experience with the related drug, paclitaxel. In this trial HSRs were not a serious problem, however, unexpected chronic toxicities developed including cumulative fluid retention, skin reactions, and asthenia. Clearly, the benefits of treatment with docetaxel must be weighed against its side effects.

Although this trial was conducted at four sites, the majority of patients entered and later found to respond to therapy were followed at only one of these sites

The small sample size in a trial such as this may be offset by the remarkable reproducibility of drug dose intensity, objective response rates and response duration among the three pivotal trials.

The investigators should be commended for their efforts in defining and demonstrating clinical activity for docetaxel in the twenty-five anthracycline-resistant patients. Effective treatment of such patients is sorely needed. The overall response rate for the 60 patients with anthracycline-resistant disease as defined in studies TAX233 and TAX267 was 48% (29 responders). Although not specified in either treatment protocol, mitoxantrone-resistant patients were included in both TAX233 and TAX267. The overall response rate in these patients was comparable (50%, 10/20 patients).

A total of 42 heavily pre-treated advanced disease patients with good performance status were entered on this trial. While these patients may be excellent protocol candidates, they may not be truly representative of the typical advanced disease patient seen in clinical practice. Again, as in the TAX233 trial, it is very difficult to ascertain what benefit docetaxel had on quality of life issues since there were so few patients evaluable for or included in such analyses.

Previous experience with other cytotoxic agents, such as doxorubicin and cisplatin, has shown that many of the anticipated side effects of these agents can be prevented or controlled. For example, hematopoietic growth factors could be employed to ameliorate the myelosuppression of docetaxel, and potentially allow the delivery of more cycles at the planned dose of 100 mg/m^2. While the overall incidence of infections was relatively low, 71% of episodes of infection (12/17) were associated with grade 3 or 4 neutropenia.

Of greater concern is the prevention and/or management of the chronic non-hematologic toxicities, in particular, fluid retention, skin and neurotoxicity. The usefulness of premedication in the TAX233 and TAX267 trials has been disappointing in this regard.

Unlike the TAX233 trial, there were no severe cases of fluid retention in this study. Clinical features of patients entered on TAX233 and TAX267 appear to be very similar, including age, incidence of baseline tumor-related lung involvement, concomitant medical conditions, and development of hypoalbuminemia/renal dysfunction. There were fewer anthracycline-resistant patients entered in TAX267 (25 vs 35), however, severe fluid retention has been noted in patients who are anthracycline-naive (see NSCLC trials). Clearly, more information is needed on factors predisposing patients to the development of clinically severe fluid retention.

Neurosensory toxicity was both more frequent and more severe in this trial, perhaps due to pre-existing factors in some of the patients as noted by the sponsor. It will be important to evaluate the effect of prior cisplatin on the development of neurotoxicity in patients on the

NSCLC trials.

In summary, the reviewer agrees with the sponsor that treatment with docetaxel provided net clinical benefit for patients with anthracycline-resistant metastatic breast cancer. In this trial there were three complete responses, one of which lasted 39+ weeks. Although severe fluid retention was not reported in this trial, two of eight patients who withdrew for toxicity did so because of fluid retention, both complete responders. Again, good performance status patients who are relatively free of concomitant medical problems and pre-existing treatment-related toxicities, and who are well informed of the results of the pivotal trials and highly motivated should ideally be selected for treatment with docetaxel.

The labeling should give a comprehensive report of the safety profile of docetaxel, enumerating both hematologic and non-hematologic toxicities. Guidelines for monitoring and managing neutropenia, fluid overload, and skin toxicity should be included. This trial alone does not support the sponsor's claim that premedication with dexamethasone for 5 days will reduce the "incidence and severity" of docetaxel-related fluid retention.

4.3 TAX221

4.31 Protocol Review

Title: Phase II Trial with Taxotere (RP 56976) in Patients with Advanced Breast Cancer (8.50.167 - 8.50.332)

Investigators: EORTC Early Clinical Trials Group

W Ten Bokkel Huinink, Chairman, The Netherlands
M Clavel, France
M Marty, France
T Tursz, France
SB Kaye, United Kingdom
E Robinson, Israel
A Sulkes, Israel
AR Hanauske, Germany
S Kaplan, Switzerland
AT Van Oosterom, Belgium
M Piccart, Belgium
N Pavlidis, Greece

Study Dates: 5/5/92 - 9/22/92
Data Cut-off Date: 12/15/93
Database Frozen: 6/22/94

Review of Protocol Amendments:

There were no protocol amendments affecting this study.

Design:

This was a phase II multicenter trial in patients with advanced breast cancer. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) determine if partial or complete responses can be achieved and their duration, if they occur, 2) determine the toxicity of docetaxel, and 3) characterize the pharmacokinetic-pharmacodynamic relationships of docetaxel.

Patient Population:

The inclusion and exclusion criteria are provided in the appendix. In summary, eligible patients were female, 18-75 years of age, with histologic proof of locally advanced, unresectable, or metastatic breast cancer. They must have at least one bidimensionally measurable lesion. They should have a baseline WHO PFS 0-2, a life expectancy $\geq$ 12 weeks, no CNS metastases, and no peripheral neuropathy > grade 2 (NCI). They could have received no more than 1 prior chemotherapy regimen for advanced disease, and no

prior paclitaxel. At least 12 months should have elapsed between the end of previous adjuvant chemotherapy and protocol entry; at least 4 weeks since the end of chemotherapy for advanced disease (6 weeks for prior mitomycin C, nitrosoureas, or carboplatin). At least 6 weeks should have elapsed between the end of hormonal therapy (as an adjuvant or to treat metastatic disease) and protocol entry, unless there is evidence of disease progression in which there is no waiting period. Previous radiotherapy was permitted, but not to a site used to assess response, and only if there had been a 4 week interval (eight if radiotherapy course was extensive).

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. Just prior to use, the solution must be diluted with 6 ml of 5% dextrose or 0.9% saline. The appropriate amount of drug is further diluted in 250 ml of 5% dextrose or 0.9% saline and administered as a continuous IV infusion using a peristaltic pump.

No prophylactic use of antiemetics, anti-infectives or antiallergics was permitted prior to the initial infusion. Antihistamines and corticosteroids could be used to treat symptomatic HSRs, or as premedication for a rechallenge (IV premedication was given within 1 hour of the docetaxel infusion, oral premedication given 12 hours prior). No prophylactic use of colony-stimulating factors was permitted, however, patients with grade 4 neutropenia and documented infection in the previous cycle could receive concomitant G-CSF with approval of the study chairman.

If patients demonstrate a CR or PR they will continue treatment until there is evidence of disease progression or unacceptable toxicity. If there is no change after 2 cycles, patients may receive treatment for a total of 3-6 cycles if there is symptomatic improvement. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Patients experiencing febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or thrombocytopenia grade 4 were allowed a 25% dose reduction. Other conditions in which a 25% dose reduction was permitted were: any grade $\geq$ 3 toxicity except alopecia and anemia, grade 2 skin toxicity or peripheral neurotoxicity. Treatment was stopped in the case of grade 3 peripheral neurotoxicity or if a severe HSR occurs during rechallenge.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or

greater increase in the size of a measurable lesion, or appearance of a new lesion. The occurrence of pleural effusion or ascites is considered disease progression if substantiated by positive cytology.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination. Chest xrays, ultrasounds, and scans of all measurable lesions were to be repeated at the end of every 2 cycles.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not specify any quality of life measures.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 14 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 11 patients would be accrued.

4.32 Study Conduct

The TAX221 trial was sponsored by RPR. Patients were accrued to 12 centers in Europe: 3 in France, 2 in Belgium, 1 in the United Kingdom, 1 in Germany, 1 in The Netherlands, 1 in Switzerland, 1 in Greece and 2 in Israel. All centers were members of the EORTC Early Clinical Trials Group. The study was monitored by regular site visits by monitors from the NDDO Data Center of EORTC (New Drug Development Office, Amsterdam) and from the Clinical Research Department of RPR. All case report forms were processed by RPR. The database was frozen on 6/22/94. All responses reported by investigators on CRFs were reviewed by an independent expert panel which included two radiologists and a medical oncologist and were recorded on response review forms (RRFs). If there were no major discrepancies between the CRF and the RRF, the data in the CRF were considered valid for analysis. If the panel's decision differed from the investigator's and the investigator agreed with the panel, then the original information from the CRF was replaced by the RRF data. If the investigator did not agree with the panel's assessment, then both CRF and RRF data were retained, but the RRF assessment was considered valid for efficacy analysis.

4.33 Efficacy Results

Eligibility:

Thirty-nine patients with advanced breast cancer were entered: 7 patients were ineligible and 1 nonevaluable for response (due to toxic death on day 9 of the first cycle); hence, 31 patients were evaluable for efficacy. Reasons for ineligibility were: two prior chemotherapy regimens for advanced disease in 2, AST > 3 x normal at baseline in 2, no measurable lesion in 2, and no prior chemotherapy in 2. All 39 patients were evaluable for toxicity.

Investigator/Site	No. of Patients Entered	No. of Responders
W Ten Bokkel Huinink, The Netherlands	3	2
M Clavel, France	1	1
M Marty, France	3	0
T Tursz, France	5	2
SB Kaye, United Kingdom	6	4
E Robinson, Israel	1	0
A Sulkes, Israel	1	0
AR Hanauske, Germany	2	1
S Kaplan, Switzerland	1	1
AT Van Oosterom, Belgium	8	5
M Piccart, Belgium	7	2
N Pavlidis, Greece	1	1

Patient Withdrawals:

Fifteen patients withdrew for disease progression and 12 withdrew for toxicity. Two patients refused further treatment and two patients died (progressive disease in 1, toxic death in 1). Eight patients withdrew for other reasons. Among the patients withdrawn due to toxicity, 8 discontinued due to fluid retention (severe in 3), 2 due to skin toxicity, 1 due to neurotoxicity, and 1 due to hematologic toxicity with infection and increased liver enzymes. Among the patients who refused further treatment, one had severe skin toxicity and the other had severe fluid retention with development of pleural effusions. Among the 8 patients who withdrew for other reasons, one had severe asthenia and deterioration of PFS from 1 to 3, 2

patients went off study because no objective response was observed (after 3 and 8 cycles, respectively) and 5 patients withdrew as no further clinical benefit was expected, even though 3 were PRs and 2 were CRs. **Comment:** *Continued treatment of a patient with stable disease beyond 6 cycles, and withdrawal of 5 responding patients prior to documentation of disease progression are protocol violations.*

Patient Characteristics:

The median age of the 39 patients was 51.0 years (range 30-73 years). The median baseline WHO performance status was 1. Among 11 patients in first line treatment, 27% were < 50 years, whereas among 28 patients in second line treatment, 54% were < 50 years. The most common type of tumor was infiltrating ductal carcinoma; receptor status on about 50% of patients was missing. Thirty-seven patients had metastatic disease, 2 had locally advanced disease. Only 21% had one organ involved, the rest had 2 or more organs involved. Specifically, 54% of patients had liver involvement, 44% had bone, 39% had superficial lymph node disease, 31% had lung disease, and 21% had pleural involvement.

Thirty-two patients had undergone surgery, 29 had prior radiotherapy, and 27 prior hormonal therapy. Twenty-eight patients received prior chemotherapy for advanced disease, two of which received 2 regimens for advanced disease. Twenty of the 28 second line therapy patients had prior therapy with doxorubicin, 5 of the 11 first line therapy patients had prior anthracycline as adjuvant therapy. Median time between last chemotherapy and first docetaxel infusion was 26 months (range 14-62 months) for first line patients and 5 months (range 1-15 months) for second line patients.

No significant concomitant medical conditions were noted except for patient 1218 (history of angina, hypertension, myocardial infarction, and deep venous thrombosis) and patient 1222 (decreased left ventricular ejection fraction due to prior anthracycline).

Comment: *Unlike the other pivotal trials in advanced breast cancer, TAX233 and TAX267, anthracycline-resistant disease was not defined in this trial. In general, second line patients were younger, more likely to have received prior anthracycline, and had a relatively short interval between last chemotherapy and docetaxel treatment as compared to first line patients.*

Drug Delivery:

A total of 197 cycles were administered: 150 (76.1%) at the initial planned dose of 100 mg/m^2, 36 (18.3%) at 75 mg/m^2 and 11 (5.6%) at 55 mg/m^2. The median number of cycles given was 5 (range 1-13). Treatment delays were related to non-hematologic toxicities in 7 patients and 13 cycles and to non-drug-related reasons in 8 patients and 11 cycles. Dose modification was due to hematologic toxicity in 5 patients and 6 cycles. Non-hematologic toxicities accounted for dose modifications in 8 patients and 9 cycles, following mild to moderate peripheral edema, skin toxicity (grade 4 in 1 patient), and grade 1 stomatitis. Most dose reductions occurred in the first 6 cycles. (See Table 27, 8.50.99)

The median cumulative dose administered was 469 mg/m^2 (range 99-884 mg/m^2); median dose intensity given was 31.3 mg/m^2/week (range 18-34 mg/m^2/week); and the median relative dose intensity was 0.94 (range 0.54-1.02). Thirty-six patients had an RDI > 0.7.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 39 patients included in the intent to treat analysis, there were 3 CRs and 16 PRs for an overall response rate of 48.7% (95% CI = 34; 65). Twelve patients had stable disease, 6 had progressive disease, and two were not evaluable. A similar response rate was observed among patients receiving first line therapy (5/11 patients, 45.5%) or second line therapy (14/28 patients, 50.0%). The 3 CRs in this study had either chest wall or superficial lymph node involvement. **Comment:** *The reviewer agrees with the sponsor's determination of overall response rates.*

The overall response rate observed in patients $\leq$ 49 years was lower (6/14 patients) as compared to patients $\geq$ 50 years (11/17).

A response rate of 66.7% (2/3) occurred in evaluable patients with skin lesions, 63.6% (7/11) in lymph nodes, 53.8% (7/13) in liver, and 25% (2/8) in lung. Responses of 50-67% were noted in second line patients in sites of lymph node, skin, lung or liver metastases.

Among 15 patients who had prior chemotherapy for advanced disease only, there was 1 CR and 11 PRs (80%); among 8 patients who had prior chemotherapy as adjuvant and for advanced disease, a 25% response rate was observed (2 PRs). Among 16 second line patients with prior exposure to anthracyclines, there were 8 PRs (50%) versus 1 CR and 5 PRs among 7 second line patients (85.7%) without prior exposure.

Comments: *The table below summarizes the 3 CRs and 16 PRs noted in the intent to treat population as recorded in Table 23A of Data Listings, 8.55.47 - 8.55.107. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensionally measurable lesion at baseline that met the protocol-defined size requirements (at least 1 diameter $\geq$ 2.5 cm on CT or ultrasound; lung lesions could be $\geq$ 1.5 cm) except for patients (no measurable lesions) and patients (lesions undersized). Patients had a major response in a lesion $\geq$ 5 cm (in lymph nodes, lung, liver, and pelvis).*

RESPONSES (ITT) - TAX221

Investigator/Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
Piccart:	Liver	47
	Rt cervical node, chest wall, skin (6), liver (4)	38
Oosterom:	Axillary lymph node	42+
	Axillary lymph node, liver	17
	Liver (2), lymph node*	17+
	Liver*	34+
	Liver*	26+
Kaplan:	Liver (2)*	49
Hanauske:	Lung*	17+
Catimel:	Skin (2)	26+
Tursz:	Pelvic mass*, intra-abdominal mass, palpable	17
	Lung (4)	4+
Kaye:	Lymph node*	23
	Lung (2)*	26
	Chest wall (2)	32
	Chest wall, lt axillary mass	41+
Pavlidis:	Lymph node	55+
Ten Bokkel:	Lymph nodes (2), liver (2)	3+
	Liver*	30

- **Response Duration**

The median duration of response in responding patients was 38 weeks (range 3+-55+ weeks, CI = 30; 49); for patients in second line therapy it was also 38 weeks (range 3+-49, CI= 30; 49). **Ten of 19 responders were censored: 2 patients due to no documentation of PD before the cut-off date, while 3 patients had further chemotherapy, 2 had further radiotherapy, and 3 had further hormonal therapy before progression.** The durations of the complete responses were 22+, 29 and 49+ weeks.

Comment: *Overall, the reviewer accepts the response durations as listed by the sponsor in Table 4.05 (8.52.156). Note that response durations for patients were calculated from the date of first docetaxel infusion to the start of new therapy (hormonal, chemotherapy or radiotherapy.*

Patients were listed as responding at the end of their last treatment cycle in Table 23A; however, Table 4.05 indicated that these patients had progressed later on. The reviewer accepts the sponsor's dates of progression as given in the Paradox 5.0 for Windows files installed on 10/28/94.

- **Other Endpoints**

The median time to first response was 15 weeks (range 3-17) for all treated patients (20/39 patients were censored).

The median time to progression was 20 weeks (range 1-55+, CI= 17; 32) among all treated patients, 28 weeks among second line therapy patients (range 1-49, CI= 17; 38). Thirteen patients were censored before progression was noted: 2 because of no documentation of progression before the cut-off date, 3 due to further chemotherapy, 5 due to further hormonal therapy, 2 due to further radiotherapy, and one due to further surgery.

The median survival time for all treated patients was 11 months (range 0.3-18.2+). On the cut-off date (12/15/93), 26 patients were dead and 13 alive. The median follow-up time is 16 months (range 14-19).

Comment: *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

There was no significant deterioration in performance status in patients in this study. Among 30 patients with baseline WHO PFS of 0 or 1, 4 patients deteriorated to PFS of 2-4 at cycle 4 (no PFS was reported for two patients). Among 14 patients with baseline PFS of 0 or 1, only 1 patient deteriorated to grade 2 at cycle 6 (no PFS was known for two patients).

Comment: *Again, the number of patients available for PFS analysis drops off with time. The reviewer accepts the sponsor's conclusion that PFS did not deteriorate appreciably in the trial. Upon review of PFS values of all patients by cycle (Table 10 of data listings, 8.53.81 - 8.53.102) only 4 patients were identified whose PFS declined to 3 or 4 while on study:*

Patient PFS 0 to 4, died of disease progression 18 days after cycle 1 infusion;
Patient PFS 0 to 4, partial responder, withdrew for toxicity after cycle 4;
Patient PFS 0 to 3, died 128 days after cycle 4 infusion of disease progression; and
Patient PFS 2 to 3, died 38 days after cycle 2 infusion of disease progression.

Evolution of analgesic requirements and tumor-related symptoms could not be analysed since no primary data were provided. The sponsor indicates that this information has been included in the ISE.

4.34 Safety Results

Of the 39 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (in 100% and 97.4% of patients, respectively), anemia (36 patients), neuro-sensory (21 patients), fever in the absence of infection (12 patients), skin (33 patients), asthenia (25 patients), alopecia (35 patients), stomatitis (15 patients), fluid retention (29 patients), weight gain or loss (14 patients), pulmonary (14 patients), infection (9 patients), febrile neutropenia (8 patients), diarrhea (16 patients), and nausea (19 patients). The vast majority of patients with grade 4 AEs had granulocytopenia (37 patients). The most frequent grade 3 AEs were leukopenia (11 patients), pulmonary (dyspnea due to pleural effusion, 4 patients), stomatitis (3 patients), and nausea, diarrhea and skin toxicity (2 patients each). (See Table 50, 8.50.121 of the study report)

Overall, 17 patients experienced 31 serious adverse events considered to be related to study drug. Infections occurred in 4 patients, febrile neutropenia in 7 patients, including one toxic death, and fluid retention in 6 patients.

- **Acute Hematologic Toxicities**

Leukopenia and neutropenia were observed in all patients evaluable for this analysis. Thirty-seven patients (97%) had grade 4 neutropenia. Out of 177 evaluable cycles (with at least one blood count between days 6 and 15) 136 (77%) showed grade 4 neutropenia. There was no cumulative myelotoxicity. There was no relationship between incidence of neutropenia and number of prior chemotherapies. The median neutrophil nadir was 0.1 x $10^3/mm^3$ (range 0-0.7) and the median day to nadir was 8 days (range 6-13). The incidence, median day to nadir, and median duration of grade 3 and 4 neutropenia was similar across all dose levels, and also among first and second line therapy patients. The median duration of grade 4 neutropenia was 7 days; 5 cycles failed to show recovery of neutrophil count by day 22 ± 3.

Thrombocytopenia was observed in 9 patients, and was grade 4 in one. The median nadir of platelets by patient was 164 x $10^3/mm^3$ (range 21-349).

Anemia was observed in 36 of 39 patients, and was grade 3 in five patients, however, 4 patients had a grade 2 anemia at baseline.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 9 patients and 13 cycles (includes 1 patient with fever and grade 4 leukopenia). Five patients developed febrile neutropenia in cycle 1; 8 events occurred with treatment of 100 mg/m^2. Infection occurred in 9 patients and 12 cycles. Grade 3 or 4 neutropenia was observed in 10/13 episodes of infection.
Comment: *The reviewer agrees with the sponsor's conclusion that the incidence of febrile neutropenia is lower than would be expected given the high frequency of grades 3 and 4 neutropenia, because of the short duration of neutropenia. There does not appear to be a cumulative effect of docetaxel on myelosuppression, allowing the potential for treatment with several cycles.*

- **Acute Non-hematologic Toxicities**

The acute non-hematologic adverse events considered possibly or probably related to docetaxel are presented in Table 59 (8.50.136) of the study report.

Hypersensitivity reactions: Four patients experienced 17 episodes of HSR; all were grade 1 or 2. All episodes occurred during the infusion. Flushing was the most frequent symptom; other symptoms included dyspnea, hypertension, and chest tightness. In patients having had a first HSR, 10 recurrent episodes were observed despite premedication with antihistamines and steroids.

Nausea, vomiting, and diarrhea was observed in 19, 13, and 16 patients, respectively, and was primarily grade 1 or 2. There were no grade 4 toxicities. Nine patients required anti-emetics. Stomatitis occurred in 15 patients, and was grade 3 in only three patients.

- **Chronic Non-hematologic Toxicities**

Table 63 (8.50.142) summarizes the chronic non-hematologic toxicities deemed possibly or probably related to docetaxel.

Fluid retention (defined as peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 29 (74.4%) of patients, and was severe in 9. Five patients had peripheral edema only, 17 had pleural effusions, 15 suffered weight gain, 3 had pericardial effusions, and 1 patient had ascites. Eight patients, 3 with severe fluid retention, discontinued treatment; all eight were partial responders. The median cumulative dose to onset of fluid retention was 400 mg/m^2 (range 100-605). A correlation between weight gain and development of fluid retention was noted in the majority of patients affected.

Comment: *There were 6 patients with severe fluid retention in addition to the 8 patients*

known to have discontinued treatment for this toxicity. Temporally, these patients went off study at a time when their fluid retention was most symptomatic. The reviewer questions the contribution fluid retention had in the decisions to stop docetaxel in these cases. Nevertheless, the reasons given in the study report for treatment discontinuation in the 6 patients (8.50.143 - 8:50.145) were:

Patient Number	Reason for Treatment Withdrawal
	Disease progression: increase in supraclavicular lymph node
	No further benefit expected with docetaxel
	Skin reaction: red, thickened, edematous skin
	Disease progression: pleural effusion worse on xray, cytology negative
	Severe weight gain, severe dyspnea
	Patient refused further therapy

The following is a review of the experience of all 14 patients with either severe fluid retention or who withdrew because of fluid retention. There were 9 partial responders. Docetaxel-related fluid retention became moderate to severe after cycle 2 (1 patient), cycle 3 (3 patients), cycle 4 (5 patients), after cycle 5 (3 patients), or after cycle 6 (2 patients). The median age was 56 years (range 30-66 years). Nine had prior treatment with one or more anthracyclines: doxorubicin (3 patients), epirubicin (5 patients), farmorubicin (2 patients), mitoxantrone (1 patient). Three patients discontinued Megace within two weeks of study entry. Twelve patients had prior radiotherapy, including two patients who had treatment to parasternal lymph nodes, two to mediastinal lymph nodes, and one to a "thoracic" field. Nine had pulmonary findings at entry, including six with pleural effusions. Thoracenteses were required to manage effusions in eleven patients, paracentesis to manage ascites in one. Patients also had small pericardial effusions. PFS remained stable for all except patient (declined from 0 to 2) and patient 'declined from 0 to 4). Three patients were noted to have declines in serum albumin < 3 g/dl; no renal abnormalities were seen. Six patients had persistent symptoms on one or more follow-up visits.

Six patients received no premedications on study. The table below summarizes the use of antihistamines (including H1 and H2 blockers) and corticosteroids in the remaining 8 patients. The clinical benefit of any one premedication regimen is difficult to discern.

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN PATIENTS EXPERIENCING MODERATE OR SEVERE FLUID RETENTION

Patient	Medication	Cycle	Indication
	Cimetidine PO, IV	1, 3	"Stomach"
	Cetirizine + Methylprednisolone	2 only	Skin Rash
	Cetirizine 20 mg PO x 4d + Methylprednisolone 32 mg PO x2d	3	Prophylaxis-Skin Rxn
	Methylprednisolone PO, IV	3	Dyspnea, Skin Rash
	Methylprednisolone 40 mg IV x1	4	Prophylaxis-Skin Rxn
	Cetirizine PO	4	Itching
	Cetirizine PO	7 and 8	Skin Reaction, Edema Rx
	Cetirizine 10-30 mg PO	1 to 3	Prophylaxis-Allergic Rxn
	+ Cimetidine 200 mg IV	1 to 3	
	+ Methylprednisolone 125 mg IV x1	3 only	Prophylaxis-Allergic Rxn
	+ Methylprednisolone taper x 6d PO	3 only	Prophylaxis-Allergic Rxn
	Dexamethasone IV	1,2	Allergic Reaction Rx
	Promethazine IV	1,2	Allergic Reaction Rx
	Cetirizine 10 mg PO + Methylprednisolone 32 mg x 4d, or 32 mg x 2d, then 16 mg x 2d PO	4 to 6	Prophylaxis-Allergic Rxn
	Dexchlorpheniramine 5 mg IV x1 + Methylprednisolone 80 mg IV x1	3 and 4	Prophylaxis-HSR
	Dexchlorpheniramine PO	2 only	Skin Reaction
	Ranitidine PO x 11d + Dexamethasone PO x2d Prednisolone PO x 6d	1 only	Acid Reflux Prophylaxis for Ranitidine Anorexia
	Prednisone taper x 3wks+	4	Dermatitis
	Cimetidine PO	2 and 3	Prophylaxis-GI Complaints

Skin toxicity occurred in 33 patients, and was grade 3 in two patients and grade 4 in 2 patients. Signs included erythema, pruritis, burning, pain, desquamation, maculae and papulae. The median cumulative dose to onset of chronic skin toxicity (not resolved within 21 days on onset) was 503 mg/m^2 (range 98-700). Nail disorder was observed in 16 patients, five cases were severe. Nail disorders were associated with skin toxicity in all 16 patients. Alopecia occurred in 35 patients and was grade 2 in most.

Neurotoxicity was observed in 21 patients, 18 with neurosensory changes only, and 3 with neurosensory and neuromotor findings. Neurosensory toxicity was grade 3 in one patient and contributed to treatment discontinuation in 2 patients. Frequent symptoms/signs were paresthesias and decrease in deep tendon reflexes. Among the 3 patients with neuromotor signs, 1 had grade 3 toxicity. Asthenia was seen in 25 patients and was severe in 6.

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: SGPT (15 patients), SGOT (14 patients), alkaline phosphatase (18 patients). Hypoalbuminemia developed in 18/33 patients; in seven, albumin levels fell between 2-3 g/dl. No patient had albumin levels < 2 g/dl; hence, correlation between severe hypoalbuminemia and fluid retention was not carried out. No patient developed increased creatinine levels.

- **Deaths on Study**

Two patients died on study. Patient died on day 9 of the first cycle with fever, grade 4 neutropenia and septic shock. Patient died on day 18 of the first cycle due to liver failure from progression of liver metastases. Her course was complicated by grade 4 neutropenia between days 8 and 14. Autopsy showed massive liver necrosis due to metastatic disease and Aspergillus pneumonia.

4.35 Publications/Abstracts

Van Oosterom AT, Piccart M, Franklin H, et al. Taxotere in advanced breast cancer: A phase II trial of the EORTC Early Clinical Trials Group. Proc ASCO 12:70, 1993. Report of 39 patients: 2 CRs and 7 PRs in evaluable patients. Myelosuppression was the dose limiting toxicity with grade 3 or 4 neutropenia developing in 26 patients. Non-hematologic toxicities included: HSR (4 patients), skin reactions (6 patients) and malaise (11 patients).

4.36 Sponsor's Conclusions

Docetaxel at the recommended dose and schedule (100 mg/m² IV over one hour, every 3 weeks) was active as a single agent in metastatic breast cancer, producing an overall response rate of 49% including 3 CRs in this trial. The median duration of response was 38 weeks. Among the 28 previously treated patients with chemotherapy for advanced disease, the overall response rate was 50%, including 1 CR. A response rate of 64% was noted in 11 patients with liver involvement.

The safety profile of docetaxel was considered "acceptable". The primary acute and chronic toxicities were manageable, except for cumulative fluid retention which was severe in "only 9 patients". Fluid retention was "slowly reversible" once docetaxel was discontinued.

In conclusion, the risk benefit ratio for docetaxel in the second line treatment of patients with metastatic breast cancer is favorable.

4.37 Reviewer's Final Conclusions

Comparison of Pivotal Trials

There are a number of features which distinguish this trial from the two US pivotal trials in metastatic breast cancer (TAX233 and TAX267). These are:

- The TAX221 trial had the greatest number of participating sites/investigators;
- There were 11 first line patients entered;
- An anthracycline-resistant patient population was not defined;
- There was no protocol-defined premedication regimen;
- Chest xrays were to be performed every 6 weeks instead of every 3 weeks;
- Size criteria for measurable lesions required CT and lung lesions to be slightly larger;
- This trial had a longer median follow-up time (16 months);
- The median response duration was longer, but 10 of 19 responders were censored for this analysis; 8 of those censored did not progress but rather switched over to other forms of treatment; and
- The incidence of moderate to severe fluid retention leading to hospitalizations, and eventual treatment discontinuation in responding patients is higher in this trial.

On the other hand, all three trials have produced surprisingly reproducible overall response rates, ranging from 46-50%. There were 3 CRs each in the TAX233 and TAX221 trials; all had either chest wall or superficial lymph node involvement. Responses in visceral sites of disease were also notable in lung (86%, TAX233), and liver (64% in second line patients, TAX221). Response duration was 21-23 weeks in the anthracycline-resistant populations defined in the TAX233 and TAX267 trials. In the TAX221, response duration was 32 weeks for seven responding second-line patients. Note that response duration as defined from the start of docetaxel treatment to the time of progression, may give an inflated measurement.

All three trials had a similar incidence/pattern of acute hematologic toxicities (incidence of grade 4 neutropenia and febrile neutropenia, neutrophil nadir, days to nadir, duration of grade 3 or 4 neutropenia, incidence of infection with grade 3 or 4 neutropenia). Despite the high incidence of grade 3 and 4 neutropenia, febrile neutropenia was experienced by only 23-36% of patients (the 23% incidence was noted in the TAX221 trial which included patients who were previously untreated with chemotherapy). These studies do point out the serious consequences of grade 3 or 4 neutropenia as 71-76% of infections occurred in association with these nadirs.

Acute HSRs did not pose as great a threat in these trials as had been anticipated from the phase I experience. Neurotoxicity was mild to moderate in all trials; grade 3 neurotoxicity was associated with predisposing factors (alcohol abuse, diabetes mellitus, prior vincristine therapy) in some cases. Severe asthenia was noted in up to 30 patients in the three trials. No analysis was given for this toxicity in the study report, and patients' PFS values did not seem to correlate with it.

In the TAX233 and TAX221 trials, management of fluid retention and skin toxicity posed a major clinical challenge. The premedications utilized were so numerous that it is difficult to conclude the benefit of any one. Patients in the TAX267 trial seemed to fair better with respect to the development of these toxicities, for reasons that are unclear at present.

Docetaxel Indication for Metastatic Breast Cancer

Effective treatment of patients with metastatic breast cancer, especially those who are found to be anthracycline-resistant is sorely needed. The introduction of docetaxel to the clinical armamentarium of medical oncologists will likely have a major impact on the choice of cytotoxic agents available and on the way in which agents are sequenced or combined in the treatment of patients with metastatic breast cancer. This assumes that docetaxel continues to perform as well in randomized clinical trials as it has in the phase II setting as presented in this NDA, and that greater facility is achieved in the prevention, recognition, and treatment of the chronic non-hematologic toxicities (fluid retention, skin toxicity, and asthenia). Since the initiation of these phase II studies, paclitaxel was approved for the treatment of metastatic breast cancer and has been used increasingly in anthracycline failures. Will docetaxel be superior to paclitaxel in the clinic? Will docetaxel be a treatment option for patients who are paclitaxel-failures?

Patients with poor performance status, intercurrent medical illness, complications of breast cancer or its previous treatment commonly present themselves for additional treatment after failing first- and second-line chemotherapy. Will such patients tolerate docetaxel as well as those in the three pivotal trials?

Moderate to severe fluid retention jeopardized treatment in as many as 23 patients in the three trials combined, many of whom were responders to therapy. What impact did this toxicity have on their quality of life? It is very difficult to get a feel for this from an

evaluation of PFS values alone. Even with the addition of the sponsor's retrospective analysis of analgesic use and tumor-related symptoms, there were too few patients evaluable for or included in such analyses to be able to study selected subsets of patients.

The ability to prevent the chronic non-hematologic reactions is hampered by a dearth of information regarding the mechanism by which they develop. Cytokine release has been proposed as the basis for the fluid retention syndrome and histamine release for the skin toxicity. To what extent are these reactions mediated by the polysorbate 80 diluent? Clearly, the problem needs further study since the usual premedications in clinical practice for preventing/ ameliorating such reactions (i.e., diphenhydramine and corticosteroids) have not offered clearcut benefit in these trials.

One is also hampered by the inability at the present time to discern which patients are at greater risk for the development of chronic toxicities. Gender and age factors, extent of pulmonary involvement by tumor, prior anthracycline treatment, prior irradiation to thoracic fields, hypoalbuminemia, hypothyroidism, cardiac or renal dysfunction may predispose patients to develop progresive pleural effusions/peripheral edema. Does docetaxel potentiate the development of edema or effusions in patients with one or more of these conditions? Admittedly, a drug that is designed for outpatient administration may find limited use in general practice if subsequent hospitalization is required for management of toxicities.

Inevitably, docetaxel will be utilized with other cytotoxics and treatment modalities (such as radiation). The toxicities of such combinations may pose great clinical challenges. For example, cisplatin, commonly used in conjunction with other agents in breast cancer, is given with large quantities of normal saline and may potentiate docetaxel-related fluid retention.

In summary, the reviewer agrees with the sponsor that treatment with docetaxel provided net clinical benefit for patients with anthracycline-resistant metastatic breast cancer, given that they are of good performance status, relatively free of concomitant medical problems and pre-existing treatment-related toxicities, well informed of the results of the pivotal trials, and highly motivated. As the randomized clinical trials have not been completed, docetaxel's efficacy compared to other agents currently used singly or in combination in metastatic breast cancer, such as doxorubicin, mitoxantrone, mitomycin C/velban and paclitaxel remains speculative.

The product labeling should give a comprehensive report of the safety profile of docetaxel, enumerating both hematologic and non-hematologic toxicities. Guidelines for monitoring and managing neutropenia, fluid overload, and skin toxicity should be included. Taken together, the three pivotal trials in breast cancer do not support the sponsor's claim that premedication with dexamethasone for 5 days will reduce the "incidence and severity" of docetaxel-related fluid retention. Future trials should be designed to identify the optimal premedication regimen for use with docetaxel.

OVERVIEW - BREAST CANCER PIVOTAL TRIALS

Endpoint	TAX233	TAX267	TAX221
Primary Study Site	MD Anderson	San Antonio	EORTC
Response Rate (%)	46	50	49
Response Duration	27 weeks	28 weeks	38 weeks
Neutropenia, Grade 3/4 (% of patients)	92	100	100
Febrile Neutropenia (% of patients)	32	36	23
Infections with Grade 3/4 Neutropenia (%)	76	71	77
Acute HSRs (% of treated patients)	2	17	10
Fluid Retention-Any (% of treated patients)	42	60	74
Fluid Retention-Serious (% of treated patients)*	17	5	36
Median Cumulative Dose to Onset- Fluid Retention	540 mg/m^2	400 mg/m^2	400 mg/m^2
Median Cumulative Dose to Onset- Skin Toxicity	398 mg/m^2	801 mg/m^2	503 mg/m^2
Neurosensory (% of treated patients)	46	79	54
Neuromotor (% of treated patients)	7	21	8
Asthenia (% of treated patients)	85	71	64

*Includes all patients with severe fluid retention, and any patients who withdrew from treatment due to fluid retention, regardless of severity

TAXOTERE® (Docetaxel) for Injection Concentrate

NDA # 20-449

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5. NSCLC Pivotal Trials - Second Line Therapy

5.1 TAX270

5.11 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Non-Small Cell Lung Cancer Previously Treated with Platinum Based Cytotoxic Chemotherapy.

Investigator: F Fossella, MD, MD Anderson Cancer Center, Houston, TX

Study Dates: 7/29/92 - 3/8/94
Data Cut-off Date: 10/31/93
Database Frozen: 6/21/94

Review of Protocol Amendments:

Two major amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable. A third amendment on 1/25/94, permitted the retreatment of patients who were CRs or PRs but who had withdrawn for reasons other than disease progression or HSR).

Amendment 1 (5/12/92): For anaphylactoid reactions of grade 1, 2, 3 (by NCI Toxicity Criteria), treatment with dexamethasone 10 mg IV and diphenhydramine 50 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For grade 4 reactions, the patient will go off study.

Amendment 2 (9/18/92): All patients may be pre-treated with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion. If despite pre-treatment, the patient experiences an anaphylactoid reaction of grade 1, 2, 3, then treatment with dexamethasone 10 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For subsequent infusions, patients should receive dexamethasone 20 mg PO 12 hours prior and diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion.

Design:

This was a single institution, open label phase II trial in patients with locally advanced or metastatic NSCLC previously treated with platinum based chemotherapy. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of

response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in patients with non-small cell lung cancer.

Patient Population:

The inclusion and exclusion criteria are provided in the appendix. In summary, eligible patients were male or female, over 18 years, with histologic proof of metastatic NSCLC. They must have at least one bidimensionally measurable lesion, a life expectancy of $\geq$ 12 weeks, and a baseline Karnofsky PFS $\geq$ 60%. Patients should not have clinical evidence of congestive heart failure or unstable angina, evidence of brain metastases, or peripheral neuropathy > grade 2. They should have received no more than two prior chemotherapy regimens, and at least one must have contained cisplatin or carboplatin. At least 30 days (48 days for mitomycin C or nitrosoureas) should have elapsed between the end of previous chemotherapy and protocol entry. Previous radiotherapy was permitted, but not to a site used to assess response. Non-evaluable lesions included bone lesions, malignant effusions, pulmonary lymphangitic spread, abnormal LFTs, and abnormal tumor markers. Comment: *The protocol does not rigorously define cisplatin-resistance.*

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. Just prior to use, the solution must be diluted with 6 ml of 5% dextrose or 0.9% saline. The appropriate amount of drug is further diluted in 250 ml of 5% dextrose or 0.9% saline and administered as a continuous IV infusion using a peristaltic pump.

No prophylactic use of antiemetics or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 2, however, pretreatment with diphenhydramine prior to infusions was permitted. No prophylactic use of colony-stimulating factors was permitted; G-CSF may be given to patients with febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or asymptomatic neutropenia grade 3 lasting > 14 days.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Patients experiencing febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or thrombocytopenia grade 4 were allowed a 25% dose reduction. Other conditions in which a 25% dose reduction was permitted were: grade 4 vomiting despite antiemetic prophylaxis, grade 3 or 4 diarrhea despite antidiarrheal treatment, and grade 2 peripheral neurotoxicity. Treatment was stopped in the case of grade 3 peripheral neurotoxicity and grade 4 HSRs.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray. Radionuclide scans and CT scans were to be repeated at the end of every 2 cycles.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not define any quality of life measures.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle. Cardiovascular toxicity was monitored by blood pressure and pulse recordings pre-infusion, at 0, 5, 10, 15, 30, 45 and 60 minutes after the start of the infusion, and 30 minutes post-infusion. In addition pre- and post-treatment EKGs were taken.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

5.12 Study Conduct

The TAX270 trial was sponsored by RPR. Patients were accrued to a single center in the US (MD Anderson Cancer Center). The study was monitored by the Clinical Research Department of RPR and all case report forms were processed by RPR. The database was frozen on 6/21/94.

5.13 Efficacy Results

Eligibility:

Forty-four patients were entered: 3 patients were ineligible and 7 nonevaluable for response; hence, 37 patients were evaluable for efficacy. All 44 patients were evaluable for toxicity. The 3 noneligible patients did not have bidimensionally measurable lesions; an additional 4 patients were deemed nonevaluable due to treatment refusal (1 patient), early death due to pulmonary embolism (1 patient), treatment withdrawal due to an HSR (1 patient), and the fourth patient was lost to follow-up.

Patient Withdrawals:

Twenty-eight patients withdrew for disease progression, three died (one due to toxicity, one due to disease progression, and one due to pulmonary embolism), and two withdrew consent. Three patients with stable disease were removed from study because maximum benefit had been achieved. Two patients were on study as of 10/31/93. Among the 6 patients withdrawn due to toxicity, three had moderate asthenia, one had severe pleural effusion, one had moderate peripheral neuritis, and one had an HSR which interrupted the first infusion.

Patient Characteristics:

The median age of the 44 patients was 57 years (range 29-71 years). The median baseline WHO PFS was 1 (Karnofsky performance status $\geq$80%). The male/female ratio was 1.4. Similar demographic characteristics were noted in second and third line therapy patients. The most frequently diagnosed histologic subtype was adenocarcinoma, followed by squamous cell and large cell carcinoma. The median time from first diagnosis to first infusion of docetaxel was 8.4 months in second line, but 16.8 months for third line therapy patients. Forty patients had metastatic disease, 4 had locally advanced disease. One-third had one organ involved, the rest had $\geq$ 2 organs involved. The lung was the major site of involvement (84%), followed by pleura (30%), lymph nodes (25%), liver (21%), and bone (14%). Fifteen patients had undergone surgery. Chemotherapy alone or in conjunction with radiotherapy were the major types of prior treatment for second line patients, while chemotherapy + surgery and chemotherapy + radiotherapy were the predominant treatments for the third line patients. Twenty-six patients had received VP16/CDDP as first or second line therapy, of which 3 achieved a PR in first line therapy. Eight patients had received VP16/carboplatin as first or second line therapy, all with no response. One CR was noted in a patient receiving VP16/CDDP/Ifosphamide as first line therapy.

Concomitant medical conditions included 11 patients with pre-existing cardiovascular disease (myocardial infarction in 4, pericardial effusion in 2 patients), 5 patients with pulmonary disease (pulmonary tuberculosis, asbestosis, bullous disease, and embolism), 2 patients with tumor-related central venous obstruction, and 3 patients with other malignancies (melanoma, bladder, and thyroid carcinoma). Comment: *Given the*

descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice, although some of them are clearly protocol violations.

Drug Delivery:

A total of 233 cycles were administered: 179 (76.8%) at the initial planned dose of 100 mg/m^2, 10 (4.3%) at 115 mg/m^2, 35 (15%) at 75 mg/m^2 and 8 (3.4%) at 55 mg/m^2. The median number of cycles given was 5 (range 1-12). Treatment delays were related to non-hematologic toxicities in 7 patients and 12 cycles (due to peripheral edema, dyspnea, neurologic and skin toxicities), and to non-drug-related reasons in 13 patient and 22 cycles (due to scheduling difficulties in 7 patients and physician discretion in 6). Dose modification was due to hematologic toxicity in 7 patients and 7 cycles, following neutropenic fever with or without infection, and to non-hematologic toxicities in 6 patients and 8 cycles, following peripheral edema, skin toxicity, infection, and neurotoxicity.

The median cumulative dose administered was 468 mg/m^2; median dose intensity given was 31mg/m^2/week; and the median relative dose intensity was 0.93 (range 0.14-1.16). Overall, 42 patients achieved an RDI of > 0.7.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 44 patients included in the intent to treat analysis, there were no CRs and 9 PRs for an overall response rate of 20.5% (95% CI = 9.8; 35). Twenty-three patients had stable disease, 10 had progressive disease, and two were not evaluable. Similar response rates were observed in second and third line therapy patients (19.2% and 22.2%, respectively).

All responders had metastatic disease. The highest response rate occurred in lymph nodes and in other soft tissue masses (40% of patients for each). Similar response rates were observed in all age categories. Six out of 8 responses were seen in adenocarcinoma.
Comment: *The reviewer agrees with the overall response rates given.*

Comments: *The table below summarizes the 9 partial responses noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.79.153 - 8.79.221. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). There were 5 responders among second line patients, 3 responders among third line patients, and 1 responder who had received three prior chemotherapies. The median age was 55 years. All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patient 768 whose lesions were slightly undersized. Note that patients had major responses in a lesion $\geq$ 5 cm (in lung).*

RESPONSES (ITT) - TAX270

Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks
	Lymph node, pleural-based mass	20
	Liver (3)	24
	Peripancreatic mass*, Rt adrenal mass	32
	Pleural-based mass*	30
	Lung*, Liver (2)*	18+
	Lt axillary lymph node	20
	Lung	37+
	Lung (3)*	18
	Lung (2)*	22+

- **Response Duration**

The median duration of response in all responding patients was 30 weeks (range 18-47 weeks). **Three of 9 responders were censored: two patients due to no documentation of progression before the cut-off date and further chemotherapy in 1 patient.**

Comment: *The reviewer accepts RPR's response durations as given in Table 4.05 of the study report (8.76.174), except for the following patients:*

Patient is listed as having a response duration of 47 weeks in Table 4.05, being censored for further chemotherapy. The reviewer finds a response duration of 37+ weeks, corresponding to the date at which an increase in the indicator lung lesion and new brain metastases were noted, shortly after the cut-off date, as listed in Table 28 of the data listings and in the Paradox 5.0 for Windows files installed 10/28/94.

Patient is listed as having a response duration of 46+ weeks, however, the last assessment of this patient occurred 6 months prior to the cut-off date. The reviewer has noted 18+ weeks using the date of last assessment.

Consequently, the reviewer finds the median duration of response to be 24 weeks for responders (range 18-37+ weeks).

- **Other Endpoints**

The median time to first response was 9 weeks (range 5-19 weeks) in 8 evaluable patients. The median time to progression was 15 weeks among all treated patients (9/44 patients were censored, 8 due to no documentation of progression before the cut-off date, and 1 due to subsequent chemotherapy). The median survival time for all treated patients was 11 months (28/44 patients were censored). **Comment:** *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

No analysis of QOL measures was included in the study report. The reviewer finds that there was no significant deterioration in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 44 at baseline to 29 at cycle 4 and to 21 at cycle 6. Review of PFS values for all patients by cycle (Table 12, 8.77.129 - 8.77.208) revealed only 2 patients with a 30% decline in PFS over baseline.

Two of 18 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement: patients One of these was a responder. Seven patients had worsening as demonstrated by the use of additional/ stronger analgesics, whereas nine had essentially no change in requirement. (See Table 32 of data listings, 8.80.171 - 8.80.213)

Table 23 of the data listings (8.79.10 - 8.79.40) provided tumor-related symptoms other than pain at baseline for 35 patients and at subsequent cycles for only 7 patients. The following symptoms were listed as "Recovered or Recovered with Sequelae", after 1 or more cycles of therapy suggesting transient improvement. Only patient had data out to cycle 4. None were responders. No conclusion can be drawn as to the effect of docetaxel treatment on tumor-related symptoms.

Tumor-Related Symptom	Patient Number
Anorexia/weight loss	
Cough/hoarseness	
Dyspnea	

5.14 Safety Results

Of the 43 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (42 and 43 patients, respectively), skin (37 patients), asthenia (34 patients), alopecia (30 patients), fluid retention (30 patients), neurosensory (29 patients), fever in the absence of infection (27 patients), anemia (27 patients), nausea (25

patients), diarrhea (23 patients), and stomatitis (21 patients). **Note patient had only one incomplete cycle and went off study due to an HSR and was not included in the overall safety analysis.**

Overall, 12 patients experienced serious AEs. There was one toxic death due to bilateral pneumonia with grade 4 neutropenia, and four other deaths that were not related to docetaxel (two occurred 30 days after the last infusion of study drug). Febrile neutropenia in 5 patients (15 events), and bilateral pleural effusion with severe dyspnea in 1 patient were deemed drug-related.

- **Acute Hematologic Toxicities**

Neutropenia was observed in 42/43 of patients evaluable for this analysis (1 patient was excluded). Thirty-seven (86%) of these had grade 3 or 4 neutropenia. Out of 209 evaluable cycles (with at least one blood count between days 6 and 15) 100 (48%) showed grade 4 neutropenia. There was no significant difference in the incidence of grade 3 or 4 neutropenia between cycles at 100 or 75 mg/m^2. There was no relationship between neutropenia and number of prior chemotherapies or time since last chemotherapy. The median neutrophil nadir was 0.2 x $10^3/mm^3$ (range 0.0-2.0) and the median day to nadir was 8 days (range 3-14); these values were unchanged across all dose levels. No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was 7 days; no cycles failed to show recovery of neutrophil count by day 22 ± 3. Patients with a delay of > 6 months between prior chemotherapy and the first docetaxel infusion tended to recover more quickly from grade 4 neutropenia.

Thrombocytopenia was observed in 1 patient, and was grade 2. There was full recovery.

Anemia was observed in 42 of 43 patients, and was grade 3 in three patients. The median nadir of hemoglobin was 9.7 g/dl (range 7.2-12.7), with a median day to nadir of 11 (range 4-26).

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 12 patients and 14 cycles; 9 patients experienced grade 4 neutropenia. Infection occurred in 9 patients and 10 cycles. Grade 4 neutropenia was observed in 6/10 episodes of infection; neutropenia was not associated with the other four infectious episodes.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Twelve patients experienced 29 episodes of HSR. All four patients with grade 3 HSRs received premedication with benadryl alone or with benadryl and decadron. The majority of these reactions occurred during the infusion, often within the first fifteen minutes, and were manifested by flushing, chest tightness and pain. Patient discontinued treatment in cycle 1 due to a grade 1 HSR.

Nausea was observed in 25 patients, but was grade 1 or 2 only. Vomiting occurred in 18 patients, but was grade 1or 2 only. Diarrhea occurred in 23 patients, and was grade 4 in two patients. Stomatitis occurred in 21 patients, and was grade 1 or 2.

Cardiac dysrhythmia occurred in 6 patients, and was grade 4 in two patients: both had pre-existing cardiovascular abnormalities, including pericardial effusion in one.

Local toxicity due to extravasation of docetaxel was reported for two patients and 10 cycles.

Thirteen patients experienced increased lacrimation that was moderate in four.

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 30 (70%) of patients, and was severe in 6. Fifteen patients had peripheral edema only, while 14 had pleural effusions and 2 had pericardial effusions. **While there was no case of pleural effusion at baseline, 12 patients did have pleural cavity involvement at baseline. All reported episodes of fluid retention were deemed possibly or probably related to docetaxel.** Three patients discontinued treatment due to fluid retention (moderate or severe), one with a PR. The median cumulative dose to onset of fluid retention was 314 mg/m^2. The duration of fluid retention is unknown since most episodes were ongoing at the time of follow-up.

Comment: *The table below summarizes premedications administered to 8 patients who either withdrew treatment for fluid retention (patients or had severe fluid retention (patients* (See Table 31, 8.80.7 - 8.80.170)

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN EIGHT PATIENTS EXPERIENCING MODERATE TO SEVERE FLUID RETENTION

Patient	Medication	Cycle	Indication
	Benadryl 25-50 mg IV Benadryl PO	4, 6 3, 6	HSR Prophylaxis Rash Treatment
	Benadryl 50 mg IV Benadryl IM	1 to 5 1	Prophylaxis Rash Treatment
	Benadryl 50 mg IV + Dexamethasone 16 mg PO x5d	2 to 10 7 to 10	Prophylaxis
	Benadryl 50 mg IV + Dexamethasone 16 mg PO x5d	1 to 6 7	Prophylaxis

Patient	Medication	Cycle	Indication
	Benadryl 50 mg IV + Dexamethasone 16 mg x1 or 4d	1 to 6 5, 6	Prophylaxis
	Benadryl 50 mg IV + Dexamethasone 10 mg IV + Dexamethasone 16 mg PO x5d Benadryl IV + Dexamethasone IV	1 to 7 5, 6, 7 6 1 and 2 1	Prophylaxis Therapeutic Therapeutic
	Benadryl 50 mg IV + Dexamethasone 16 mg PO x5d	1 to 5 5	Prophylaxis
	Benadryl 50 mg IV	1, 2, 3	Prophylaxis

Comment: ***The median age of this group was 59 years (range 47-67 years); there were 6 males and 2 females. Six patients had pleural cavity involvement at baseline. Four patients had received surgery, four radiotherapy, and all systemic platinum-based chemotherapy. Two patients required thoracenteses. Serum albumin levels were normal in all; serum creatinine levels were elevated in only 1 patient. There were 4 PRs in the group, all with severe reactions. The clinical benefit of any one premedication is difficult to discern.***

Skin toxicity occurred in 37 patients, and was grade 3 in two patients. Signs included erythema, pruritis, dry skin and desquamation. Twenty-nine patients had chronic toxicity, exceeding 22 days. The median cumulative dose to onset of chronic skin toxicity was 300 mg/m^2. Nail disorder was observed in 26 patients; all but one had associated skin toxicity. Alopecia occurred in 30 patients; most had pre-existing incomplete alopecia due to prior chemotherapy.

Neurosensory toxicity was observed in 29 patients, grade 3 in 4 patients. **Patient had grade 2 paresthesia due to prior chemotherapy and subsequently withdrew from docetaxel treatment due to moderate peripheral neuritis.** Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Fifteen patients experienced neuromotor sign , three patients had grade 3 weakness. Asthenia was seen in 34 patients and was severe in 4. Note that asthenia in patient 769 was also reported as neuromotor toxicity.
Comment: ***Patient baseline grade 2 neurotoxicity is a protocol violation.***

- **Laboratory Tests**

In 37 evaluable patients, elevations of the following parameters were seen: SGPT (7 patients), SGOT (9 patients), total bilirubin (1 patient), alkaline phosphatase (16 patients). Hypoalbuminemia ($\leq$ 3 g/dl) developed in 3/41 patients. Grade 3 hypomagnesemia was observed in 1 patient. Only 4 patients developed increased creatinine levels (grade 1 in all).

- **Deaths on Study**

There was one toxic death on this study in patient who experienced grade 4 neutropenia and bilateral pneumonia in cycle 2. There were two deaths within 30 days of treatment in patient who suffered spinal cord compression in cycle 1 and died on day 12 of cardiac arrest, and in patient who died on day 12 of cycle 1 of a massive pulmonary embolism. There were two additional deaths: patient died of progressive liver metastases 1.5 months after his last docetaxel infusion; and, patient died on day 38 of cycle 4 of pneumonia.

5.15 Publications/ Abstracts

Fossella FV, Lee DM, Shin M, et al. Taxotere (Docetaxel): An Active Agent for Platinum-Refractory Non-Small Cell Lung Cancer (NSCLC): Preliminary Report of a Phase II Study. Proc ASCO 13:336, 1994. Report on 44 patients: 32 were "platinum-refractory" on the basis of progressive disease on platinum-containing chemotherapy, 10 had no response to $\geq$ 2 cycles of platinum-containing chemotherapy, and 2 had recurrence 3 and 8 months after adjuvant platinum-containing chemotherapy. Nine of 42 evaluable patients had PRs; median duration of PR was 17 weeks (from first documentation of PR to disease progression). Major toxicities included: myelosuppression, HSR, cumulative fluid retention syndrome, dermatitis, asthenia. Authors conclude safety profile is "acceptable".

5.16 Sponsor's Conclusions

The sponsor states that the overall response rate of 20.5%, median response duration of 30 weeks, and median time to progression of 15 weeks observed in NSCLC patients who failed carboplatin or CDDP are remarkable considering the experience with active platinum-based regimens in this disease. RPR's review of the literature indicates that CDDP, vindesine, vinblastine, mitomycin C and ifosphamide each have single agent activity > 15%, and that the mitomycin C/vinblastine/CDDP regimen produces a 20% response rate as first line therapy, but only a 6% response rate when used as second line therapy. The sponsor points out that the median time to progression of 15 weeks speaks to the therapeutic benefit of docetaxel for patients with stable disease.

RPR claims that the feasibility of the recommended dose and schedule was confirmed in this study given the relative dose intensity achieved, and that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with taxoids were seen with docetaxel: neutropenia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, nail disorders, anemia, and cardiac dysrrthmias. These were mild in general, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, only 12 patients experienced febrile neutropenia and only 9 patients had infections.

Hypersensitivity reactions leading to treatment discontinuation occurred in only 1 patient who had a background of allergy. "This toxicity is now well-known and fully manageable."

Serious toxicities were febrile neutropenia, neutropenic infection, pleural effusion, asthenia, and there was one toxic death due to pneumonia during neutropenia. Neurotoxicity was not worsened by docetaxel.

Fluid retention was unexpected as it was rarely reported in the phase I studies. Three patients discontinued treatment and six were classified as having "severe" cases; thus treatment was jeopardized "for 7% of the patients who had a benefit from docetaxel regarding tumor response." Note that 12 patients had pleural cavity involvement at baseline, a well-known complication of lung cancer.

"The risk:benefit ratio is in favor of docetaxel in the treatment of patients with NSCLC, and specifically in those patients in whom cisplatin-containing combinations have failed."

5.17 Reviewer's Conclusions

The reviewer agrees with RPR that the overall response rate of 20.5% in patients previously treated with platinum-based chemotherapy is very promising, given the efficacy of earlier chemotherapy regimens in these same patients. Note that only 3/26 patients had a PR to VP16/CDDP (11.5% response rate) and 0/8 responded to VP16/carboplatin. Furthermore,

response rates were surpisingly similar for both the second and third line patients.

Platinum-resistance was not rigorously defined in the treatment protocol. Hence, seven of the nine responders had received one prior chemotherapy regimen containing cisplatin, one responder had received two prior chemotherapy regimens containing cisplatin, and one responder had received three prior chemotherapy regimens, two containing cisplatin and one containing carboplatin. (This last patient represents a protocol violation.) Note that this was not the case in 2/3 breast cancer pivotal trials which very clearly defined anthracycline-resistance (TAX233 and TAX267).

The hematologic toxicities of docetaxel are consistent with those reported for other taxoids and with the experience in the breast cancer pivotal trials. Again, the incidence of grade 3 or 4 neutropenia is extremely high (86%), but the incidence of febrile neutropenia was only 27%. While the overall incidence of infections was low, 60% of episodes of infection (6/10) were associated with grade 4 neutropenia.

Fluid retention caused treatment discontinuation of docetaxel treatment in 3/44 (7%) of patients in this trial. Note that fluid retention compromised treatment for 4/9 (44%) responders, and for at least 8/44 (18%) patients in this trial. The median cumulative dose of docetaxel at onset of fluid retention, 314 mg/m^2, was somewhat lower in this trial, corresponding to three cycles of treatment. In the breast cancer pivotal trials, the median cumulative dose at onset of fluid retention was 540, 400, and 400 mg/m^2 for TAX233, TAX267, and TAX221, respectively. Pre-existing cardiopulmonary conditions, including pleural cavity involvement by tumor, may have played a role in the development of fluid retention.

The reviewer agrees that management of acute HSRs was not treatment limiting. Despite prior use of cis-platin, neurotoxicity did not appear to be exacerbated, although patients with pre-existing grade 2 peripheral neuropathy may not tolerate docetaxel well.

Based on the information presented for this single institution trial, the reviewer finds that any conclusion on the risk/benefit ratio for docetaxel in the therapy of patients with cisplatin-treated NSCLC would be premature. Please refer to Section 5.27 (following the review of the TAX271 trial) for the reviewer's final conclusions. The reviewer does not agree that this study has demonstrated any significant benefit to use of dexamethasone 16 mg PO x5 days as premedication in the prevention of severe fluid retention.

5.2 TAX271

5.21 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Non-Small Cell Lung Cancer Previously Treated with Platinum Based Cytotoxic Chemotherapy.

Investigators: H Burris MD, Cancer Therapy and Research Center, San Antonio, TX
T Dobbs, MD, Baptist Regional Cancer Center, Knoxville, TN
P Eisenberg, MD, Marin Oncology Associates, Ross, CA

Study Dates: 6/15/92 - 11/4/94
Data Cut-off Date: 10/31/93
Database Frozen: 6/23/94

Review of Protocol Amendments:

Four major amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (5/12/92): Same as TAX270

Amendment 2 (9/18/92): Same as TAX270

Amendment 3 (5/17/93): Pretreatment with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion and dexamethasone 8 mg bid PO for 5 days starting 1 day prior to docetaxel was mandated for all patients. Patients who are already receiving steroids for treatment or prevention of side effects should continue their regimen.

Amendment 4 (1/24/94): This amendment permitted the retreatment of patients who were CRs or PRs but who had withdrawn for reasons other than disease progression or HSR. (Same as TAX270)

Design:

This was a multicenter, open label phase II trial in patients with locally advanced or metastatic NSCLC previously treated with platinum based chemotherapy. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of

Request for Information

Amendment to NDA # 20,449

TAXOTERE® (Docetaxel) for Injection Concentrate

From: Division of Oncology and Pulmonary Drug Products, HFD-150

To: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Date: May 17, 1995

Information to be Conveyed to the Sponsor:

The purpose of the End-of-Phase 2 Meetings on June 6, 1995, will be to determine whether the proposed clinical plans are adequate for submission for the indications in breast (first line) or lung cancer (first or second line). **This meeting is not intended to deal with specific safety, pharmacology/toxicology or chemistry issues.**

Please provide the following materials on or before June 1, 1995.

Breast Cancer: First Line

1. Updated versions of the protocols for each of the ongoing phase 3 trials: TAX303, TAX304, and TAX311

2. A list of questions to be discussed at the meeting

Non-Small Cell Lung Cancer: First and Second Line

1. A list of questions to be discussed at the meeting

response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in patients with non-small cell lung cancer.

Patient Population:

The inclusion and exclusion criteria are identical to those for TAX270 (see appendix). In brief, eligible patients were male or female, over 18 years, with histologic proof of metastatic NSCLC. They must have at least one bidimensionally measurable lesion, a life expectancy of $\geq$ 12 weeks, and a baseline Karnofsky PFS $\geq$ 60%. They should have received no more than two prior chemotherapy regimens, and at least one must have contained cisplatin or carboplatin. **Comment:** *Cisplatin-resistance was not rigorously defined in the protocol.*

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. The overall procedure for drug administration is the same as for TAX270.

No prophylactic use of antiemetics, colony-stimulating factors, or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 3, however, pretreatment with diphenhydramine and dexamethasone prior to infusions was mandated.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Guidelines for dose reductions were the same as in TAX270.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray; radionuclide scans, CT scans were to be repeated at the end of every 2 cycles.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not define any quality of life measures.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

5.22 Study Conduct

The TAX271 trial was sponsored by RPR. Patients were accrued to three centers in the US (30 were treated at San Antonio, and 7 each at Knoxville, TN, and Ross, CA). The study was monitored by the Quality Assurance Department of RPR and all case report forms were processed by RPR. The database was frozen on 6/23/94.

5.23 Efficacy Results

Eligibility:

Forty-four patients were entered: 8 patients were ineligible and 1 nonevaluable for response; hence, 35 patients were evaluable for efficacy. All 44 patients were evaluable for toxicity. Reasons for ineligibility were: no bidimensionally measurable lesion at baseline in 4 patients, brain metastases at baseline in 2, no documentation of platinum-failure in 1, and serious pneumonia at baseline in 1. In addition, 1 patient was nonevaluable because of early death due to docetaxel-related pneumonia in cycle 1.

Patient Withdrawals:

Twenty-two patients withdrew for disease progression, nine died, two withdrew consent, and 1 was lost to follow-up. Four patients were on study as of 10/31/93. Among the 6 patients withdrawn due to toxicity, 5 had mild to moderate fluid retention, and one had a severe cerebrovascular accident and grade 4 thrombocytopenia. Among the 9 deaths, 8 patients died from progressive disease (3 deaths occurred in conjunction with drug-related pneumonia), and 1 had recurrent pulmonary emboli.

Patient Characteristics:

The median age of the 44 patients was 57.5 years (range 43-77 years). The median baseline Karnofsky performance status was $\geq$80%. The male/female ratio was 0.8. The most frequently diagnosed histologic subtype was adenocarcinoma, followed by squamous cell and large cell carcinoma. The 3 centers differed in regard to male/female ratio (ratio of 2.5 at Knoxville, TN), baseline Karnofsky PFS (57% of patients had a baseline PFS of 60-70% at Ross, CA), and frequency of tumor histologies (adenocarcinoma was present in only 1 patient at Knoxville). The median time from first diagnosis to first infusion of docetaxel was 9 months. Thirty-four patients had metastatic disease, 10 had locally advanced disease. One-third had one organ involved, the rest had $\geq$ 2 organs involved. The lung was the major site of involvement (86%), with regional lymph nodes and pleura the next most common sites (32%). Other common sites were bone (25%) and liver (21%). Twelve patients had undergone surgery. Chemotherapy alone or in conjunction with radiotherapy were the major types of prior treatment. Seventeen patients had received VP16/CDDP, 9 had VP16/carboplatin, and the remainder had other platinum-based regimens as first line therapy. Second line regimens were too varied to easily categorize. Eight patients responded to first line therapy, including two CRs and 1 PR on VP16/CDDP/Ifosphamide. No patients responded to second line chemotherapy.

Concomitant medical conditions included 10 patients with cardiovascular disease (coronary artery disease in 3, pericarditis/tamponade in 2 patients, arrthmias in 4, pulmonary embolism in 1). Comment: *Given the descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice, although some of them are clearly protocol violations.*

Drug Delivery:

A total of 187 cycles were administered: 149 (80%) at the initial planned dose of 100 mg/m^2, 2 (1%) at 115 mg/m^2, and 36 (19%) at 75 mg/m^2. The median number of cycles given was 4 (range 1-11). The median number of cycles was 5 at San Antonio, but only 2 or 3 at the other two sites, a significant difference. Treatment delays were related to non-hematologic toxicities in 14 patients and 20 cycles (due to fluid retention, fatigue, grade 4 neutropenia with pneumonia), and to non-drug-related reasons in 8 patients and 12 cycles. Patient 528 was treated on a q4 week schedule after suffering a DVT in cycle 3. Dose modification was due primarily to hematologic toxicity in 8 patients and 8 cycles, following neutropenic fever with or without infection.

The median cumulative dose administered was 338 mg/m^2; median dose intensity given was 30.5 mg/m^2/week; and the median relative dose intensity was 0.91 (range 0.57-1.13). Overall, 40 patients achieved an RDI of > 0.7.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 44 patients included in the intent to treat analysis, there were no CRs and 6 PRs for an overall response rate of 13.6% (95% CI = 5; 27). Eighteen patients had stable disease, 16 had progressive disease, and four were not evaluable.

Five of the six patients who showed a partial response had locally advanced disease; 5 of the responders were second line patients. Four responders had only lung involvement. The median age was 65.5 years. **Comment:** *The reviewer agrees with the overall response rates given. All responders were treated at San Antonio, the site with the highest median number of treatment cycles delivered.*

Comments: *The table below summarizes the 6 partial responses noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.86.32 - 8.86.96. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patients whose lesions were slightly undersized. Note that patients had major responses in a lesion $\geq$ 5 cm (in lung).*

RESPONSES (ITT) - TAX271

Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks
	Lung*	17+
	Lung	26
	Lung*	29
	Lung*	29
	Lung (2)*	18+
	Lung*	23

- **Response Duration**

The median duration of response in all responding patients (intent to treat analysis) was 26 weeks. **Two of 6 responders were censored due to no documentation of progression**

before the cut-off date. Comment: *The reviewer accepts RPR's response durations as given in Table 4.02b of the study report (8.83.116), including 29 weeks for patient The date of progression for this patient was recorded in the Paradox 5.0 for Windows files installed on 10/28/94.*

- **Other Endpoints**

The median time to first response was 6 weeks (range 5-11) in 6 evaluable patients. The median time to progression was 12 weeks (range 2-29 weeks) among all treated patients (7/44 patients were censored due to no documentation of progression before the cut-off date). The median survival time for all treated patients was 6 months (23/44 patients were censored). **Comment:** *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

Table 6.32 of the study report (8.83.263 - 8.83.269) reveals that there was no significant change in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 44 at baseline to 21 at cycle 4 and to 13 at cycle 6. Review of PFS values for all patients by cycle, including end of study assessments (Table 12 of data listings, 8.84.115 - 8.84.179), revealed 8 patients with $\geq$ 30% decline in PFS over baseline while on the study.

Table 6.29a of the study report (8-83-248) presents the evolution of tumor-related pain for 9 patients tracked through cycle 4. One patient was noted as improved, 4 patients as unchanged, and 4 as worsened. Analgesic use was recorded in Table 32 of data listings, 8.86.257 - 8.86.294. Again, only one of 14 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement, five had essentially no change in requirement, and eight patients had worsening as demonstrated by the use of additional and/or stronger analgesics. Patient 514 with improvement in tumor-related pain and analgesic requirement was a PR.

Tumor-related symptoms other than pain consisted primarily of cough, dyspnea, anorexia, and fatigue. Table 6.30a of the study report (8.83.256) presents the evolution of tumor-related symptoms for 14 patients tracked through cycle 4. Two patients had improvement in cough and two patients had improvement in dyspnea

Comment: *The reviewer examined Table 23 of the data listings (8.85.271 - 8.85.308) which recorded tumor-related symptoms for 33 patients at baseline but only for 7 patients at cycle 4. Despite this the following symptoms were reported as "Recovered or Recovered with Sequelae", even though they were graded as mild to moderate in severity at recovery:*

Tumor-Related Symptom	Patient Number	Tumor-Related Symptom	Patient Number
Anorexia		Weight Loss	
Hemoptysis		Hoarseness	
Dyspnea		Peripheral Edema	
Cough			

A likely explanation for the discrepancy in findings between the study report and data listings is that the latter showed improvements in any and all symptoms, even those lasting only 1 or 2 cycles. **Note that of the 15 patients with any improvement in tumor-related symptoms, only 2 are PRs This suggests that some patients may have had transient symptomatic benefit from treatment, even without achieving a major tumor response.**

5.24 Safety Results

The most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (43 and 40 patients, respectively), asthenia (30 patients), alopecia (29 patients), skin (25 patients), neurosensory and neuromotor (23 and 14 patients each), stomatitis (18 patients), anemia (17 patients), fluid retention (16 patients), pulmonary (10 patients), HSR (10 patients), infection, diarrhea, and nausea (9 patients each).

Overall, 15 patients experienced 35 serious AEs that were possibly or probably related to study drug. Eight patients died within one month of their last drug infusion, 7 patients of progressive disease (3 deaths occurred in conjunction with drug-related pneumonia), and one due to recurrent pulmonary emboli from a known inferior vena cava clot. Note that a ninth patient died 33 days after docetaxel treatment of progressive disease

- **Acute Hematologic Toxicities**

Leukopenia was observed in all 41 patients evaluable for this analysis (patient did not have blood counts between days 2-19 of any cycle, and patients 502 and 504 had G-CSF in all cycles and were excluded). Forty patients had neutropenia, grade 3 in 6 (15%) and grade 4 in 29 (71%). Out of 187 evaluable cycles (with at least one blood count between days 6-15) 77 (52%) showed grade 4 neutropenia. There was no significant difference in the incidence of grade 3 and 4 neutropenia between cycles at 100 or 75 mg/m^2. There was no relationship between neutropenia and number of prior chemotherapies or time since last chemotherapy. The median neutrophil nadir was 0.2 x 10^3/mm^3 (range 0.0-2.0) and the median day to nadir was 7 days (range 6-35). The median neutrophil nadir was lower for the 100 than for the 75 mg/m^2 dose (0.4 vs 0.9 x 10^3/mm^3). The median duration of grade 3 or 4 neutropenia was 7 days for both dose levels; only three cycles failed to show recovery

of neutrophil count by day 22±3.

Thrombocytopenia was observed in 2 patients and 7 cycles. One patient had grade 4 toxicity requiring platelet transfusions, and associated with positive occult blood in stools and a cerebrovascular accident (patient . . This patient was removed from study.

Anemia was observed in 41 of 43 patients, and was grade 3 in four patients and grade 4 in 1.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 10 patients and 14 cycles. Grade 4 neutropenia developed in 13 of these 14 treatment cycles; these cycles were all dosed at 100 mg/m². Eleven episodes of infection occurred in 9 patients. Grade 3 or 4 neutropenia was observed in 6/11 episodes of infection.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Ten patients experienced 15 episodes of HSR; no episode was grade 3 or higher, 9/15 episodes occurred despite premedication with diphenhydramine + steroids. The majority of these reactions occurred during the infusion, often within the first fifteen minutes of the infusion, manifested by flushing and dyspnea. **Comment:** *No conclusions can be drawn regarding the efficacy of any one premedication regimen in preventing/ameliorating HSRs.*

Nausea was observed in 9 patients, and was grade 3 in three patients and grade 4 in 1. Vomiting related to docetaxel occurred in 3 patients, but was grade 1 or 2 only. Diarrhea occurred in 9 patients, and was grade 3 in one patient, and grade 4 in another. Stomatitis occurred in 18 patients, and was grade 3 in only 2 patients.

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was docetaxel-related in 16 patients and severe in 2. Five patients had peripheral edema only, while 7 had pleural effusions and 2 patients had pericardial effusions. Five patients discontinued treatment due to fluid retention. The median cumulative dose to onset of fluid retention was 497 mg/m². Weight gain was not related to fluid retention.

Comment: *The table below summarizes premedications administered to 6 patients who either withdrew from treatment for fluid retention (patients or had severe fluid retention*

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN SIX PATIENTS EXPERIENCING FLUID RETENTION

Patient	Medication	Cycle	Indication
	None	-	-
	Benadryl 50 mg IV + Solumedrol 100 mg IV	1 only	"Therapeutic"
	Benadryl 50 mg IV + Solucortef 100 mg IV	2 only	Prophylaxis and "therapeutic"
	Benadryl 50 mg IV + Prednisone 50 mg PO	3 only	Prophylaxis
	Solucortef 100 mg IV	3 only	"Therapeutic"
	Benadryl 50 mg IV	4 to 11	Prophylaxis
	Benadryl 50 mg IV	1, 3, 4	Prophylaxis
	Dexamethasone 20 mg IV x1	4 to 10	Prophylaxis
	None	-	-
	Benadryl 50 mg IV + Dexamethasone 20 mg PO x2d	1, 2	Prophylaxis
	Benadryl 50 mg IV	2	"Therapeutic"
	Benadryl 50 mg IV + Dexamethasone 20 mg IV	3, 4	Prophylaxis
	+ Dexamethasone 20 mg PO x3d	4 only	Prophylaxis
	Benadryl 25 mg IV + Dexamethasone 16 mg PO x5d	5, 6	Prophylaxis
	Benadryl 25 mg IV	7 only	Prophylaxis
	Benadryl 25 mg IV + Dexamethasone 16 mg PO x5d	1 only	Prophylaxis
	Benadryl 25 mg PO	2	Insomnia
	Dexamethasone 16 mg PO x5d	2 to 5	Prophylaxis
	Dexamethasone 8 mg PO qd	5	Brain Metastases

Comment: *The median age of this group was 59 years (range 50-69 years); 3were males and 3 females. Five patients had lung involvement, 1 had a pleural effusion, and 1 had a pericardial effusion at baseline. Two patients had received surgery, three radiotherapy, and all systemic platinum-based chemotherapy. Serum albumin levels were abnormal in 4; serum creatinine levels were elevated in 3 patients. There were 3 PRs in the group, all with moderate reactions. The clinical benefit of any one premedication cannot be discerned.*

Skin toxicity occurred was docetaxel-related in 25 patients. One patient experienced grade 3 and 2 patients grade 4 toxicity. Signs included erythema, pruritis, dry skin, maculae,

papulae, and exfoliation. Nail disorder was observed in 5 patients, only one had associated skin toxicity. Alopecia occurred in 30 patients; most had pre-existing incomplete alopecia.

Neurosensory toxicity was considered docetaxel-related in 23 patients, grade 3 in 2 patients. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Fourteen patients experienced neuromotor signs, six patients had grade 3 weakness. Other toxicities reported were grade 4 blindness (in a patient who also had a cerebrovascular accident), grade 1 or 2 headache, and grade 1 or 2 constipation. Asthenia was seen in 30 patients and was severe in 6. **Forty-six cycles of AEs were coded as both neuromotor under NCI criteria and as asthenia (COSTART) involving 16 patients.** Thirteen of these patients had fatigue or weakness. Thus, the number of neuromotor events may be inflated.

- **Laboratory Tests**

In 43 evaluable patients, elevations of the following parameters were seen: SGPT (12 patients), SGOT (13 patients), total bilirubin (9 patients), alkaline phosphatase (19 patients), hypocalcemia (15 patients), hypomagnesemia (9 patients). Ten patients developed increased creatinine levels (grade 3 in one).

- **Deaths on Study**

There were 9 deaths on study if patient is included (died 33 days after docetaxel infusion). Eight patients died from progressive disease (3 deaths occurred in conjunction with drug-related pneumonia), and 1 had recurrent pulmonary emboli. **Comment:** *Patient likely represents a toxic death.*

Patient Number	Cause of Death
	Grade 4 neutropenia and pneumonia on cycle 1, day 8; died on day 13 Autopsy revealed widespread metastatic disease.
	Progression of lung disease, cycle 4
	Progression of lung disease, cycle 3
	Brain metastasis, with uncal herniation, cycle 2
	Disease progression, cycle 2
	Pulmonary emboli from inferior vena cava source, cycle 2
	Bilateral pneumonia, cycle 3
	Grade 3 neutropenia, rt pleural effusion, progressive lung disease, possible pneumonia, cycle 5
	Disease progression, cycle 1

5.25 Publications/ Abstracts

There were no publications.

5.26 Sponsor's Conclusions

RPR claims that the feasibility of the recommended dose and schedule of docetaxel was confirmed in this study. The relative dose intensity of 0.9 shows that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with taxoids were seen with docetaxel: neutropenia, anemia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, and nail disorders. These were mild in general, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, only 10 patients experienced febrile neutropenia and only 9 patients developed docetaxel-related infections. RPR points out that infection is the major complication of patients with lung tumors and has a significant impact on their survival.

Serious toxicities were febrile neutropenia and neutropenic infection. There were no toxic deaths, although one patient died due to pneumonia during neutropenic fever, associated with progressive disease.

Hypersensitivity reactions did not lead to treatment discontinuation in any patient. RPR contends that "this toxicity is now well-known and fully manageable." Neurotoxicity was not worsened by docetaxel.

Fluid retention was unexpected as it was rarely reported in the phase I studies. Five patients discontinued treatment and one additional patient was classified as "severe"; thus treatment was jeopardized "for 11.4 % of the treated patients despite the clinical benefit these patients experienced from docetaxel regarding tumor response." Note that 14 patients had baseline pleural disease, a well-known complication of lung cancer.

"The risk:benefit ratio is in favor of docetaxel in the treatment of patients with NSCLC, and specifically in those patients in whom cisplatin-containing combinations have failed."

5.27 Reviewer's Final Conclusions

The reviewer agrees that the overall response rate of 13.6% in patients previously treated with platinum-based chemotherapy is optimistic, given that 0/32 patients in this trial responded to second line therapy prior to entry. In addition, response rates were surpisingly similar for both the second and third line patients.

Cisplatin-resistance was not rigorously defined in a prospective manner in the treatment protocol. Hence, four responders had received one prior chemotherapy regimen containing

cisplatin, one had received one prior chemotherapy regimen containing carboplatin, and one had received three prior chemotherapy regimens, one of which contained cisplatin. (This last patient represents a protocol violation.)

The TAX271 multicenter trial in previously treated patients, found the overall response rate for docetaxel to be somewhat lower than that reported for the single institution TAX270 trial (13.6% vs 20.5%). This figure is more typical of the performance of known "active" agents in this disease. Pooling the 88 patients from TAX270 and TAX271 together, the overall response rate for all treated patients was 17% (15/88); similarly, the overall response rate was 17% for second line patients (10/58), and 17% for third or more line patients (5/30). Locally advanced disease patients experienced a response rate of 36% (5/14), as compared to metastatic disease patients with only 13.5% (10/74). Although the number of locally advanced patients is small, this trend is consistent with conclusions from a published meta-analysis (Donnadieu et al, 1991) which showed superior response rates in patients with stage III versus stage IV NSCLC.

The median response duration as defined by the investigator leads to an inflated value since it includes time to first response. Hence, the true duration of a PR in these trials is probably closer to 20 rather than 30 weeks. The sponsor's contention of clinical benefit to patients with disease stabilization must be weighed against docetaxel's safety profile. Review of PFS values of patients on study proved inconclusive given the large numbers of patient withdrawals for disease progression patients, respectively), and the occurrence of serious AEs in 12 and 15 patients during the course of each trial. Other QOL measures were not formally evaluated prospectively. Insufficent data is presented on analgesic use and tumor-related symptoms to draw any definite conclusion of clinical benefit of docetaxel for many of the patients.

The hematologic toxicities of docetaxel are consistent with those reported for other taxoids and with the experience in the breast cancer pivotal trials. The incidence of grade 3 or 4 neutropenia in both trials is extremely high (86% in each), but the incidence of febrile neutropenia was low at 22% (27% in TAX270). While the overall incidence of infections was also low, 6/11 (55%) of episodes of infection were associated with grade 3 or 4 neutropenia. This figure is very similar to that found in TAX270 (60%).

Fluid retention caused treatment discontinuation of docetaxel treatment in 5/44 (11.4%) of patients in the TAX271 trial. Note that fluid retention compromised treatment for 3/6 (50%) of responders, and for at least 6/44 (13.6%) patients. The median cumulative dose of docetaxel at onset of fluid retention, 497 mg/m^2, was in keeping with that reported for the breast cancer pivotal trials (the median cumulative dose at onset of fluid retention was 540, 400, and 400 mg/m^2 for TAX233, TAX267, and TAX221, respectively). Pre-existing cardiopulmonary conditions, including pleural cavity involvement by tumor, may have played a role in the development of fluid retention.

The reviewer agrees that management of acute HSRs was not treatment limiting. Despite

prior use of cis-platin, neurotoxicity did not appear to be exacerbated, although patients with pre-existing grade 2 peripheral neuropathy may not tolerate docetaxel well.

Patients with unresectable or metastatic NSCLC are typically treated with a first line chemotherapy regimen for palliation. In the case of treatment failure, these patients often do not receive any other chemotherapy treatment due to their overall poor prognosis and sequelae from prior therapy. In fact, use of chemotherapy as first line therapy for these patients remains controversial.

Despite the promising single agent activity demonstrated in these two phase II trials, well-controlled, randomized clinical trials would be required to fully evaluate docetaxel as a second line agent in the setting of metastatic or locally advanced NSCLC. Such trials should focus heavily on quality of life issues defined in a prospective manner. The benefit of premedication(s) in the prevention of severe fluid retention should also be evaluated. Based on the information presented for the two pivotal trials in cisplatin-treated NSCLC patients, TAX270 and TAX271, the reviewer does not agree that the risk/benefit ratio favors docetaxel for approval.

OVERVIEW - NSCLC PIVOTAL TRIALS

Endpoint	TAX232	TAX269	TAX231	TAX223	TAX270	TAX271
Primary Study Site	MD Anderson	San Antonio	Sloan Kettering	EORTC	MD Anderson	San Antonio
Response Rate (%)	31.7	27	20.5**	21.4	20.5	13.6
Response Duration	19 weeks	28 weeks	23 weeks	41 weeks	30 weeks	26 weeks
Neutropenia, Grade 3/4 (% of patients)	97	93	87	85	86	86
Febrile Neutropenia (% of patients)	24	35	27	17	27	22
Infections with Grade 3/4 Neutropenia (%)	57	83	43	82	60	55
Acute HSRs (% of treated patients)	37	29	73	29	27	23
Fluid Retention-Any (% of treated patients)	66	46	41	45	68	36
Fluid Retention-Serious (% of treated patients)*	22	10	2	12	18	14
Median Cumulative Dose to Onset- Fluid Retention	305 mg/m^2	476 mg/m^2	442 mg/m^2	403 mg/m^2	314 mg/m^2	497 mg/m^2
Median Cumulative Dose to Onset- Skin Toxicity	205 mg/m^2	398 mg/m^2	300 mg/m^2	523 mg/m^2	300 mg/m^2	300 mg/m^2
Neurosensory (% of treated patients)	59	60	43	38	67	52
Neuromotor (% of treated patients)	27	27	8	5	35	32
Asthenia (% of treated patients)	68	63	51	60	79	68

*Includes all patients with severe fluid retention, and any patients who withdrew from treatment due to fluid retention, regardless of severity

**Partial responses only

TAXOTERE® (Docetaxel) for Injection Concentrate

NDA # 20-449

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REVIEWER NOTE

At the time of the submission of the Safety Update Report (11/7/94), Rhone-Poulenc Rorer stated their claim relative to the non-small cell lung cancer indication now reads:

> **"Non-small cell lung cancer: Taxotere® (docetaxel) for Injection Concentrate is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy".**

The only change made reflects deletion of the word "even".

In light of this change, the following studies of docetaxel as first line therapy for NSCLC, TAX232, TAX269, TAX231, and TAX223, should be considered supportive rather than pivotal. Studies TAX270 and TAX271 evaluating docetaxel as second line therapy for NSCLC remain pivotal.

6. NSCLC Pivotal Trials - First Line Therapy

6.1 TAX232

6.11 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Non-Small Cell Lung Cancer Previously Untreated with Cytotoxic Chemotherapy.

Investigator: F Fossella, MD, MD Anderson Cancer Center, Houston, TX

Study Dates: 7/92 - 2/93
Data Cut-off Date: 10/31/93
Database Frozen: 6/17/94

Review of Protocol Amendments:

Two major amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (5/12/92): For anaphylactoid reactions of grade 1, 2, 3 (by NCI Toxicity Criteria), treatment with dexamethasone 10 mg IV and diphenhydramine 50 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For grade 4 reactions, the patient will go off study.

Amendment 2 (9/18/92): All patients may be pre-treated with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion. If despite pre-treatment, the patient experiences an anaphylactoid reaction of grade 1, 2, 3, then treatment with dexamethasone 10 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For subsequent infusions, patients should receive dexamethasone 20 mg PO 12 hours prior and diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion.

Design:

This was a single institution, open label phase II trial in patients with locally advanced or metastatic NSCLC previously untreated with chemotherapy. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in patients with non-small cell lung cancer.

Patient Population:

The inclusion and exclusion criteria are provided in the appendix. In summary, eligible patients were male or female, over 18 years, with histologic proof of metastatic NSCLC. They must have at least one bidimensionally measurable lesion, a life expectancy of $\geq$ 12 weeks, and a baseline Karnofsky PFS $\geq$ 60%. Patients should not have clinical evidence of congestive heart failure or unstable angina, evidence of brain metastases, or peripheral neuropathy > grade 2. They should not have received prior chemotherapy. Previous radiotherapy was permitted, but not to a site used to assess response. Non-evaluable lesions included bone lesions, malignant effusions, pulmonary lymphangitic spread, abnormal LFTs, and abnormal tumor markers.

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. Just prior to use, the solution must be diluted with 6 ml of 5% dextrose or 0.9% saline. The appropriate amount of drug is further diluted in 250 ml of 5% dextrose or 0.9% saline and administered as a continuous IV infusion using a peristaltic pump.

No prophylactic use of antiemetics or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 2, however, pretreatment with diphenhydramine prior to infusions was permitted. No prophylactic use of colony-stimulating factors was permitted; G-CSF may be given to patients with febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or asymptomatic neutropenia grade 3 lasting > 14 days.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Patients experiencing febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting > 7 days, or thrombocytopenia grade 4 were allowed a 25% dose reduction. Other conditions in which a 25% dose reduction was permitted were: grade 4 vomiting despite antiemetic prophylaxis, grade 3 or 4 diarrhea despite antidiarrheal treatment, and grade 2 peripheral neurotoxicity. Treatment was stopped in the case of grade 3 peripheral neurotoxicity and severe HSRs occurring despite "maximum pretreatment with corticosteroids and antihistamines".

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in

the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray. Radionuclide scans and CT scans were to be repeated at the end of every 2 cycles.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not define any quality of life measures.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

6.12 Study Conduct

The TAX232 trial was sponsored by RPR. Patients were accrued to a single center in the US (MD Anderson Cancer Center). The study was monitored by the Clinical Research Department of RPR and all case report forms were processed by RPR. The database was frozen on 6/17/94.

6.13 Efficacy Results

Eligibility:

Forty-one patients were entered: 4 patients were ineligible and 2 nonevaluable for response; hence, 35 patients were evaluable for efficacy. All 41 patients were evaluable for toxicity. Three ineligible patients did not have bidimensionally measurable lesions; an additional patient was considered ineligible due to pre-existing superior vena cava syndrome and, hence, a shorter life expectancy and unstable cardiovascular status. Two patients were deemed nonevaluable due to absent post-baseline tumor measurements; in the case of patient an acute HSR interrupted the cycle 2 infusion and no further treatment was given.

Patient Withdrawals:

Thirty patients withdrew for disease progression, and two died (one due to drug-related neutropenic pneumonia, one due to disease progression). Three withdrew consent: two due to physician discretion, and one with a PR who felt he had reached maximum benefit from docetaxel. One patient was on study as of 10/31/93 with stable disease. Among the 5 patients withdrawn due to toxicity, 1 had a severe HSR, 3 had moderate asthenia, and 1 had severe pleural effusions.

Patient Characteristics:

The median age of the 41 patients was 63 years (range 39-75 years). The median baseline Karnofsky performance status was 90%. The male/female ratio was 2.4. The most frequently diagnosed histologic subtype was adenocarcinoma. The median time from first diagnosis to first infusion of docetaxel was 4 months. Thirty-nine patients had metastatic disease, 2 had locally advanced disease. One-quarter had one organ involved, the rest had $\geq$ 2 organs involved. The lung was the major site of involvement (88%), with regional lymph nodes and pleura the next most common sites (32% each). Eight patients had undergone surgery only, 11 had radiation only, 6 had surgery and radiation, and 16 had no prior therapy.

Concomitant medical conditions included 7 patients with a history of cardiovascular disease (including coronary artery disease in 3 and arythmias in 1); 8 patients with hypothyroidism, and 1 patient with superior vena cava syndrome. Comment: *Given the descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice, although some of them are clearly protocol violations.*

Drug Delivery:

A total of 197 cycles were administered: 147 (75%) at the initial planned dose of 100 mg/m^2, and 31 (16%) at 75 mg/m^2. The median number of cycles was 4 (range 1-12). Thirteen patients had at least one dose reduction and 21 had at least one dose delay. Five patients discontinued treatment due to toxicity. Non-hematologic toxicities were the principal cause of both treatment delays and dose reductions in patients.

The median cumulative dose administered for all patients was 404 mg/m^2 (range 100-1200); median dose intensity given was 32 mg/m^2/week; and the median relative dose intensity was 0.97 (range 0.5-1.1). Overall, 85% of patients achieved an RDI of > 0.7 in this trial.

A variety of premedications were given, including H1 antihistamines only in 24 patients, short steroid courses in 6 and long steroid courses in 1.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 41 patients included in the intent to treat analysis, there were no CRs and 13 PRs for an overall response rate of 31.7%. Six had stable disease, 17 had progressive disease, and five were not evaluable. All responders had metastatic disease, and a WHO PFS of 0 or 1. Eight responders were 65 or younger. The response rate in lung was 32%, in liver 11%.
Comment: *The reviewer agrees with the overall response rates given.*

Comments: *The table below summarizes the 13 partial responses noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.99.131 - 8.99.190. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patients*
Note that patient had a major response in a lesion ≥ 5 cm (peripancreatic mass).

RESPONSES (ITT) - TAX232

Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks
	Liver (2)*	18
	Peripancreatic mass*	19+
	Lt adrenal mass*	19
	Lung (1*, 2, 3)	17
	Lung*	15
	Lung (2)*	32
	Lung	19
	Supraclavicular lymph node	17
	Lung (3)*, pleural-based mass	20
	Breast mass*, axillary lymph node	19
	Lung (4)	25+
	Lung (1, 2*)	25
	Lung (2), liver*	21

- **Response Duration**

The median duration of response in all 13 responding patients (intent to treat analysis) was 19 weeks. **Two of 13 responders were censored due to no documentation of progression before the cut-off date (patient withdrew consent and patient discontinued due to toxicity).**

Comment: *The reviewer accepts RPR's response durations as given in Table 4.05 of the study report (8.96.116). Response durations for patients are calculated to the date of death as recorded in the Paradox 5.0 for Windows files (installed on 10/28/94) as no documentation of progression was provided in Table 28 of the data listings.*

- **Other Endpoints**

The median time to first response was calculated to be 6 weeks. The median time to progression was 14 weeks among all treated patients (9/41 patients were censored, 6 due to no documentation of progression before the cut-off date, and 3 patients who received further therapy before progression). The median survival time for all treated patients was 13 months (68% of patients were alive at the cut-off date). The Kaplan-Meier estimate of the one-year survival rate for all patients was 58%. **Comment:** *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

No analysis of QOL measures was included in the study report. The reviewer finds that there was no significant deterioration in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 41 at baseline to 28 at cycle 4 and to 16 at cycle 6. Review of PFS values for all patients by cycle, including end of study (Table 12 of the data listings, 8.97.122 - 8.97.191), revealed that 6 patients experienced a 30% or more decline in PFS over baseline while on study.

One of 22 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement; seven patients had worsening as demonstrated by the use of additional/stronger analgesics, whereas fourteen had essentially no change in requirement. (See Table 32 of data listings, 8.100.177 - 8.100.217)

Tumor-related symptoms consisted primarily of cough, dyspnea, and pain at one or more sites. Table 23 (8.99.14 - 8.99.33) provided tumor-related symptoms at baseline for 33 patients and at subsequent cycles for only 8 patients. Despite this, the following symptoms were listed as "Recovered" (graded as mild in severity at recovery):

Tumor-Related Symptom	Patient Number	Tumor-Related Symptom	Patient Number
Anorexia/weight loss		Pain	
Cough		Dyspnea	

Docetaxel treatment appears to have caused a transient improvement in tumor-related symptoms in these six patients, two of which were PRs (patients

6.14 Safety Results

Of the 41 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (40 and 39 patients each), alopecia (40 patients), skin (33 patients), anemia (31 patients), asthenia (28 patients), fluid retention (27 patients), nausea (26 patients), diarrhea (25 patients), neurosensory (24 patients), fever in the absence of infection (20 patients), nail disorder (19 patients), HSR and stomatitis (15 patients each), pulmonary toxicity and vomiting (13 patients each).

Overall, 17 patients experienced serious AEs. Two patients died during the treatment period, one due to neutropenic fever with pneumonia and one due to disease progression. There were 12 other deaths which occurred at least 30 days after the last infusion, one of which was possibly related to docetaxel (hypotension, supraventricular tachycardia).

- **Acute Hematologic Toxicities**

Leukopenia was observed in 40/41 patients and was grade 3 or 4 in 75%. Forty patients (97%) had grade 3 or 4 neutropenia. There was no difference in the incidence of grade 3 and 4 neutropenia between cycles at 100 or 75 mg/m^2. The median neutrophil nadir was 0.2 x 10^3/mm^3 (range 0.0-2.8) and the median time to nadir was 8 days (range 3-14). The median neutrophil nadir was no different for the 100 or the 75 mg/m^2 dose, although the median day to nadir was 8 versus 12 days. No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was 7 days; only one cycle failed to show recovery of neutrophil count by day 22$\pm$3.

Thrombocytopenia was observed in 4 patients. Two patients had grade 3 toxicity.

Anemia was observed in 35 patients, and was grade 3 in two patients. The nadir for hemoglobin was 10.5 g/dl and the median day to nadir was 8 days.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 10 patients and 16 cycles. Thirteen of 16 episodes were associated with grade 4 neutropenia. Docetaxel-related infections occurred in 6 patients and 7 cycles. Four of 7 episodes of infection were associated with grade 3 or 4 neutropenia.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Fifteen patients experienced 33 episodes of HSR; no episode was grade 4. Most reactions occurred during the infusion, often within the first fifteen minutes of the infusion, manifested by flushing, dyspnea, and chest tightness. One patient discontinued treatment due to an HSR (patient Premedication with antihistamines (in nearly all patients) did not prevent HSR.

Nausea was observed in 26 patients, and was grade 3 in one patient and grade 4 in another. Vomiting occurred in 13 patients, and was grade 4 in two. Diarrhea occurred in 25 patients, and was grade 3 in two patients, and grade 4 in another. Stomatitis occurred in 15 patients, and was grade 1 or 2 only.

Five patients had grade 1 or 2 cardiac dysrhythmias.

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 27 patients, and was severe in 8. Ten patients had peripheral edema only, while 17 had pleural effusions and 3 had pericardial effusions. Two patients discontinued treatment due to moderate or severe fluid retention, one with a PR. The median cumulative dose to onset of fluid retention was 305 mg/m^2. Weight gain was not related to fluid retention.

Comment: *The table below summarizes premedications administered to 9 patients who either withdrew treatment for fluid retention (patients or had severe fluid retention (patients (See Table 31, 8.100.7 - 8.100.176)*

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN NINE PATIENTS EXPERIENCING MODERATE TO SEVERE FLUID RETENTION

Patient	Medication	Cycle	Indication
	Benadryl 25 mg IV + Solucortef 100 mg IV	1	Prophylaxis
	Benadryl 50 mg IV	2 to 7	Prophylaxis
	+ Dexamethasone 10-50 mg IV	3 to 7	
	+ Dexamethasone 12-24 mg PO	2, 3	
	Zantac PO	5 to 7	GI Prophylaxis
	Prednisone PO	6, 7	Skin Swelling
	Benadryl PO	2 only	Sleep
	Zantac PO	2 only	GI Prophylaxis

Patient	Medication	Cycle	Indication
	Benadryl 50 mg IV Zantac PO	1 to 4 0 to 4	Prophylaxis GI Prophylaxis
	Benadryl 50 mg IV Benadryl 75-150 mg PO	1 to 4 1 to 3	Prophylaxis Skin Reaction
	Benadryl 50 mg IV + Dexamethasone 10 mg IV	1 to 7 3 to 7	Prophylaxis
	Benadryl 50 mg IV Prednisone 10-90 mg PO Solumedrol IV x 7-18d Zantac PO	1 to 4 0 to 4 3, 4 3, 4	Prophylaxis Asthma/COPD Asthma/COPD GI Prophylaxis
	Benadryl 50 mg IV Pepcid PO	1, 2 1, 2	Prophylaxis Esophagitis
	Benadryl 50 mg IV + Dexamethasone 16 mg PO x1-5d	1 to 8 3 to 8	Prophylaxis

Comment: *The median age of this group was 61 years (range 42-74 years); all were males. All had pleural effusions at baseline. Two patients had received surgery, five had radiotherapy. Four patients required diuretics, four were treated for dyspnea/bronchospasm, and two for skin reactions. Serum albumin levels $\leq$ 3 g/dl were noted in 3; serum creatinine levels were not elevated in any patient. There were 2 PRs in this group, patient with moderate and patient with severe fluid retention. The clinical benefit of any one premedication is difficult to discern.*

Skin toxicity occurred in 33 patients and was grade 3 in five. Signs included erythema, pruritus, dry skin, maculae, and desquamation. **Chronic skin toxicity occurred in 30 (73%) patients, and was grade 3 in four.** The median cumulative dose at onset of chronic skin toxicity was 205 mg/m^2. Nail disorder was observed in 20 patients and was associated with skin changes in 15. Alopecia occurred in 98% of patients.

Neurosensory toxicity was noted in 24 patients, and was grade 1 or 2 only except for one patient with grade 3 foot drop that was reclassified as not related to docetaxel by the investigator after the database was frozen. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. **Eleven patients experienced neuromotor signs: the majority of cases of "weakness", "malaise", and "asthenia" were reported as neuromotor toxicity.** Asthenia (malaise/fatigue/lethargy syndrome) was recorded for 28 patients and was severe in two. In 3 patients, asthenia was the reason for dose modication, treatment delay or discontinuation of therapy.

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: SGOT (14 patients, grade 4 in one), SGPT (8 patients, grade 4 in one), total bilirubin (grade 3-4 in two patients), alkaline phosphatase (13 patients), hypomagnesemia (8 patients). Five patients developed increased creatinine levels (none were grade 3).

- **Deaths on Study**

There were two deaths within 30 days of docetaxel treatment: patient experienced docetaxel-related grade 4 neutropenia, thrombocytopenia, and pneumonia in cycle 4; patient died in cycle 7 due to tumor-related hemorrhage. Two patients died on day 37: patient (after cycle 2) of disease-related respiratory failure; and, patient (after 6 cycles) of supraventricular tachycardia and hypotension possibly related to docetaxel. In addition, there were 10 deaths between days 44 and 342 from the last docetaxel infusion, all due to disease progression.

6.15 Publications/ Abstracts

Fossella FV, Raber M, Lee JS, et al. Taxotere (Docetaxel): An Active Agent for Recurrent/Metastatic Non-Small Cell Lung Cancer (NSCLC): Preliminary Report of a Phase II Study. Proc ASCO 13:336, 1994. Report on 41 patients: 13 of 39 evaluable patients had PRs; median duration of PR was 14 weeks (from first documentation of PR to disease progression). Grade 3/4 neutropenia occurred in 97% of patients, with febrile neutropenia in 17%. Other major toxicities include: HSR, cumulative fluid retention syndrome, dermatitis, asthenia. Authors conclude safety profile is "acceptable".

Fossella FV, Lee JS, Murphy WK, et al. Phase II Study of Docetaxel for Recurrent or Metastatic Non-Small Cell Lung Cancer. J Clin Oncol 12:1238-1244, 1994.
Final published report of the TAX232 trial. In the discussion, the authors point out that "early recognition" and "timely initiation of diuretics" will be important in the management of fluid retention. Potential predisposing factors in patients in this study were: preexisting pleural effusion (8 patients), pleural metastases (1 patient), prior thoracotomy (3 patients), and prior chest irradiation (7 patients).

6.16 Sponsor's Conclusions

The sponsor states that the overall response rate of 31.7%, median response duration of 19 weeks, and median time to progression of 14 weeks observed in previously untreated NSCLC patients are remarkable considering the experience with active platinum-based regimens in this disease. RPR's review of the literature indicates that CDDP, vindesine, vinblastine, mitomycin C and ifosphamide each have single agent activity > 15%, and that the mitomycin C/vinblastine/CDDP regimen produces a 20% response rate as first line therapy in NSCLC. The sponsor points out that the median time to progression of 14 weeks speaks to the therapeutic benefit of docetaxel for patients with stable disease.

RPR states that the feasibility of the recommended dose and schedule was confirmed in this study. The relative dose intensity of 0.97 shows that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with vinca alkaloids and taxoids were seen with docetaxel: neutropenia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, nail disorders, and anemia. These were mild in general, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, only 10 patients experienced febrile neutropenia. There were 11 patients with infection, of which 6 were treatment-related.

Serious toxicities were febrile neutropenia and neutropenic infection, dehydration related to vomiting, and pleural effusion. There were two drug-related deaths, one due to neutropenic pneumonia and the other due to supraventricular tachycardia and hypotension.

Hypersensitivity reactions lead to treatment discontinuation in one patient, although in most cases patients were able to complete their infusions after the reaction had resolved with or without intervention.

Fluid retention was unexpected as it was rarely reported in the phase I studies. Two patients discontinued treatment, one of which was a PR. This toxicity compromised treatment for 4.9% of patients.

The risk:benefit ratio is in favor of docetaxel in patients with untreated NSCLC. Premedication will be given in subsequent studies to control fluid retention and HSRs.

6.17 Reviewer's Conclusions

The reviewer agrees with RPR that the overall response rate of 31.7% in previously untreated patients with NSCLC is very promising, given the efficacy of earlier chemotherapy regimens in these same patients. Note that in the TAX270 trial conducted by the same investigator, NSCLC patients were enrolled with prior therapies: only 3/26 patients had a PR to VP16/CDDP (11.5% response rate) and 0/8 responded to VP16/carboplatin.

The hematologic toxicities of docetaxel are consistent with those reported for other taxoids and with the experience in the breast cancer pivotal trials. Again, the incidence of grade 3 or 4 neutropenia among patients is extremely high (97%), but the incidence of febrile neutropenia was only 24%. While the overall incidence of infections was low, 57% of episodes of infection (4/7) were associated with grade 3 or 4 neutropenia.

Fluid retention caused treatment discontinuation of docetaxel treatment in 2/41 (5%) of patients in this trial. Note that fluid retention compromised treatment for 2/13 (15%) responders, and for at least 9/41 (22%) patients in this trial. The median cumulative dose of docetaxel at onset of fluid retention, 305 mg/m^2, was strikingly similar to that found in previously treated NSCLC patients enrolled by the same investigator in the TAX270 trial (314 mg/m^2). Note that in the breast cancer pivotal trials, the median cumulative dose at onset of fluid retention was higher at 540, 400, and 400 mg/m^2 for TAX233, TAX267, and TAX221, respectively. Pre-existing cardiopulmonary conditions, including tumor-related pleural effusions may have contributed to the development of fluid retention in some of these patients.

The reviewer agrees that management of acute HSRs was not treatment limiting. Neurotoxicity was not a serious clinical problem. The asthenia syndrome was fairly common but not well described in the study report.

Based on the information presented for this single institution trial, the reviewer finds that any conclusion on the risk/benefit ratio for docetaxel in the first line therapy of patients with locally advanced or metastatic NSCLC would be premature. Please refer to Section 6.47 (following the review of the TAX trial) for the reviewer's final conclusions. The reviewer does not agree that this study has demonstrated any significant benefit to use of dexamethasone 16 mg PO x5 days as premedication in the prevention of severe fluid retention.

6.2 TAX269

6.21 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Non-Small Cell Lung Cancer Previously Untreated with Cytotoxic Chemotherapy.

Investigators: H Burris MD, Cancer Therapy and Research Center, San Antonio, TX
T Dobbs, MD, Baptist Regional Cancer Center, Knoxville, TN
P Eisenberg, MD, Marin Oncology Associates, Ross, CA

Study Dates: 6/29/92 - 7/6/93
Data Cut-off Date: 10/31/93
Database Frozen: 6/24/94

Review of Protocol Amendments:

Four major amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (5/12/92): Same as TAX232

Amendment 2 (9/18/92): Same as TAX232

Amendment 3 (5/17/93): Pretreatment with diphenhydramine 50 mg IV 30 minutes prior to docetaxel infusion and dexamethasone 8 mg bid PO for 5 days starting 1 day prior to docetaxel was mandated for all patients. Patients who are already receiving steroids for treatment or prevention of side effects should continue their regimen.

Amendment 4 (1/25/94): This amendment permitted the retreatment of patients who were CRs or PRs but who had withdrawn for reasons other than disease progression or HSR. (Same as TAX232)

Design:

This was a multicenter, open label phase II trial in patients with locally advanced or metastatic NSCLC previously treated with platinum based chemotherapy. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of

response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in patients with NSCLC cancer.

Patient Population:

The inclusion and exclusion criteria are identical to those for TAX232 (see appendix). In brief, eligible patients were male or female, over 18 years, with histologic proof of metastatic NSCLC. They must have at least one bidimensionally measurable lesion, a life expectancy of $\geq$ 12 weeks, and a baseline Karnofsky PFS $\geq$ 60%. No prior chemotherapy was permitted.

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. The overall procedure for drug administration is the same as for TAX270.

No prophylactic use of antiemetics, colony-stimulating factors, or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 3, however, pretreatment with diphenhydramine and dexamethasone prior to infusions was mandated.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Guidelines for dose reductions were the same as in TAX232.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray; radionuclide scans, CT scans were to be repeated at the end of every 2 cycles. **Comments:** *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not define any quality of life measures.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued.

6.22 Study Conduct

The TAX269 trial was sponsored by RPR. Patients were accrued to three centers in the US (34 were treated at San Antonio, 2 at Knoxville, TN, and 12 at Ross, CA). The study was monitored by the Quality Assurance Department of RPR and all case report forms were processed by RPR. The database was frozen on 6/24/94.

6.23 Efficacy Results

Eligibility:

Forty-eight patients were entered: 7 patients were ineligible and 3 nonevaluable for response; hence, 38 patients were evaluable for efficacy. All 48 patients were evaluable for toxicity. The reasons for ineligibility were: no baseline lesion meeting minimum size requirements in 4, patient's unique target lesion was previously irradiated in 1, brain metastases in 1, and prior endometrial cancer in 1 patient. Three additional patients were nonevaluable for response because 2 died and 1 withdrew consent before tumor measurements were made.

Patient Withdrawals:

Twenty-five patients withdrew for disease progression, eight died, one withdrew consent, one was lost to follow-up, one received additional chemotherapy from another physician, and nine patients were on study as of 10/31/93. Among the 3 patients withdrawn due to toxicity, 1 had grade 3 neurotoxicity, 1 had severe asthenia, and 1 had severe pleural effusions.

Patient Characteristics:

The median age of the 48 patients was 64 years (range 40-79 years). The median baseline Karnofsky performance status was 90%. The male/female ratio was 1.5. The most frequently diagnosed histologic subtype was adenocarcinoma. The median time from first diagnosis to first infusion of docetaxel was 1.4 months. Thirty-nine patients had metastatic disease, 9 had locally advanced disease. One-quarter had one organ involved, the rest had

$\geq$ 2 organs involved. The lung was the major site of involvement (92%), with regional lymph nodes and pleura the next most common sites (in 31 and 25% of patients). Eleven patients had undergone surgery, 13 had radiation only, 4 had surgery and radiation, and 24 had no prior therapy. **Concomitant medical conditions included 3 patients with a history of cardiac arythmias and 5 patients with hypothyroidism. Comment:** *Given the descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice.*

Drug Delivery:

A total of 224 cycles were administered: 167 (75%) at the initial planned dose of 100 mg/m^2, and 46 (21%) at 75 mg/m^2. The median number of cycles was 5 (range 1-9). Eighteen patients had at least one dose reduction and 27 had at least one dose delay. Non-hematologic toxicities were the principal cause of treatment delays; non-hematologic and hematologic toxicities contributed to the dose reductions in patients.

The median cumulative dose administered for all patients was 431 mg/m^2 (range 96-840); median dose intensity given was 31.5 mg/m^2/week; and the median relative dose intensity was 0.95 (range 0.5-1.1). For patients receiving < 5 cycles, the RDI was 0.87 or greater; for patients receiving > 5 cycles, the RDI = 0.78, indicating that most patients had a dose reduction after four cycles.

Sixteen patients received premedication with diphenhydramine 50 mg IV 30 minutes prior to the docetaxel infusion + dexamethasone 8 mg PO bid x 5 days; 16 patients received only diphenhydramine 50 mg IV prior to the infusion; and 16 patients received no premedication.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 48 patients included in the intent to treat analysis, there were no CRs and 13 PRs for an overall response rate of 27%. Ten responders were treated at San Antonio, 2 at Ross, CA, and 1 at Knoxville, TN. Nineteen had stable disease, 10 had progressive disease, and six were not evaluable. Nine responders had metastatic disease to one or two organ sites only; all responders had a Karnofsky PFS of $\geq$ 80%. **Comment:** *The reviewer agrees with the overall response rates given.*

Comments: *The table below summarizes the 13 partial responses noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.107.7 - 8.107.72. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensional indicator lesion at baseline that met the protocol-defined size requirements (2 cm x 2 cm for lesions on CT scan or ultrasound; 1 cm x 1 cm for lesions on chest xray or physical exam) except for patient 457 (no lesion) and for*

patients *whose lesions were slightly undersized. Note that patients had major responses in a lesion ≥ 5 cm (in lung, liver and lymph nodes).*

RESPONSES (ITT) - TAX269

Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
Burris:	Lung*	35
	Lung	29
	Lung (1, 2*, 3*)	28
	Lung (2)*	32+
	Lung	24
	Lung (1, 2*, 3)	25
	Lung, Lt adrenal mass	18
	Lung*	25+
	Parasternal lymph node	19+
	Lung*, liver (1, 2*)	18
Dobbs:	Lung*	18
Eisenberg:	Lung*	19+
	Lung, mediastinal lymph nodes (1*, 2*, 3, 4, 5*), palpable neck node	19+

- **Response Duration**

The median duration of response in all 13 responding patients (intent to treat analysis) was 28 weeks. **Five of 13 responders were censored due to no documentation of progression before the cut-off date. Comment:** *The reviewer cannot reconcile the response duration for patient of 48 weeks in Table 4.03b of the study report (8.103.114) with the information in Table 28 of the data listings which indicates a 35% increase in the size of the sole indicator lesion in the lung at 35 weeks. The reviewer accepts the sponsor's response durations for the remainder of the patients.*

- **Other Endpoints**

The median time to first response was calculated to be 6 weeks (range 4-13 weeks). The median time to progression was 17 weeks among all treated patients (11/48 patients were censored, 10 due to no documentation of progression before the cut-off date, and 1 patient who received further therapy before progression). The median survival time for all treated patients was 7 months (26 patients patients were alive at the cut-off date). Comment: *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting.*

- **Quality of Life Assessments**

Table 6.99 of the study report (8.103.310 - 8.103.316) reveals that there was no significant change in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 48 at baseline to 29 at cycle 4 and to 18 at cycle 6. Comment: *Review of PFS values for all patients by cycle, including end of study assessments (Table 12 of data listings, 8.104.119 - 8.8104.196), revealed 8 patients with $\geq$ 30% decline in PFS over baseline while on the study. Note that patient experienced an increase in PFS from 70% at baseline to 100% at cycle 2, returning to 80% at cycle 4.*

Table 6.96a of the study report (8.103.295) presents the evolution of tumor-related pain for 16 patients tracked through cycle 4. Three patients were noted as improved, 8 as unchanged, and 5 as worsened. In addition, analgesic use was recorded in Table 32 of data listings, 8.108.7 - 8.108.57. Four of 27 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement, fourteen had essentially no change in requirement, and nine had worsening as demonstrated by the use of additional and/or stronger analgesics. Two of the patients with an improvement in tumor-related pain and analgesic requirement were also PRs (patients .

Tumor-related symptoms consisted primarily of cough, hemoptysis, dyspnea, anorexia, fatigue, and pain at one or more sites. Tables 6.97a and b of the study report (8.103.303 - 8.103.305) present the evolution of tumor-related symptoms for 17 patients tracked through cycle 4. One patient had improvement in fatigue, two patients had improvement in dyspnea, and three patients had improvement in cough . Of these, only patient is a PR.

Comment: *The reviewer examined Table 23 of the data listings (8.106.215 - 8.106.247) which recorded tumor-related symptoms for 39 patients at baseline but only for 3 patients at cycle 4. Despite this the following symptoms were reported as "Recovered or Recovered with Sequelae", even though they were graded as mild to moderate in severity at recovery:*

Tumor-Related Symptom	Patient Number	Tumor-Related Symptom	Patient Number
Anorexia		Fatigue	
Peripheral Edema		Pain (all sites)	
Dyspnea		Cough/ Hemoptysis	

A likely explanation for the discrepancy in findings between the study report and data listings is that the latter showed improvements in any and all symptoms, even those lasting 1 or 2 cycles. **Note that of the 16 patients with any improvement in tumor-related symptoms, only 3 are PRs ! This suggests that some patients may have had transient symptomatic benefit from treatment, even without achieving a major tumor response.**

6.24 Safety Results

Of the 48 treated patients, the most frequent possibly or probably related AEs were: anemia (46 patients), leukopenia and granulocytopenia (42 patients each), alopecia (36 patients), asthenia (30 patients), neurosensory (29 patients), skin (26 patients), fever in the absence of infection (21 patients), fluid retention (22 patients), diarrhea (19 patients), nausea (18 patients), febrile neutropenia and stomatitis (16 patients each), allergy (14 patients), neuromotor (13 patients), and vomiting (10 patients).

Overall, 38 patients experienced serious AEs. Eight patients died within one month of treatment, 17 died more than one month later. **Comment:** *Of the 8 early deaths, 3 were complicated by docetaxel-related infections, and 1 by docetaxel-related pericardial effusion.*

- **Acute Hematologic Toxicities**

Leukopenia was observed in 42/44 patients and was grade 3 or 4 in 77%. Forty-one patients (93%) had grade 3 or 4 neutropenia. There was no difference in the incidence of grade 3 and 4 neutropenia between cycles at 100 or 75 mg/m^2. The median neutrophil nadir was 0.2 x 10^3/mm^3 (range 0.0-5.1) and the median time to nadir was 7 days (range 6-13). The median neutrophil nadir was no different for the 100 or the 75 mg/m^2 dose. No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was only 4 days; no cycle failed to show recovery of neutrophil count by day 22$\pm$3.

Thrombocytopenia was observed in 3 patients. One patient had grade 4 toxicity.

Anemia was observed in 46/48 patients, and was grade 3 in three patients and grade 4 in two

patients. Seven patients received blood product support.

Febrile neutropenia (fever $\geq$ 38°C with grade 3 or 4 neutropenia) occurred in 16 patients and 20 cycles. In addition, one episode of grade 3 or 4 neutropenia with grade 1 fever requiring IV antibiotics was considered serious. There were six treatment-related infections, 5 of which occurred in patients with grade 4 neutropenia.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Fourteen patients experienced 28 episodes of docetaxel-related HSR; no episode was grade 4. Premedications were given prior to 23 of these episodes: diphenhydramine only in 7, dexamethasone only in 1, and diphenhydramine + dexamethasone in 15. Most reactions occurred during the infusion, often within the first fifteen minutes of the infusion, manifested by flushing and chest tightness, followed by rash, hypertension, dyspnea, diarrhea, nausea and vomiting.

Nausea was observed in 18 patients, and was grade 3 in three patients and grade 4 in one. Vomiting occurred in 10 patients, and was grade 4 in one. After cycle 1 prophylaxis was permitted and treatment-related nausea/vomiting became infrequent. Diarrhea occurred in 19 patients, and was grade 3 in two patients. Stomatitis occurred in 16 patients, and was grade 1 or 2 only.

Eight patients had treatment-related cardiac abnormalities: hypotension was associated with atrial flutter (patient . . with an HSR (patient , and with sepsis, congestive heart failure and death (patient

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 22 patients, and was severe in 5. Eleven patients had peripheral edema only, while 8 had pleural effusions and 1 had a pericardial effusion. Patient a partial responder, discontinued treatment after cycle 8 due to severe bilateral pleural effusions. The median cumulative dose to onset of fluid retention was 473 mg/m^2. Weight gain was not related to fluid retention.

Comment: *The table below summarizes premedications administered to 5 patients who had severe fluid retention. (See Table 31 of data listings, 8.107.122- 8.107.339) All five were treated at San Antonio. The median age of this group was 53 years (range 50-75 years); three were males. Only one had pleural effusions at baseline. No patient had received surgery, three had radiotherapy. Four patients required diuretics. Serum albumin levels $\leq$ 3 g/dl were noted in all; serum creatinine levels were elevated in one patient. There were 3 PRs in this group. The clinical benefit of any one premedication is difficult to discern.*

USE OF ANTIHISTAMINES AND CORTICOSTEROIDS IN FIVE PATIENTS EXPERIENCING SEVERE FLUID RETENTION

Patient	Medication	Cycle	Indication
	None	-	-
	Prednisone 20 mg PO qd Benadryl 25-50 mg IV + Dexamethasone 20 mg IV + Dexamethasone 16 mg PO x5d Zantac PO	0 to 6 1 to 5 2, 3, 4, 6 5 only 5 only	Cough Prophylaxis GI Prophylaxis
	Decadron PO qd Benadryl PO, IV Benadryl 50 mg IV + Dexamethasone 20 mg IV Tagamet PO, IV	0, 1 1, 2 2 only 1, 2	Brain Metastases Sleep Prophylaxis GI Prophylaxis
	Benadryl 25-50 mg IV + Dexamethasone 4-16 mg PO x5d	1 to 5 3, 4, 5	Prophylaxis
	Benadryl 25 mg IV + Dexamethasone 16 mg PO x5d	2 to 7 2, 3, 5, 7	Prophylaxis

Skin toxicity occurred in 26 patients and was grade 4 in three. Signs included erythema, pruritus, dry skin, maculae, and papulae. Nail disorder was observed in 9 patients and was associated with skin changes in 6. One patient had a severe reaction (onycholysis). Alopecia occurred in 36 patients.

Neurosensory toxicity was noted in 29 patients, and was grade 1 or 2 only except for three patients with grade 3 toxicities. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Thirteen patients experienced neuromotor signs, grade 3 in 6. **Only 7 patients had specific neuromotor problems, the rest could be considered to have asthenia.** Asthenia was recorded for 30 patients and was severe in twelve.

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: SGOT (16 patients), SGPT (13 patients), total bilirubin (7 patients), alkaline phosphatase (17 patients), hypomagnesemia (9 patients), hypocalcemia (13 patients). There was one case of hypercalcemia (grade 4). Six patients developed increased creatinine levels (grade 1-2 only).

- **Deaths on Study**

There were 8 deaths on study, as shown below. **Comment:** *Death was complicated by docetaxel-related toxicities in 4 patients; this is not clearly reflected in Tables 9, 10, and 40 of the study report (8.101.63, 8.101.64, 8.101.113).*

Patient Number	Cause of Death
	Grade 4 neutropenia; bronchial obstruction by tumor, cycle 3
	Grade 4 neutropenia; bronchial obstruction by tumor and docetaxel-related pneumonia, cycle 4
	Pneumonia with leukocytosis, disease progression, cycle 2
	Docetaxel-related infection with renal and respiratory failure, cycle 2
	Cardiopulmonary arrest, cycle 8
	Grade 4 neutropenia, increased docetaxel-related pericardial effusion, disease progression, cycle 1
	Grade 4 neutropenia, pulmonary and peripheral edema, disease progression, cycle 1
	Grade 4 leukopenia, docetaxel-related sepsis, cycle 1

6.25 Publications/ Abstracts

Burris H, Eckardt J, Fields S, et al. Phase II Trials of Taxotere in Patients with Non-small Cell Lung Cancer. Proc ASCO 12:335, 1993. Preliminary report of chemotherapy-naive and previously-treated (with cisplatin) patients with NSCLC: 3 PRs out of 14 chemotherapy-naive patients, and 3 PRs out of 15 previously-treated patients were noted. Toxicities included grade 4 neutropenia, that was brief and well-tolerated, mild dermatitis, localized fluid accumulations, and brief anaphylactoid reactions responsive to diphenhydramine.

6.26 Sponsor's Conclusions

RPR points out that the partial response rate of 27% for docetaxel as first line therapy in patients with locally advanced or metastatic NSCLC is remarkable. The response duration of 28 weeks for docetaxel in these patients also serves to confirm its activity as a single agent.

The feasibility of the recommended dose and schedule was confirmed in this study. The relative dose intensity of 0.95 shows that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with vinca alkaloids and taxoids were seen with docetaxel: neutropenia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, nail disorders, and anemia. These were mild in general, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, only 3 patients required treatment delays. Sixteen patients experienced febrile neutropenia. There were 6 drug-related infections, however, infection is a well-recognized complication of lung cancer.

Serious toxicities were: neutropenic infection, HSRs, hypotension, and pleural effusion. There were two drug-related deaths, one due to neutropenic pneumonia and the other due to supraventricular tachycardia and hypotension.

Hypersensitivity reactions did not lead to treatment discontinuation, and in most cases patients were able to complete their infusions after the reaction had resolved with or without intervention.

Fluid retention was unexpected as it was rarely reported in the phase I studies and was cumulative. No patient discontinued treatment because of this toxicity. Note that both pleural and pericardial effusions are known complications of lung tumors.

The risk:benefit ratio is in favor of docetaxel in patients with untreated NSCLC.

6.27 Reviewer's Conclusions

The reviewer agrees that the overall response rate of 27% in patients previously untreated with chemotherapy in this multicenter trial is optimistic, and surprisingly similar to that reported for the single institution TAX232 trial (31.7%).

The median response duration as defined by the investigator leads to an inflated value since it includes time to first response. Hence, the true duration of a PR in this trial is probably closer to 20 rather than 30 weeks. The sponsor's contention of clinical benefit to patients with disease stabilization must be weighed against docetaxel's safety profile. Review of PFS values, analgesic use, and tumor-related symptoms failed to show any demonstrable benefits to docetaxel treatment, although transient symptomatic improvement of tumor-related

symptoms was observed in a third of patients.

Four of eight deaths on study (within 30 days of last infusion) were apparently complicated by docetaxel-related toxicities, infections in patients and pericardial effusion in patient This incidence is somewhat higher than that reported by these same investigators in previously-treated NSCLC patients (3/9 deaths were docetaxel-related in TAX271), and much higher than that reported by the MD Anderson Cancer Center in previously untreated or previously treated NSCLC patients (1 toxic death each in TAX232 and TAX270).

The hematologic toxicities of docetaxel are consistent with those reported for other taxoids and with the experience in the breast cancer pivotal trials. The incidence of grade 3 or 4 neutropenia in patients is extremely high (93%), but the incidence of febrile neutropenia was low at 35%. While the overall incidence of infections was also low, 5/6 (83%) of episodes of infection were associated with grade 3 or 4 neutropenia. Note that the incidence of febrile neutropenia and of grade 3/4 neutropenia with infection reported in this trial is higher than that reported for the TAX232 trial and for the two trials in previously treated NSCLC patients (TAX270 and TAX271), and may explain, in part, the reason for the higher mortality in this trial.

Fluid retention caused treatment discontinuation of docetaxel treatment in patient 453 in this trial. Note that RPR's conclusion that no patients withdrew from treatment due to fluid retention contradicts their statement on page 8.101.64 of the study report. The median cumulative dose of docetaxel at onset of fluid retention, 476 mg/m², was in keeping with that reported by these same investigators for previously-treated NSCLC patients (497 mg/m², TAX271) and with that reported in the breast cancer pivotal trials (the median cumulative dose at onset of fluid retention was 540, 400, and 400 mg/m² for TAX233, TAX267, and TAX221, respectively).

The reviewer agrees that management of acute HSRs was not treatment limiting. Neurotoxicities did not appear to be unmanageable.

Patients with unresectable or metastatic NSCLC are typically treated with a first line chemotherapy regimen for palliation, although use of chemotherapy as first line therapy for these patients remains controversial. Despite the promising single agent activity demonstrated in these two phase II trials, well-controlled, randomized clinical trials would be required to fully evaluate docetaxel as a first line agent in the setting of metastatic or locally advanced NSCLC. Such trials should focus heavily on quality of life issues defined in a prospective manner. The benefit of premedication(s) in the prevention of severe fluid retention should also be evaluated. Based on the information presented for the two pivotal trials in previously-untreated NSCLC patients, TAX232 and TAX269, the reviewer does not agree that the risk/benefit ratio favors docetaxel for approval.

6.3 TAX231

6.31 Protocol Review

Title: Phase II Trial of RP 56976 in Patients with Stage III or IV Non-Small Cell Lung Cancer Previously Untreated with Cytotoxic Chemotherapy.

Investigators: J Rigas, MD, Memorial Sloan Kettering Cancer Center, New York, NY

Study Dates: 5/24/92 - 7/28/93
Data Cut-off Date: 10/31/93

Review of Protocol Amendments:

Five major amendments were incorporated into the protocol. These primarily addressed the prophylaxis regimen for anaphylactoid reactions. The original protocol contained no provision for HSRs (hypersensitivity reactions) since in European trials, the incidence and severity of HSRs (21% mild/moderate, 2% severe) were considered acceptable.

Amendment 1 (6/10/92): For anaphylactoid reactions of grade 1, 2, 3 (by NCI Toxicity Criteria), treatment with dexamethasone 10 mg IV and diphenhydramine 50 mg IV will be permitted 30 minutes prior to resumption of an interrupted docetaxel infusion. For grade 4 reactions, the patient will go off study.

Amendment 2 (9/18/92): Same as TAX232, TAX269

Amendment 3 (6/15/93): The dose level was reduced from 100 to 75 mg/m² for the last 20 patients enrolled in the study, and two dose reductions per patient (75 to 55 mg/m² and 55 to 40 mg/m²) were permitted. Pretreatment with prednisone 50 mg PO bid was required, starting the day before docetaxel and continuing for two days after the infusion.

Amendment 4 (7/9/93): The total number of patients was increased from 40 to 49; ranitidine was permitted as treatment for anaphylactoid reactions.

Amendment 5 (1/25/94): This amendment permitted the retreatment of patients who were CRs or PRs but who had withdrawn for reasons other than disease progression or HSR. (Same as TAX232, TAX269)

Design:

This was a single institution, open label phase II trial in patients with locally advanced or metastatic NSCLC previously treated with platinum based chemotherapy. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m² IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) estimate the objective response rate and duration of response, 2) determine the toxicity and reversibility of toxicity, and 3) determine the pharmacokinetics of docetaxel in patients with NSCLC cancer.

Patient Population:

The inclusion and exclusion criteria are similar to those for TAX232 (see appendix). In brief, eligible patients were male or female, over 18 years, with histologic proof of metastatic NSCLC, confirmed at MSKCC. Patients must have a life expectancy of $\geq$ 12 weeks, and a baseline Karnofsky PFS $\geq$ 60%. No prior chemotherapy was permitted. Patients may have measurable or evaluable lesion(s) which have not been radiated; examples of evaluable lesions are confluent lung or skin metastases. Patients who have only ascites, pleural effusions, bone, brain or leptomeningeal metastases, or elevated serum enzymes as sole indicator lesions will be excluded. **Comment:** *This is the only pivotal trial which enrolled patients on the basis of evaluable disease.*

Procedure:

Docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks was administered to the first 29 patients, 75 mg/m^2 IV over 1 hour every 3 weeks to the last 20 patients. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. The overall procedure for drug administration was the same as for TAX232 and TAX269.

No prophylactic use of antiemetics, colony-stimulating factors, or antiallergics was permitted prior to the initial infusion. Following the acceptance of amendment 3, however, pretreatment with pednisone prior to and following infusions was mandated.

If patients demonstrate a CR, PR, or stable disease, treatment will continue until there is evidence of disease progression or unacceptable toxicity. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient. Guidelines for dose reductions were the same as in TAX232 and TAX269, except, that dose reductions were permitted for grade 3 neutropenia (in addition to grade 4 neutropenia) when associated with fever requiring IV antibiotics (described in Amendment 1).

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. For measurable indicator lesions, a CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions.

Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion.

For evaluable indicator lesions, assessment of response by at least two reviewers was required. A CR was defined as disappearance of all tumor for a minimum of 4 weeks. A PR was noted if there was a decrease of 50% in the diameter for unidimensional lesions or any decrease in the size of the lesion for a minimum of 4 weeks. Progressive disease was defined as unequivocal worsening of any evaluable lesion or the appearance of a new lesion.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination or chest xray; radionuclide scans, CT scans were to be repeated at the end of every 2 cycles. **The primary clinical endpoint was the objective response rate defined as % CR + % PR + % Improvement.** Secondary endpoints were the number of cycles to maximal response, duration of response, changes in performance status, pre-existing symptoms, and analgesic use. **Comments:** *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 20 patients would be accrued. As a result of the decision to lower the initial dose to 75 mg/m² to avoid toxicity at the higher dose (Amendment 3), the sample size was increased to 49 patients (Amendment 4). This would allow treatment of 20 patients at the lower dose. "While this will not be a sufficient number to precisely define the response rate at the lower dose, it will give enough descriptive information to suggest whether further evaluation of the lower dose is warranted."

6.32 Study Conduct

The TAX232 trial was sponsored by RPR. Patients were accrued to a single center in the US (Memorial Sloan Kettering Cancer Center). The study was monitored by RPR and all case report forms were processed by RPR. All responses reported by the investigator were reviewed by an independent panel; the experts' judgment of response is reported.

6.33 Efficacy Results

Eligibility:

Forty-nine patients were entered: 2 patients were ineligible and 4 nonevaluable for response; hence, 45 patients were evaluable for efficacy. All 49 patients were evaluable for toxicity. Two patients were ineligible due to absence of baseline radiographic studies, and two additional patients were nonevaluable because of incomplete tumor measurements.

Patient Withdrawals:

Twenty-nine patients withdrew for disease progression, four died (one due to toxicity, two due to disease progression, and one due to cardiac arrest), two withdrew consent, and 1 was lost to follow-up. Six patients were on study as of 10/31/93. Among the 7 patients withdrawn due to toxicity, 2 were thought to be unrelated to study drug (anxiety and dyspnea in 1 patient each), 2 had mild paresthesias, one had skin toxicity/possible extravasation, one had persistent grade 3 hyperbilirubinemia despite dose reduction, and one had a grade 2 HSR. Of the 3 patients who withdrew consent or were lost to follow-up, 2 had allergic reactions and dyspnea, and the third experienced hemorrhage due to severe esophagitis.

Patient Characteristics:

The median age of the 49 patients was 60 years (range 42-77 years). The baseline Karnofsky performance status was 60-70% in 49% of patients (62% of patients in the high dose group and 30% of patients in the low dose group had PS values of 60-70%). The male/female ratio was 1.5. The most frequently diagnosed histologic subtype was adenocarcinoma. The median time from first diagnosis to first infusion of docetaxel was 1.5 months. Forty-two patients had metastatic disease, 7 had locally advanced disease. Only 16% of patients had one organ involved, and the rest had $\geq$ 2 organs involved. The lung was the major site of involvement (94%), with regional lymph nodes and pleura the next most common sites (59 and 53%, respectively). Eight patients had undergone surgery only, 11 had radiation only, four had surgery and radiation, and 38 had no prior therapy. Concomitant medical conditions included 10 patients with history of drug allergy/ asthma, and 12 patients with a history of cardiovascular disease (including coronary artery disease in 7 and arrthmias in 4). Comment: *Given the descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice.*

Drug Delivery:

A total of 219 cycles were administered: 76 (35%) at the initial planned dose of 100 mg/m^2, and 97 (44%) at 75 mg/m^2. The median number of cycles was 3 (range 1-15) for the 100 mg/m^2 group; 11 patients had at least one dose reduction and 8 had at least one dose delay. Three patients in this group discontinued treatment due to toxicity. The median number of

cycles was 3.5 (range 1-10) for the 75 mg/m^2 group; 6 patients had at least one dose reduction and 7 had at least one dose delay. Four patients in this group discontinued treatment due to toxicity. Non-hematologic toxicities more frequently accounted for treatment delays in patients treated at 100 mg/m^2. Both hematologic and non-hematologic toxicities resulted in dose reductions.

The median cumulative dose administered for all patients was 300 mg/m^2 (range 75-1069); median dose intensity given was 25 mg/m^2/week; and the median relative dose intensity was 0.98 (range 0.6-1.0). Overall, 41 patients achieved an RDI of > 0.7 in this trial.

At the high dose, 16 patients received no premedication for the first cycle, 12 received diphenhydramine only, and one patient continued on their prestudy regimen of dexamethasone. At the low dose, all 20 patients received the Prednisone premedication regimen as per Amendment 3.

Efficacy Results:

- **Tumor Response Rate**

Among the 49 patients included in the intent to treat analysis, there were no Crs, 10 Prs, and 5 improvements for an overall response rate of 30.6% (CI: 18-45%). **Eight of the 10 PRs received 100 mg/m^2.** Seventeen had stable disease, 13 had progressive disease, and four were not evaluable. Considering only the partial responses, the overall response rate for all treated patients decreases to 20.4%. Among the 29 patients who received the 100 mg/m^2 dose, the overall response rate was 34.5% or 27.6%, excluding improvements. There were no clear differences in response rates when patients were analyzed by number of organs involved, by PFS or by histology. Nine of the 10 responders had metastatic disease, 5 of 10 responders had a Karnofsky PFS of 60-70%. **Comment:** *The reviewer agrees with the overall response rates given. Note that this is the only pivotal trial that includes improvements in the calculation of the overall response rate. The frequency of responses among patients with lower PFS values (60-70%) is encouraging.*

Comments: *The table below summarizes the 10 partial responses and 5 improvements noted in the intent to treat population as recorded in Table 28 of Data Listings, 8.93.218 - 8.93.307. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensional or evaluable indicator lesion at baseline that met protocol-defined size requirements. Note that patients had major responses in a lesion $\geq$ 5 cm (in lung). Patient numbers followed by (I) represent the improvements.*

RESPONSES (ITT) - TAX231

Patient Number	Sites of Response	Response Duration (wks)
	Lung (2)*, lymph node mass*	19
	Lung	15
	Lung (1*, 2)	10
	Lung*, lymph node	23
	Lung	14
	Lung (1, 2*)	26
	Pleural-based mass	25
	Lung*	43+
	Lung (1, 2, 3, 4)	22
	Lung, liver*	41+
	Lung*	22
	Lung masses (2), pleural effusion, interstitial pattern	29+
	Lung masses (3)	26+
	Lung (2)	17+
	Lung, lymph node masses (2)	13+

- **Response Duration**

The median duration of response in all 15 responding patients (intent to treat analysis) was 23 weeks (range 10-43+). Six of 15 responders were censored due to no documentation of progression before the cut-off date. **Comment:** *The reviewer accepts RPR's calculation of response duration.*

- **Other Endpoints**

The median time to first response was 15 weeks (range 3-18). The median time to progression was 11 weeks (range 1-43+ weeks) among all treated patients (11/49 patients were censored, 7 due to no documentation of progression before the cut-off date, and 4

stable disease patients who received further chemotherapy before progression). The median survival time for all treated patients was 7 months (21/49 patients were censored). **Comment:** *These additional efficacy endpoints were not protocol-defined objectives. Survival, in particular, is of limited value in the phase II setting. Despite this, it is encouraging to note that 5 responding patients treated with the 100 mg/m² dose were alive more than 1 year after study entry (see Francis et al., JCO, 1994).*

- **Quality of Life Assessments**

Table 6.99 of the study report (8.88.305 - 8.88.312) reveals that there was no significant change in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 49 at baseline to 23 at cycle 4 and to 13 at cycle 6. No patient ever had a PFS of 100%. **Comment:** *Review of PFS values for all patients by cycle, including end of study assessments (Table 12 of data listings, 8.91.122 - 8.91.197), revealed 2 patients with a 30% decline in PFS over baseline while on the study.*

Table 6.96a of the study report (8.88.285 - 8.88.286) presents the evolution of tumor-related pain for 15 patients tracked through cycle 4. Two patients were noted as improved, 12 as unchanged, and 1 as worsened. In addition, analgesic use was recorded in Table 32 of data listings, 8.94.193 - 8.94.232. Six of 16 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement, eight had essentially no change in requirement, and two had worsening as demonstrated by the use of additional and/or stronger analgesics. Four of the patients with an improvement in tumor-related pain and/or analgesic requirement were also responders (patients

Tumor-related symptoms consisted primarily of cough, hemoptysis, dyspnea, anorexia, fatigue, and pain at one or more sites. Tables 6.96b, c, d, and 6.97 of the study report (8.88.289 - 8.88.299) present the evolution of tumor-related symptoms for 21 patients tracked through cycle 4. Two patients had improvement in fatigue, six patients had improvement in dyspnea, and four patients had improvement in cough Of these, patients are responders.

Comment: *The reviewer examined Table 23 of the data listings (8.93.17 - 8.93.76) which recorded tumor-related symptoms for 49 patients at baseline but only for 5 patients at cycle 4. Despite this the following symptoms were reported as "Recovered or Recovered with Sequelae", even though they were graded as mild to severe at recovery:*

Tumor-Related Symptom	Patient Number	Tumor-Related Symptom	Patient Number
Anorexia		Fatigue	
Cough/ Hemoptysis		Pain (all sites)	
Dyspnea/ Wheeze		Fevers/ Sweats	

A likely explanation for the discrepancy in findings between the study report and data listings is that the latter showed improvements in any and all symptoms, even those lasting 1 or 2 cycles. **Note that of the 22 patients with any improvement in tumor-related symptoms, only 11 are responders. This suggests that some patients may have had transient symptomatic benefit from treatment, even without achieving a major tumor response.**

6.34 Safety Results

Of the 49 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (45 patients each), alopecia (40 patients), anemia (38 patients), allergy (36 patients), skin (28 patients), asthenia (24 patients), nausea (22 patients), stomatitis (21 patients), neurosensory (21 patients), fluid retention (20 patients), and fever in the absence of infection (20 patients), diarrhea (19 patients), and vomiting (14 patients). Asthenia was more frequent among patients receiving 100 mg/m^2 (62% of patients) as compared to 35% of patients receiving 75 mg/m^2. **Whether this is related to the lower dose or the routine use of steroids in the latter group is unclear. Fluid retention, however, was equal in frequency in both groups.**

Overall, 32 patients experienced 96 serious AEs, of which 61 were deemed possibly or probably related to study drug. Among these 32 patients, 20 were treated at the high dose, and 12 at the low dose.

- **Acute Hematologic Toxicities**

Leukopenia was observed in 45/47 patients and was grade 3 or 4 in 60%. Forty-one patients (87%) had grade 3 or 4 neutropenia. Out of 189 evaluable cycles (with at least one blood count between days 6-15) 139 (73%) showed grade 3 or 4 neutropenia. There was no significant difference in the incidence of grade 3 and 4 neutropenia between cycles at 100 or 75 mg/m^2. The median neutrophil nadir was 0.6 x 10^3/mm^3 (range 0.0-14.2) and the median time to nadir was 9 days (range 6-15). The median neutrophil nadir was no different for the 100 or the 75 mg/m^2 dose. No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was 7 days; no cycles failed to show recovery of neutrophil count by day 22$\pm$3.

Thrombocytopenia was observed in 3 patients. One patient had grade 3 toxicity.

Anemia was observed in 38 patients, and was grade 3 in two patients and grade 4 in 1. This latter patient (1018) had esophagitis and hemorrhage.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 13 patients and 16 cycles. Twelve of 16 episodes were associated with grade 4 neutropenia. Infections occurred in 6 patients and 7 cycles. Three of 7 episodes of infection were associated with grade 4 neutropenia.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Thirty-six patients experienced 65 episodes of drug-related HSR; 3 episodes were grade 3 and none was grade 4. The frequency of HSRs was identical at both dose levels. All reactions occurred during the infusion, often within the first fifteen minutes of the infusion, manifested by flushing, dyspnea, chest tightness, and back pain. Two patients discontinued treatment due to an HSR (patients The latter patient experienced an HSR despite prophylaxis. **Comment:** *Note that the first 16 patients received no premedication, the next 13 patients received diphnehydramine premedication, and the last 20 patients received Prednisone according to Amendment 3. The incidence of HSRs in these groups was 56%, 61%, and 75%, respectively, suggesting little benefit of premedications in the prevention of HSRs.*

Nausea was observed in 22 patients, and was grade 3 in two patients. Vomiting occurred in 14 patients, but was grade 1 or 2 only. Diarrhea occurred in 19 patients, and was grade 3 in one patient, and grade 4 in another. Stomatitis occurred in 21 patients, and was grade 3 in 2. **Comment:** *Nausea, vomiting, and stomatitis were more frequent in the high dose group.*

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 20 patients, and was severe in only 1. Seven patients had peripheral edema only, while 6 had pleural effusions. No patient discontinued treatment due to fluid retention. Patient was a 55 year old male with a RML mass who had prior thoracotomy but no prior chest irradiation. His course was complicated by severe edema and pleural effusion beginning in cycle 5, despite Prednisone premedication. **There was no difference in the incidence or severity of fluid retention in the high and low dose groups.** The median cumulative dose to onset of fluid retention was 442 mg/m^2 for the 100 mg/m^2 group and 298 mg/m^2 for the 75 mg/m^2 group, corresponding to 4 cycles of treatment in each group. Weight gain was related to fluid retention: all 12 patients with weight gain on study had fluid retention. **Comment:** *Elevated aldosterone levels (> 330 pg/ml) were documented in 2 patients with fluid retention, one of whom also had elevated renin levels, consistent with intravascular volume contraction (see Francis et al., JCO, 1994).*

Skin toxicity occurred in 28 patients and was grade 3 in two. Signs included erythema, pruritus, dry skin, maculae, and papulae. **The incidence and severity of skin toxicity was higher for the patients receiving 100 mg/m^2, however, all but one of these patients received no premedication or diphenhydramine only.** Nail disorder was observed in 12 patients and was mild to moderate. Alopecia occurred in 40 patients with equal frequency in both groups.

Neurosensory toxicity was noted in 21 patients, and was grade 1 or 2 only. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Four patients experienced neuromotor signs, grade 1 or 2 only. Asthenia was seen in 25 patients and was severe in 1. **Neurotoxicity and asthenia were more common in the high dose group.**

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: SGOT (10 patients), total bilirubin (2 patients, both grade 4), alkaline phosphatase (18 patients), hypocalcemia (15 patients), hypomagnesemia (17 patients, grade 4 in 1). Five patients developed increased creatinine levels (none were grade 3).

- **Deaths on Study**

Four patients died within one month of their last drug infusion, including one toxic death. All of these had received the 100 mg/m^2 dose.

Patient Number	Cause of Death
	Cardiac arrest, not drug-related, cycle 1
	Disease progression, cycle 3
	Disease progression, cycle 1
	Docetaxel-related pneumonia with respiratory failure, cycle 3

6.35 Publications/ Abstracts

Francis PA, Rigas JR, Kris MG, et al.: Phase II Trial of Docetaxel in Patients with Stage III and IV Non-Small Cell Lung Cancer. J. Clin. Oncol. 12:1232-1237, 1994. Published report on 29 patients treated with docetaxel 100 mg/m^2: overall response rate was 38%, median duration of response was 5.3 months. Six patients were alive > 1 year from study entry, five of these had a major response to treatment. Discussion section gives comaprison of docetaxel and paclitaxel.

Rigas JR, Francis PA, Kris MG, et al.: Phase II Trial of Taxotere in Non-Small Cell Lung

Cancer. Proc ASCO 12:336, 1993. Preliminary report on 22 patients: overall response rate was 28% in 18 patients. Major toxicities were HSRs, neutropenia, skin rash, sensory neuropathy and fluid retention.

6.36 Sponsor's Conclusions

The partial response rate of 20.5% (or 30.6% for PRs and improved patients) for docetaxel as first line therapy in patients with locally advanced or metastatic NSCLC is remarkable, given the known single agent activity of other cytotoxics used in this setting (CDDP, vindesine, vinblastine, mitomycin C, ifosphamide, and paclitaxel). The sponsor makes reference to three studies (Eagan et al., 1979; Kris et al., 1985; Jett et al., 1989) which have shown that improvement in patients with non-measurable disease is, in fact, equivalent to a partial response. The response duration of 23 weeks for docetaxel in these patients also serves to confirm its activity as a single agent.

The feasibility of the recommended dose and schedule was confirmed in this study. The relative dose intensity of 0.9 shows that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with taxoids were seen with docetaxel: neutropenia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, nail disorders, and anemia. These were mild, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, only 13 patients experienced febrile neutropenia.

Serious toxicities were febrile neutropenia and neutropenic infection. There was one toxic death in a patient who died due to Gram negative pneumonia.

Hypersensitivity reactions lead to treatment discontinuation in two patients, although most patients were able to complete their infusions after the reaction had resolved with or without intervention.

Fluid retention was unexpected as it was rarely reported in the phase I studies. No patient discontinued treatment. No difference in incidence or severity was seen at the two dose levels.

Nausea, vomiting, stomatitis, neurotoxicity, and asthenia were more common in the high dose than in the low dose group; skin toxicity was more common and severe in the high dose group.

The risk:benefit ratio is in favor of docetaxel in patients with untreated NSCLC. The overall response rate is more favorable for the 100 mg/m^2 dose, while the safety profile is more favorable for the 75 mg/m^2 .

- **Reviewer's Conclusions**

There are a number of features unique to this trial which allow some critical observations to be made. First and foremost, there were two different doses, 100 and 75 mg/m², used as initial therapy in previously untreated patients with NSCLC. While other pivotal trials included patients treated at the 75 mg/m² dose, this was as a result of dose reduction after 1 or more cycles at the 100 mg/m² dose.

Although the numbers of patients are too small for a formal comparison of the two dose levels, distinct trends do begin to emerge. Essentially, overall response rates are superior in the high dose group, at the expense of safety. Nausea, vomiting, stomatitis, neurotoxicity, and asthenia were more common in the high dose than in the low dose group; skin toxicity was more common and severe in the high dose group. On the other hand, there was no difference in the incidence of myelosuppression, acute HSRs, fluid retention, or alopecia.

This trial does include patients with, and assesses tumor responses in evaluable lesions. Thus, the overall response rate among the 29 patients who received the 100 mg/m² dose, declines from 34.5% to 27.6% when improved patients are excluded. Among the 20 patients who received the 75 mg/m² dose, the overall response rate declines from 20% to 10% when improved patients are excluded. The response rate for the high dose group is consistent with those reported in previously untreated patients in the TAX232 and TAX269 trials (31.7% and 27%, respectively). The response duration of 23 weeks in this trial falls midway between that reported in the other two trials (19 weeks in TAX232 and 28 weeks in TAX269). The report of 5 responders living more than 1 year after study entry (Francis et al., JCO, 1994) is consistent with the notion that response to treatment correlates with survival, which is critical to the assessment of clinical benefit of this agent. Well-controlled randomized trials should be capable of demonstrating efficacy, including survival benefit, in the face of acute and chronic toxicity.

The hematologic toxicities of docetaxel are consistent with those reported for other taxoids and with the experience in other pivotal trials in this application. The incidence of grade 3 or 4 neutropenia in patients is extremely high (87%), but the incidence of febrile neutropenia was low at 27%. While the overall incidence of infections was also low, 3/7 (43%) of episodes of infection were associated with grade 3 or 4 neutropenia. There was one toxic death. Note that the incidence of febrile neutropenia, of grade 3/4 neutropenia with infection, and of toxic deaths reported in this trial is consistent with that reported for the TAX232 and TAX223 trials in previously untreated patients and for the two trials in previously treated NSCLC patients (TAX270 and TAX271).

Severe fluid retention was rare in this trial, and caused no patient to discontinue treatment in this trial. This may be related to the lower median number of treatment cycles delivered in this trial compared to the other pivotal trials in breast and lung cancer (3 versus 4-5). Note that the median cumulative dose of docetaxel at onset of fluid retention, 442 mg/m², was in keeping with that reported for previously-treated NSCLC patients (497 mg/m², TAX271) and

for previously untreated patients in the TAX269 and TAX223 trials (476 and 403 mg/m^2, respectively).

The reviewer agrees that management of acute HSRs was not treatment limiting, although the incidence of such reactions was remarkably higher than in any other pivotal trial. The reviewer cannot account for this finding. Neurotoxicities did not appear to be unmanageable.

Patients with unresectable or metastatic NSCLC are typically treated with a first line chemotherapy regimen for palliation, although use of chemotherapy as first line therapy for these patients remains controversial. Despite the promising single agent activity demonstrated in these three phase II trials, well-controlled, randomized clinical trials would be required to fully evaluate docetaxel as a first line agent in the setting of metastatic or locally advanced NSCLC. Such trials should focus heavily on quality of life issues defined in a prospective manner. The benefit of premedication(s) in the prevention of severe fluid retention should also be evaluated. Based on the information presented for the three pivotal trials in previously-untreated NSCLC patients, TAX232, TAX269, and TAX232, the reviewer does not agree that the risk/benefit ratio favors docetaxel for approval.

6.4 TAX223

6.41 Protocol Review

Title: Phase II Trial with Taxotere in Patients with Non-Small Cell Lung Cancer

Investigators: EORTC Early Clinical Trials Group

TH Cerny, MD, Study Chairman, Bern, Switzerland
S Kaplan, Switzerland — C Sessa, Switzerland
P Siegenthaler, Switzerland — M Clavel, France
T Tursz, France — S Aamdal, Norway
AT Van Oosterom, Belgium — SB Kaye, United Kingdom
E Robinson, Israel — A Sulkes, Israel
U Bruntsch, Germany — HJ Schmoll, Germany
AR Hanauske, Germany — N Pavlidis, Greece
WW Ten Bokkel Huinink, The Netherlands

Study Dates: 5/15/92 - 4/4/93
Study Cut-Off Date: 12/31/93
Database Frozen: 3/30/94

Review of Protocol Amendments:

There were no protocol amendments affecting this study.

Design:

This was a phase II multicenter trial in patients with previously untreated NSCLC. The initial planned treatment was docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks.

Objectives:

The primary objectives were to 1) determine if partial or complete responses can be achieved and their duration, if they occur, 2) determine the toxicity of docetaxel, and 3) characterize the pharmacokinetic-pharmacodynamic relationships of docetaxel.

Patient Population:

The inclusion and exclusion criteria are provided in the appendix. In summary, eligible patients were male or female, 18-75 years of age, with histologic or cytologic proof of locally advanced or metastatic NSCLC. They must have at least one bidimensionally measurable lesion, have a baseline WHO PFS 0-2, a life expectancy $\geq$ 12 weeks, no CNS metastases, and no peripheral neuropathy > grade 2 (NCI). They could have received no

prior chemotherapy.

Procedure:

Patients will receive docetaxel in polysorbate 80 at 100 mg/m^2 IV over 1 hour every 3 weeks. Study medication was supplied as a concentrated solution containing 40 mg/ml in polysorbate 80 for intravenous administration. Just prior to use, the solution must be diluted with 6 ml of 5% dextrose or 0.9% saline. The appropriate amount of drug is further diluted in 250 ml of 5% dextrose or 0.9% saline and administered as a continuous IV infusion using a peristaltic pump.

No prophylactic use of antiemetics, anti-infectives or antiallergics was permitted prior to the initial infusion. Antihistamines and corticosteroids could be used to treat symptomatic HSRs, or as premedication for a rechallenge (IV premedication was given within 1 hour of the docetaxel infusion, oral premedication given 12 hours prior). No prophylactic use of colony-stimulating factors was permitted, however, patients with grade 4 neutropenia and documented infection in the previous cycle could receive concomitant G-CSF with approval of the study chairman.

If patients demonstrate a CR or PR they will continue treatment until there is evidence of disease progression or unacceptable toxicity. If there is no change after 2 cycles, patients may receive treatment for a total of 3-6 cycles if there is symptomatic improvement. Treatment could be delayed no more than 1 week to allow recovery from a prior toxicity. A maximum of two 25% dose reductions was permitted per patient (100 to 75 mg/m^2 and 75 to 55 mg/m^2). Patients experiencing febrile ($\geq$ 38°C) neutropenia grade 4, asymptomatic neutropenia grade 4 lasting $>$ 7 days, or thrombocytopenia grade 4 were allowed a 25% dose reduction. Other conditions in which a 25% dose reduction was permitted were: any grade $\geq$ 3 toxicity except alopecia and anemia, grade 2 skin toxicity or peripheral neurotoxicity. Treatment was stopped in the case of grade 3 peripheral neurotoxicity or if a severe HSR occurs during rechallenge.

Efficacy Definitions:

Responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor. A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, or appearance of a new lesion. The occurrence of pleural effusion or ascites is considered disease progression if substantiated by positive cytology. The development of brain metastases is considered disease progression, even if the patient is responding outside the brain.

Response duration was defined as follows: for CRs, the time of documentation of the CR to disease progression; for PRs, the time of initial dose of docetaxel to disease progression.

Tumor measurements were to be recorded at the end of every cycle by physical examination. Chest xrays, ultrasounds, and scans of all measurable lesions were to be repeated at the end of every 2 cycles.

Comments: *Response duration as defined in this trial (from the start of therapy to the time of progression) may give an inflated measurement of this important clinical endpoint. Other than performance status, the protocol does not specify any quality of life measures. Chest xrays are performed after every cycle in the US trials.*

Toxicity Definitions:

Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria (see appendix) and recorded for each treatment cycle.

Statistical Plan:

A two-stage design was used: accrual was to be discontinued if no responses were observed in the first 20 patients; if at least 1 response is observed in the initial cohort of patients, then an additional 15 patients would be accrued.

6.42 Study Conduct

The TAX223 trial was sponsored by RPR. Patients were accrued to 16 centers in Europe: 2 in France, 1 in Belgium, 1 in the United Kingdom, 3 in Germany, 1 in The Netherlands, 4 in Switzerland, 1 in Norway, 1 in Greece and 2 in Israel. All centers were members of the EORTC Early Clinical Trials Group. The study was monitored by regular site visits by monitors from the NDDO Data Center of EORTC (New Drug Development Office, Amsterdam) and from the Clinical Research Department of RPR. All case report forms were processed by RPR. The database was frozen on 3/30/94. Four response review meetings were held between September 1992 and June 1993. A final consensus meeting was held in January 1994, including the study chairman and the sponsor, to reach final agreement on patient eligibility, evaluability, overall response, and date of progression.

6.43 Efficacy Results

Eligibility:

Forty-three patients were entered: 6 patients were ineligible and 2 nonevaluable for response; hence, 35 patients were evaluable for efficacy. Forty-two patients were evaluable for toxicity (note patient was registered but never treated due to the presence of grade II neurotoxicity). Reasons for ineligibility were: lack of measurable lesions in 3, incorrect histology in 1, unstable cardiovascular condition in 1, and no treatment in 1. Two additional patients were nonevaluable due to early discontinuation of treatment in cycle 2 due to HSRs (patients .

Investigator/Site	No. of Patients Entered	No. of Responders
TH Cerny, Switzerland	2	0
S Kaplan, Switzerland	6	2
C Sessa, Switzerland	2	0
P Siegenthaler, Switzerland	2	0
M Clavel, France	1	0
T Tursz, France	3	2
WW Ten Bokkel Huinink, The Netherlands	1	0
SB Kaye, United Kingdom	1	0
E Robinson, Israel	4	0
A Sulkes, Israel	2	1
AR Hanauske, Germany	2	0
U Bruntsch, Germany	1	1
HJ Schmoll, Germany	4	1
AT Van Oosterom, Belgium	4	2
N Pavlidis, Greece	5	0
S Aamdal	3	0

Patient Withdrawals:

Eighteen patients withdrew for disease progression, seven died, and three withdrew consent. Six stable disease patients were on study as of 12/93. Among the 8 patients withdrawn due to toxicity, 2 had HSRs, 1 had moderate neurotoxicity, 1 had severe asthenia, 1 had venous thrombosis at the injection site, and 3 had edema and/or pleural effusion. Among the 7 deaths, two were due to disease progression, three to toxicity, and two were not drug-related.

Patient Characteristics:

The median age of the 42 patients was 59.5 years (range 38-74 years). The median baseline WHO performance status was 1. The male/female ratio was 3.7. The most

frequently diagnosed histologic subtype was adenocarcinoma. The median time from first diagnosis to first infusion of docetaxel was 2 months. Twenty-five patients had metastatic disease, 17 had locally advanced disease. One-third had one organ involved, and the rest had $\geq$ 2 organs involved. The lung was the major site of involvement (86%), with regional lymph nodes the next most common site (55%). Six patients had undergone surgery, 5 had radiation only, 6 had surgery and radiation, and 25 had no prior therapy.

Concomitant medical conditions in patient (a history of prior myocardial infarction and cardiac bypass, thrombosis of the vena cava, prior pulmonary embolism) made him ineligible. Patient had a prior myocardial infarction with ongoing cardiac dysrythmia. Most of the patients had chronic airways obstruction, hypertension, and arteriosclerosis. **Comment:** *Given the descriptions of disease extent, prior therapies, and concomitant illness, the patients entered on this trial appear to be representative of the patients with advanced NSCLC seen in general medical practice.*

Drug Delivery:

A total of 191 cycles were administered: 142 (74%) at the initial planned dose of 100 mg/m^2, and 45 (24%) at 75 mg/m^2. The median number of cycles was 4 (range 1-12). Seventeen patients had at least one dose reduction and 9 had at least one dose delay. Eight patients discontinued treatment due to toxicity. Non-hematologic toxicities were the principal cause of treatment delays and dose reductions in patients.

Median dose intensity given was 30.8 mg/m^2/week; and the relative dose intensity was > 0.7 for 95% of the patients.

Efficacy Endpoints:

- **Tumor Response Rate**

Among the 42 patients included in the intent to treat analysis, there was 1 CR and 8 PRs for an overall response rate of 21.4% (CI: 10.3; 36.8). Seventeen had stable disease, 11 had progressive disease, and five were not evaluable. Of the nine responders, 1 was female, 6 had a WHO PFS of 0, and 6 had metastatic disease. The response rate in the lung was 39%, in lymph nodes, 11%, and in other visceral organs, 25%. Patient had small cell lung cancer and had a partial response in a lung primary indicator lesion lasting 5 months; at the consensus meeting, it was decided to include this response in the intent to treat analysis. **Comment:** *The reviewer agrees with the sponsor's overall response rate, although no tumor measurements were provided on patient*

*The table below summarizes the 1 CR and 8 PRs noted in the intent to treat population as recorded in Table 23C of Data Listings, 8.114.59 - 8.114.94. Tumor sites in bold typeface had complete regressions; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensionally measurable lesion at baseline that met the protocol-*

defined size requirements (at least 1 diameter ≥ 2.5 cm on CT or ultrasound; lung lesions could be ≥ 1.5 cm) except for patient (no measurable lesions) and patient (lesions undersized). Patients had a major response in a lesion ≥ 5 cm (in lung and adrenal).

RESPONSES (ITT) - TAX221

Investigator/Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
Oosterom:	Lung, adrenal*	41
	Lung*, lymph node*	20
Kaplan:	Lung (2)*	18
	Lung*	36
Tursz:	Lung (1*, 2, 3)	15
	Lung	29
Schmoll:	Lung	34
Bruntsch:	Lung (1*, 2)	48
Sulkes:	Not Available - Wrong Histology	24

- **Response Duration**

The median duration of response in responding patients (intent to treat analysis) was 41 weeks. **Four of 9 responders were censored as they received additional chemotherapy or radiotherapy without documentation of progression before the cut-off date. Comment:** *The reviewer accepts the sponsor's calculation of response duration; the dates of further treatment for patients were verified in Table 29 of the data listings, 8.114.182 - 8.114.186.*

- **Other Endpoints**

The median time to first response was calculated to be 6 weeks (range 5-12 weeks). The median time to progression was 15 weeks among all treated patients (9/42 patients were censored; all patients received further therapy before progression). The median survival time for all treated patients was 11 months (19% of patients were alive at the cut-off date). The estimated one-year survival rate is 30%.

- **Quality of Life Assessments**

Although Table 4.19 of the study report was omitted, PFS values were recorded in Table 10 of the data listings (8.112.62 - 8.112.84). There was no significant change in performance status in the majority of patients in this study, although the number of patients with PFS determinations dropped from 42 at baseline to 24 at cycle 4 and to 17 at cycle 6. Among 17 patients with baseline PFS of 0 or 1, only 4 patients deteriorated to a PFS of 2 at cycle 6. In addition, two patients were identified whose PFS declined to 3 while on the study:
Patient PFS 0 to 3, developed severe peripheral edema/pleural effusions, severe asthenia, and grade 4 skin toxicity by cycle 6;
Patient PFS 0 to 3, died of disease progression 15 days after cycle 4 infusion.

Analgesic use was recorded in Table 24 A and B of data listings, 8.114.95 - 8.114.158. One of 9 patients requiring analgesics (and for whom data was available at baseline and at cycle 4) had an improvement in analgesic requirement, five had essentially no change in requirement, and three had worsening as demonstrated by the use of additional and/or stronger analgesics. Patient with an improvement in analgesic requirement was also a responder.

Comment: *Evolution of tumor-related symptoms could not be analyzed since no primary data were provided.*

6.44 Safety Results

Of the 42 treated patients, the most frequent possibly or probably related AEs were: leukopenia and granulocytopenia (40 patients each), alopecia (39 patients), anemia (30 patients), asthenia (25 patients), skin (25 patients), fluid retention (19 patients), neurosensory (16 patients), nausea (14 patients), diarrhea and allergy (12 patients each), vomiting (8 patients), fever in the absence of infection (10 patients), pulmonary toxicity (9 patients), and infection (8 patients).

Overall, 21 patients experienced serious AEs. Seven patients died within one month of treatment. The 3 toxic deaths were due to sepsis with grade 4 neutropenia, fungal pneumonia with grade II neutropenia, and heart failure after pulmonary edema/fluid retention.

- **Acute Hematologic Toxicities**

Leukopenia was observed in 40/41 patients and was grade 3 or 4 in 71%. Thirty-five patients (85%) had grade 3 or 4 neutropenia. The incidence of grade 3 or 4 neutropenia was similar at the 75 and 100 mg/m^2 dose levels. The median neutrophil nadir was 0.4 x 10^3/mm^3 (range 0.1-2.4) and the median time to nadir was 7 days (range 6-16). No cumulative myelotoxicity was observed. The median duration of grade 4 neutropenia was 9 days; no cycle failed to show recovery of neutrophil count by day 22$\pm$3.

Thrombocytopenia, grade 1 was observed in 1 patient.

Anemia was observed in 36/41 patients, and was grade 3 in one patient. The median nadir for hemoglobin was 11.2 g/dl (range 7.2-13), with a median day to nadir of 8 days.

Febrile neutropenia (neutropenia with fever > 38°C and grade 3 or 4 neutropenia) occurred in 7 patients and 8 cycles. All but one episode was associated with dose level 100 mg/m^2. There were eleven treatment-related infections, 9 of which occurred in the setting of grade 3 or 4 neutropenia.

- **Acute Non-hematologic Toxicities**

Hypersensitivity reactions: Twelve patients experienced HSRs; no episode was grade 4. Premedication of 6 patients with H1 antagonists and corticosteroids did not appear to prevent a subsequent HSR, but the severity of reactions seemed to be lessened. Most reactions occurred during the infusion, often within the first fifteen minutes of the infusion, manifested by flushing, dyspnea, and chest tightness. Only 2 patients discontinued treatment due to HSRs. **Pulmonary toxicity in 9 patients is included in HSRs and fluid retention.**

Nausea was observed in 16 patients, and was grade 3 in two patients. Vomiting occurred in 8 patients, and was grade 4 in one. Diarrhea occurred in 12 patients, and was grade 3 in one patient and grade 4 in another. Diarrhea lead to hospitalization in two patients, although treatment with docetaxel was not discontinued. Stomatitis occurred in 5 patients, and was grade 3 in one.

Two patients had treatment-related cardiac abnormalities, both related to fluid retention. One of these patients died with cardiac dysrhythmia.

- **Chronic Non-hematologic Toxicities**

Fluid retention (peripheral edema or facial edema, pleural effusion, ascites, and/or pericardial effusion with or without weight gain) was observed in 19 patients, and was moderate in 9 and severe in 1. Four patients had peripheral edema only, while 12 had pleural effusions and 2 had pericardial effusions. Three patients discontinued treatment due to fluid retention, and there was one toxic death due to fluid retention. The median cumulative dose to onset of fluid retention was 403 mg/m^2. Duration of edema is unknown as most cases were ongoing at the time of follow-up. Weight gain with moderate fluid retention was noted in six cases.

Comment: *Fluid retention compromised treatment for at least 5 patients: had severe toxicity, patient died, and patients discontinued therapy. Of these, three were either complete or partial responders. The median age of this group was 62 years (range 53-73 years); all were males. Only one had pleural effusions at baseline. One patient had prior surgery, two had radiotherapy. Serum albumin levels $\leq$ 3 g/dl were*

noted in 2; serum creatinine levels were elevated in one patient. No patient received premedication; patient received daily Prednisone in cycle 6 for treatment of bronchitis.

Skin toxicity occurred in 25 patients and was grade 3 in two and grade 4 in one. Signs included erythema, pruritus, dry skin, maculae, and papulae. Thirteen patients developed chronic skin changes. The median cumulative dose at the onset of skin toxicity was 523 mg/m^2. No patient discontinued treatment due to skin toxicity. Nail disorder was observed in 8 patients and was associated with skin changes in all. Two patients had onycholysis. Alopecia occurred in 93% of patients.

Neurosensory toxicity was noted in 16 patients, and was grade 1 or 2 only. Frequent symptoms/signs were numbness/tingling and decrease in deep tendon reflexes. Two patients had specific neuromotor problems, grade 1 or 2 only. Asthenia was recorded for 25 patients and was severe in four. Patient discontinued treatment due to severe asthenia.

- **Laboratory Tests**

In evaluable patients, elevations of the following parameters were seen: total bilirubin, grade 3 in one patient), alkaline phosphatase (14 patients, grade 1 or 2 only), creatinine (grade 2, associated with death due to fungal pneumonia). Note that Tables 8.01 and 8.02 of the study report refer to a different trial (TAX257).

- **Deaths on Study**

Seven patients died within one month of their last drug infusion, including three toxic deaths in patients

Patient Number	Cause of Death
	Disease progression, cycle 4
	Staphylococcus epidermidis septicemia, grade 4 neutropenia, cylce 2
	Candida tropicalis pneumonia, grade 2 neutropenia, cycle 6
	Disease progression, cycle 3
	Cardiopulmonary arrest, cycle 1
	Cerebral hemorrhage, cycle 3
	Pulmonary edema, cardiac failure, cycle 5

6.45 Publications/ Abstracts

Cerny TH, Wanders J, Kaplan S, et al.: Taxotere is an Active Drug in Non-Small Cell Lung Cancer: A Phase II Trial of the Early Clinical Trials Group. Proc ASCO 12:331, 1993. Preliminary report on 43 patients: overall response rate was 33% in 24 patients. Major toxicities were neutropenia, HSRs, fatigue, nausea, vomiting, diarrhea, and alopecia.

6.46 Sponsor's Conclusions

The sponsor points out that the partial response rate of 21% for docetaxel as first line therapy in patients with locally advanced or metastatic NSCLC is remarkable. The response duration of 41weeks for docetaxel in these patients also serves to confirm its activity as a single agent.

The feasibility of the recommended dose and schedule was confirmed in this study. The relative dose intensity of 0.92 shows that overall toxicity did not jeopardize treatment compliance and tolerability.

The usual toxicities encountered with vinca alkaloids and taxoids were seen with docetaxel: neutropenia, nausea, vomiting, diarrhea, stomatitis, neurotoxicities, alopecia, nail disorders, and anemia. These were mild, except for the neutropenia. Hematologic toxicity was not cumulative. Despite the high incidence of grade 4 neutropenia, no patient required treatment delays. Neutropenic infections were associated with two deaths. Among patients who developed infection, half of them were neutropenic and the other half were not. This is not surprising since infection is a well-recognized complication of lung cancer.

Hypersensitivity reactions lead to treatment discontinuation in two patients, although most patients completed their infusions after the reaction resolved with or without intervention.

Fluid retention was unexpected as it was rarely reported in the phase I studies and was cumulative. Three patients discontinued treatment because of this toxicity and one patient died due to heart failure related to pulmonary edema. Thus treatment was compromised in 9.5% of patients due to this toxicity. Note that both pleural and pericardial effusions are known complications of lung tumors.

Asthenia affected 25 patients and lead to treatment discontinuation in 1 and general deterioration in a second responding patient.

The risk:benefit ratio is in favor of docetaxel in patients with untreated NSCLC, despite the incidence of treatment-related infections and fluid retention.

6.47 Reviewer's Final Conclusions

Comparison of Pivotal Trials - NSCLC First Line

There are a number of features which distinguish this trial from the three US pivotal trials in previously untreated metastatic or locally advanced non-small cell lung cancer (TAX232, TAX269, and TAX231). These are:

- The TAX223 trial had the greatest number of participating sites/investigators;
- There was no protocol-defined premedication regimen;
- Chest xrays were to be performed every 6 weeks instead of every 3 weeks;
- Size criteria for measurable lesions required CT and lung lesions to be slightly larger;
- This trial had a longer median follow-up time; and
- The median response duration was longer, but 4 of 9 responders were censored for this analysis; all those censored did not progress but rather switched over to other forms of treatment.

On the other hand, all four trials have produced surprisingly reproducible overall response rates, ranging from 21 to 32%, including 1 CR in the TAX223 trial. Responses primarily occurred in the lung and thoracic lymph nodes; other visceral sites of response included liver and adrenal. With the exception of the TAX223 trial, response durations were in the range of 19-28 weeks. Note that response duration as defined from the start of docetaxel treatment to the time of progression, may give an inflated measurement.

All four trials had a similar incidence/pattern of acute hematologic toxicities: a high incidence of grade 3 or 4 neutropenia (in 85-97% of patients), but a low incidence of febrile neutropenia (17-35% of patients). These studies do point out the serious consequences of grade 3 or 4 neutropenia as 43-83% of infections occurred in association with these nadirs. Note that 17-57% of infections across all four trials were not associated with grade 3 or 4 neutropenia - consistent with the fact that infection, particularly pneumonia, is a known complication of lung cancer.

With the exception of the TAX231 trial, acute HSRs did not pose as great a threat as had been anticipated from the phase I experience. Neurotoxicity was frequent but mild to moderate in severity in all trials. Asthenia was also frequent, occurring in 51-68% of patients: this incidence is actually somewhat lower than that observed in trials involving second line patients (68-79% for NSCLC, 71-85% for breast cancer). This suggests that the underlying disease process may be contributing to this problem.

Fluid retention occurred in 41-68% of patients, and was clinically significant (either rated as severe, or resulting in patient withdrawal or death) in 2-22% of patients. In the TAX231 trial which treated patients at two initial doses (100 or 75 mg/m^2), there was no discernible difference in the incidence of fluid retention in the two groups. Premedication regimens were numerous making it difficult to conclude the benefit of any one. In fact, patients in the

TAX223, who were not routinely premedicated, fared no worse. The reviewer cannot fully account for the markedly low incidence of clinically significant fluid retention as defined above in the TAX231 trial - the lowest incidence of any pivotal trial in this application. However, patients entered on this trial received the lowest median number of treatment cycles (3), so that half the patients did not reach the cumulative dose at onset of fluid retention. Predisposing factors for the development of severe fluid retention remain to be substantiated, although pre-existing pleural effusions or pleural-based masses, prior thoracotomy, and prior chest irradiation have been suggested and should be further studied.

Docetaxel Indication for Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Effective treatment of patients with locally advanced or metastatic non-small cell lung cancer is sorely needed. The single agent activity of docetaxel, in terms of overall response rate and duration of response in the phase II setting, appears to be comparable to the most active cytotoxic agents used in the treatment of inoperable NSCLC: including cisplatin, ifosphamide, mitomycin C, vinblastine, vincristine, vinorelbine, and paclitaxel. Pooling the 176 patients from all four pivotal trials in previously untreated patients, the overall response rate for all patients was 26% (45/176). Similarly, for locally advanced disease patients, the overall response rate was 23% (8/35), and 26% (37/141) for metastatic disease patients. Clearly, it remains to be shown 1) if docetaxel will continue to perform as well in randomized, well-controlled trials as it has in the phase II trials presented herein, and 2) whether greater success may be achieved in the prevention, recognition, and treatment of the chronic non-hematologic toxicities (particularly, fluid retention, skin toxicity, and asthenia).

Given that the use of cytotoxic chemotherapy as initial therapy for inoperable NSCLC remains controversial, it becomes difficult to accept the risks of docetaxel treatment in light of its numerous toxicities, expected and unexpected, that have been reproducibly demonstrated in virtually all the pivotal trials, regardless of indication. No doubt, some patients have derived benefit from treatment. Although of a limited nature, there was some evidence presented that patients, even non-responders, experienced transient (less than 4 cycles or 12 weeks) improvement in tumor-related symptoms. Francis et al, JCO, 1994, reported that 5 responders remained alive more than one year after study entry. These findings are extremely encouraging, and warrant greater study in the setting of well-controlled randomized trials.

Additional studies may demonstrate that use of hematopoietic growth factors may ameliorate docetaxel-induced myelosuppression. This is of particular importance in NSCLC patients who are at risk for the development of post-obstructive pneumonias, often complicated by bacterial superinfection.

Severe fluid retention remains a major challenge. No predisposing factor(s) have been clearly substantiated to date. The mechanism by which this toxicity develops has not been elucidated. No clear cut benefit of any premedication(s) has yet been demonstrated. No reduction in the incidence of fluid retention could be demonstrated with treatment at the

lower dose, although this did appear to ameliorate other toxicities. There is also the risk that drug may accumulate in third-space compartments, resulting in a prolonged plasma half-life and additional toxicity in patients with peripheral edema, pleural effusions and ascites. There has been some suggestion of this in a few patients who have experienced multiple moderate to severe toxicities, including fluid retention, skin and neurotoxicities. Comparison of pharmacokinetic data on patients developing fluid retention and on those who do not may shed some light on the following questions: 1) should patients with peripheral edema, pleural effusions, or ascites at baseline receive docetaxel at all? 2) and, if edema/effusions/ascites develop on docetaxel, should treatment be discontinued until there is complete resolution after diuresis or thoracentesis?

Inevitably, docetaxel will be utilized with other cytotoxics and treatment modalities (such as radiation). The toxicities of such combinations may pose great clinical challenges. For example, cisplatin, commonly used in conjunction with other agents in non-small cell lung cancer, is given with large quantities of normal saline and may potentiate docetaxel-related fluid retention.

In summary, the reviewer does not agree with the sponsor that treatment with docetaxel provided net benefit for previously untreated patients with locally advanced or metastatic non-small cell lung cancer. As randomized clinical trials have not been performed, docetaxel's efficacy compared to other agents, such as cisplatin, remains speculative.

In addition, results from the pivotal trials in NSCLC do not support the sponsor's claim that premedication with dexamethasone for 5 days will reduce the "incidence and severity" of docetaxel-related fluid retention. Future trials should be designed to identify the optimal premedication regimen and monitoring program for patients receiving docetaxel.

OVERVIEW - NSCLC PIVOTAL TRIALS

Endpoint	TAX232	TAX269	TAX231	TAX223	TAX270	TAX271
Primary Study Site	MD Anderson	San Antonio	Sloan Kettering	EORTC	MD Anderson	San Antonio
Response Rate (%)	31.7	27	20.5**	21.4	20.5	13.6
Response Duration	19 weeks	28 weeks	23 weeks	41 weeks	30 weeks	26 weeks
Neutropenia, Grade 3/4 (% of patients)	97	93	87	85	86	86
Febrile Neutropenia (% of patients)	24	35	27	17	27	22
Infections with Grade 3/4 Neutropenia (%)	57	83	43	82	60	55
Acute HSRs (% of treated patients)	37	29	73	29	27	23
Fluid Retention-Any (% of treated patients)	66	46	41	45	68	36
Fluid Retention-Serious (% of treated patients)*	22	10	2	12	18	14
Median Cumulative Dose to Onset- Fluid Retention	305 mg/m^2	476 mg/m^2	442 mg/m^2	403 mg/m^2	314 mg/m^2	497 mg/m^2
Median Cumulative Dose to Onset- Skin Toxicity	205 mg/m^2	398 mg/m^2	300 mg/m^2	523 mg/m^2	300 mg/m^2	300 mg/m^2
Neurosensory (% of treated patients)	59	60	43	38	67	52
Neuromotor (% of treated patients)	27	27	8	5	35	32
Asthenia (% of treated patients)	68	63	51	60	79	68

*Includes all patients with severe fluid retention, and any patients who withdrew from treatment due to fluid retention, regardless of severity

**Partial responses only

TAXOTERE® (Docetaxel) for Injection Concentrate

NDA # 20-449

Integrated Summaries, ODAC Meeting, Recommended Regulatory Action

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7. Integrated Summary - Metastatic Breast Cancer

7.1 Program Overview

Volume 8.118 of the July 27, 1994, submission contains a summary of efficacy and safety results for 10 phase II studies with docetaxel as single agent chemotherapy for metastatic breast cancer. This information was also submitted on two diskettes in WordPerfect 6.0 for Windows on September 6, 1994.

Three studies are considered pivotal as they have been conducted in patients previously treated with metastatic breast cancer: TAX233, TAX267, and TAX221 (28 patients only). The supportive trials were conducted in previously untreated patients: TAX228, TAX237, TAX266, TAX280, and TAX221 (11 patients only). Altogether, there were 111 patients in pivotal trials and 174 in supportive trials. In addition, there were 206 patients in 3 Japanese studies (TAX242, TAX279, and TAX289) which are reported separately due to the lower recommended dose (60 mg/m^2) used, and different methodology employed in the assessment and evaluability of response.

Table 4, 8.118.24, lists the criteria for inclusion, toxicity, and efficacy for the 7 pivotal and supportive studies. All protocols required female patients with histologically and/or cytologically confirmed adenocarcinoma of the breast, with at least one bidimensionally measurable lesion. Only the TAX233 and TAX267 trials prospectively defined patients as anthracycline-resistant. The initial planned dose for previously treated patients was 100 mg/m^2, given as a one hour infusion every 3 weeks. The initial planned dose for previously untreated patients was either 100 or 75 mg/m^2. **Comment:** *The original protocols for TAX233 and TAX267 did not specify anthracenedione-resistance, although 20 patients designated as such have been pooled with the 60 anthracycline-resistant patients (and with 3 patients who were later found not to be resistant to either drug) in the respective study reports and integrated summary. Note also that among these 83 resistant patients, 49 were retrospectively defined in the integrated summary as refractory since they developed progressive disease as the best response while receiving an anthracycline/anthracenedione-containing regimen.*

7.2 Patient Characteristics

Among the 285 patients, 2 never received treatment and 27 were considered non-eligible, primarily due to the absence of bidimensionally measurable lesions at baseline. Thus, 256 patients were eligible. Of these, 242 (86% of all registered patients) were evaluable for response. Reasons for nonevaluability included insufficient tumor measurements, early death or study termination (not due to disease progression), and concurrent anticancer therapies.

Overall, 122 patients (43%) withdrew due to progressive disease. Fifty-one percent of all previously treated patients withdrew due to disease progression as compared to 35% of all previously untreated patients, a significant difference. Among the 87 patients withdrawing

due to toxicity, 68 were previously untreated and 19 were previously treated. The major toxicity leading to withdrawal was fluid retention, involving 60 patients; 41 of these were treated in European trials (TAX221, TAX237, and TAX280) in which investigators unfamiliar with this toxicity withdrew patients when it was observed. Other toxicities leading to treatment discontinuation were skin rash (5 patients), neurotoxicity (4 patients), HSRs (2 patients), myelosuppression (3 patients), and asthenia (8 patients).

Patient prognostic factors were well-balanced across all studies. The median age of all women entered in the phase II trials was 51 years (range 27-80), with a median WHO performance status of 1. The most common histology was infiltrating ductal carcinoma. The vast majority had metastatic disease (96%), and liver was the most frequent site, followed by bone, lymph nodes, and lung. Nearly one-half of patients had $\geq$ 3 organs involved. Most patients had prior anticancer therapy: surgery in 229 patients, radiotherapy in 183, chemotherapy in 194, and hormonal therapy in 157. Few concomitant medical conditions were noted, except for 22 patients with asthma/drug allergies, and 4 patients with cardiac disease. **Comment:** *Despite the preponderance of negative prognostic factors (liver metastasis, number of organs involved), these patients had a remarkably good performance status.*

Among the 111 previously treated patients, 65% of treatment cycles were administered at the 100 mg/m^2 dose level; among the 83 anthracycline-resistant patients, 60% of cycles were administered at this level. The median number of cycles delivered was 5 in both groups. However, the median dose intensity and median relative dose intensity were significantly lower in anthracycline-resistant patients as compared to all previously treated patients ($p = 0.03$, Tables 17 and 18, 8.118.48). One-half of previously treated patients, including the subgroup of anthracycline-resistant patients, required treatment delays; non-hematologic toxicities accounted for such delays in 63% of patients. **Comment:** *Note that the number of patients who were truly anthracycline-resistant and who received docetaxel at the planned dose and frequency is considerably less than 83.*

7.3 Efficacy

The overall response rate, using WHO criteria, among the 111 previously treated patients (intent to treat analysis) was 49%, including 4 CRs and 50 PRs. A similar overall response rate was noted among the 83 anthracycline-resistant patients: 48%, including 3 CRs and 37 PRs. No major difference was noted in the overall response rate for doxorubicin- or mitoxantrone-resistant patients. Among the worse prognosis group, defined as anthracycline-refractory, there were 3 CRs and 16 PRs (overall response rate of 39%).

Among 105 previously treated patients with baseline visceral metastases, the overall response rate was 55% (no CRs); among 68 anthracycline-resistant patients with baseline visceral metastases the overall response rate was 53%; and among 46 anthracycline-refractory patients with baseline visceral metastases, the overall response rate was 49%. Similar response rates were noted in liver and lung as in soft tissue sites (49-58%); this was not the case with respect to complete responses, however. Patients with 1 organ involved experienced a

significantly higher response rate than patients with 2 or more organs involved (p=0.02). Patients with a better WHO baseline performance status (0 or 1) had a higher response rate than those with a baseline performance status of 2. The overall response rate was the same for patients under and over 50 years of age.

Duration of response for all responders was defined in the study protocols from the time of the first infusion to the time of progression; patients receiving further anticancer therapy, prior to the documentation of disease progression were censored. A similar median duration of response among the previously treated patients (28 weeks) and anthracycline-resistant patients (27 weeks) was noted. **Comment:** *Note that by definition these response durations would include the time to first response. In addition, although all studies were initiated around the same time, the European trial (TAX221) had a cut-off date that was 6 weeks longer than for the US/Canadian trials.*

Other efficacy endpoints included in the integrated summary, although not defined as protocol objectives were: time to progression (19 weeks for both previously treated and anthracycline-resistant patient groups), and survival (11 months for previously treated and 10 months for anthracycline-resistant patients).

No statistical difference on efficacy endpoints was determined for the two planned doses studied in this program (100 vs 75 mg/m^2). **Comment:** *These studies were not designed to investigate dose response and effect of premedication on response.*

Although no Quality of Life questionnaire was utilized in these phase II studies, changes in analgesic requirement and tumor-related symptoms were to be monitored prospectively in the US trials. In addition, performance status was analyzed retrospectively for all trials.

Of 283 patients treated with docetaxel, there were 172 with performance status recorded at cycle 4, and 100 patients with performance status recorded at cycle 6. Performance scores for the majority of patients remained stable or improved, regardless of subgroup. Twelve of 51 patients taking analgesics at baseline and cycle 4 had improvement in analgesic requirement; 8 of these were responders.

7.4 Safety

7.41 Hematologic Toxicity

A total of 273 serious adverse events were reported for 134 patients (see Table 39, 8.118.88). There were 10 deaths reported within 30 days of the last infusion of docetaxel, 3 of which were drug-related. The majority of patients with grade 4 events had neutropenia. Neutropenia was reported for 273 evaluable patients, and was grade 3 or 4 in 97% of these. The median nadir of neutrophils was 0.2 x 10^9 mm^3 and the median days to nadir was 8. The median duration of grade 3 or 4 neutropenia was 7 days (range 1-27 days). Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 75 (27%) of patients.

Among previously treated patients, there were 19 of 47 episodes of infection (40%) with grade 3 or 4 neutropenia. The incidence of infection was higher in patients premedicated with longterm corticosteroids. **Comment:** *Note that the TAX233, TAX267, and TAX221 study reports state the incidence of infection with grade 3 or 4 neutropenia was 71-77%.*

Thrombocytopenia was reported for 33 patients, 4 of which had concomitant hemorrhage. Anemia was more common, developing in 92% of patients; 18 patients received transfusions.

7.42 Non-Hematologic Toxicity

As no difference was observed between patients treated with a planned dose of 100 or 75 mg/m², only results for the 228 high dose patients were discussed in the integrated summary.

The overall incidence of acute HSRs was 28% (64 patients), with 5% of patients having grade 3 or 4 reactions. The incidence and severity of HSRs were not decreased by the use of antihistamine/corticosteroid premedications.

Nausea was observed in 51% of patients, and was grade 3 in 6%. Vomiting was observed in 33%, grade 3 or 4 in 3%. Diarrhea was observed in 48%, grade 3 or 4 in 3%. Stomatitis occurred in 54%, and was grade 3 or 4 in 11%. Premedication had no effect.

Fluid retention (including peripheral, localized or generalized edema, pleural effusion, ascites, pericardial effusion, weight gain) was observed in 148 patients (65%), and was severe in 34 patients (15%). Thirty patients experienced weight gain, edema, and pleural effusion. The median cumulative dose to onset of fluid retention was 385 mg/m², corresponding to < 4 cycles. Use of corticosteroids (with/without anti-H1 antagonists) reduced the incidence of fluid retention to 37-50%, as compared to anti-H1 antagonists alone or no premedication. Use of corticosteroids also delayed the onset of fluid retention as compared to no premedication, although there was no difference between short and long corticosteroid regimens (day before/day of treatment vs day before and up to 4 days after treatment). **Comment:** *The 15% incidence of severe reactions underestimates the number of patients whose treatment with docetaxel was compromised by fluid retention, as 44/148 patients discontinued treatment due to this toxicity, some with mild-moderate toxicities.*

Skin toxicities included erythema, pruritus, macular rash, swelling, papulae, desquamation, hyperpigmentation, dry skin and pain. The overall incidence was 72%; premedication with short course corticosteroids (with or without anti-H1 antagonists) was associated with the lowest incidence (61%). Note that skin toxicity with the docetaxel 75 mg/m² dose occurs less frequently and is of lessened severity. The overall incidence of nail changes was 35% (including discoloration, pain, and onycholysis). Sixteen patients developed local skin reactions at the injection site. Alopecia occurred in 80% of patients.

The overall incidence of neurosensory toxicity was 61%, and was severe in 5%. The manifestations of this toxicity were paresthesias of hands and feet, dyesthesias, and burning

pain. Neuromotor toxicity was observed in 19%, and was severe in 5%. Other types of neurotoxicity included headache (7%) and constipation (4%). Asthenia was observed in 72%, and was severe in 16%. Premedication had no effect on neurotoxicity or asthenia.

Cardiac toxicity was manifested primarily as dysrythmia (5 patients). One patient each had cardiac dysfunction, ischemia, and pericardial effusion (not related to fluid retention). Myalgias were reported in 30%, arthralgias in 6%. Premedications had no effect.

Docetaxel-related elevations of SGOT and SGPT occurred in 36% and 25% of patients, respectively. These were grade 1 or 2 primarily. Elevations of alkaline phosphatase were seen in 33%, and were grade 3 in 3%. Elevations of total bilirubin were seen in only 11%, but all were grade 2 or higher. Grade 1 increases in creatinine were noted in 6%.

7.5 Japanese Studies

The TAX242, TAX279, and TAX289 studies enrolled 190 eligible patients with a median age of 53 (range 29-79 years) and a median WHO performance status of 0. Of these, 170 had prior chemotherapy. The most common histologies seen were solid tubular and scirrhous carcinoma, and the most frequent sites of metastasis were in lymph nodes, followed by "reccurence", lung and bone. Docetaxel was administered at 60 mg/m² over one hour.

The overall response rate (intent to treat analysis) was 43%, including 10 CRs and 78 PRs. Response rates at individual sites ranged from 61% in liver, 56% in lymph nodes, 54% in "reccurence", 52% in breast, to 40% in lung. The overall response rate among patients previously treated with chemotherapy was 47%, and 49% among 121 anthracycline-pretreated patients. **Comment:** *The reported response rates are surprisingly high, even in liver, despite the lower dose used in these trials.*

Adverse reactions were graded according to Japanese Society for Cancer Therapy Guidelines and presented in Tables 62 and 63 (8.118.121 - 8.118.122). Neutropenia occurred in 96% of patients, and was grade 3 or 4 in 88%. Thrombocytopenia was noted in 12% of patients, and was grade 3 or 4 in 5 patients. Anemia occurred in 63% of patients, and was grade 3 or 4 in 11 patients. **Comment:** *The incidence of neutropenia and thrombocytopenia in the Japanese trials is identical to that reported for the high dose US/Canadian and EORTC trials described above; however, the incidence of grade 3 or 4 neutropenia and of anemia was lower in the Japanese trials.*

The most common non-hematologic toxicities among 188 patients were alopecia (87%), anorexia (70%), fatigue (66%), nausea and vomiting (61%), fever (43%), skin rash (27%), diarrhea (26%), stomatitis (20%), arthralgia/myalgia/pain (14%), peripheral neuropathy (13%), edema (12%), and allergy/shock (4%). **Comment:** *With the exception of alopecia, fatigue, nausea and vomiting, the incidence of non-hematologic toxicities, including laboratory abnormalities, is much lower in the Japan experience. The spectrum of toxicities is similar, however, to that observed in the high dose studies conducted in other countries.*

8. Integrated Summary - Metastatic Non-Small Cell Lung Cancer

8.1 Program Overview

Volume 8.119 of the July 27, 1994, submission contains a summary of efficacy and safety results for 9 phase II studies with docetaxel as single agent chemotherapy for metastatic non-small cell lung cancer (NSCLC). This information was also submitted on two diskettes in WordPerfect 6.0 for Windows on September 6, 1994.

The TAX270 and TAX271 conducted in 88 previously treated patients with metastatic NSCLC were pivotal; the TAX223, TAX231, TAX232, and TAX269 conducted in 181 previously untreated patients were supportive. Altogether, there were 269 patients in pivotal trials. In addition, there were 201 patients in 3 Japanese studies (TAX241, TAX284, and TAX290) which are reported separately due to the lower recommended dose (60 mg/m²) used, and different methodology employed in the assessment and evaluability of response.

Table 4, 8.119.20, lists the criteria for inclusion, toxicity, and efficacy for the 6 pivotal studies. All protocols required male or female patients with histologically and/or cytologically confirmed NSCLC, either stage IV or unresectable stage III. At least one bidimensionally measurable lesion was required, except in the TAX231 trial in which patients were eligible even with only one non-measurable lesion. The initial planned dose in the pivotal trials was 100 mg/m², given as a one hour infusion every 3 weeks, except for the TAX231 trial in which 20 previously untreated patients received 75 mg/m². **Comment:** ***All but one patient on the TAX270 and TAX271 trials failed to respond to cisplatin and/or carboplatin; hence, "failure to platinum" is synonymous with "previously treated".***

8.2 Patient Characteristics

Among the 269 patients, 1 never received treatment and 40 were considered non-eligible, primarily due to the absence of bidimensionally measurable lesions at baseline. Thus, 228 patients were eligible. Of these, 215 (80% of all registered patients) were evaluable for response. Reasons for nonevaluability included insufficient tumor measurements, early death or study termination (due to toxicity).

Overall, 148 patients withdrew due to progressive disease and 35 patients withdrew due to toxicity. The frequency of treatment withdrawal was similar for previously treated and previously untreated patients. The major toxicity leading to withdrawal was fluid retention, involving 10 patients, followed by asthenia (8 patients), neurotoxicity (6 patients), HSRs (5 patients). There were 9 toxic deaths, involving infection in 8 patients.

The median age of all patients entered in the phase II trials was 61 years (range 29-79), with a male:female ratio of 1.6, and a median WHO performance status of 1. The most common histology was adenocarcinoma. The vast majority had metastatic disease (82%) with lung, lymph nodes and pleura the most frequent sites. Nearly 3/4 of patients had $\geq$ 2 organs

involved. Statistical differences between previously treated and previously untreated patients at baseline were noted with respect to: 1) time from diagnosis to first infusion: longer in the previously treated patients, 2) age: previously untreated patients were older, 3) WHO PFS: more previously untreated patients had a performance status of 0, 4) sex: the male:female ratio is higher in the previously treated group, and 5) histology: there are more cases of squamous carcinoma and carcinoma, unspecified, in the previously treated group. **Comment:** *Given the findings described below, factors 2, 3, and 4 would favor previously untreated patients.*

Prior anticancer therapy included : surgery in 72 patients, radiotherapy in 105, and chemotherapy in 88. Concomitant medical conditions included 68 patients with asthma/COPD/ respiratory problems, and 75 patients with cardiovascular disease. **Comment:** *Compared to the patients with metastatic breast cancer, patients in these trials were older, less heavily pretreated, and had more comorbid disease. These findings are not unexpected given the natural history of NSCLC.*

Out of 1251 treatment cycles given, 860 (69%) were given at the initial dose of 100 mg/m² and 290 (23%) at 75 mg/m² (includes 63 cycles at an initial dose of 75 mg/m²). The median cumulative dose given was 399 mg/m². The median relative dose intensity was similar in previously untreated and previously treated patients. Treatment delays were required in 41% of patients and dose modifications in 35%.

8.3 Efficacy

Ten patients with responses in evaluable lesions only (TAX231) were kept in the intent to treat analysis, but recorded as "no change". The overall response rate, using WHO criteria, among the 88 previously treated patients was 17%, including 15 PRs. The overall response rate was 27% (1 CR, 42 PRs) among the 160 previously untreated patients dosed at 100 mg/m², but only 10% among the 20 previously untreated patients dosed at 75 mg/m².

Among 206 patients with baseline visceral metastases, the overall response rate was 27% (1 CR). Response rates in liver, lung, and lymph nodes ranged from 20-32%. The highest response rates were seen in adenocarcinoma (31%) and carcinoma, not otherwise specified (29%). Patients with 1 organ involved experienced a significantly higher response rate than patients with 2 or more organs involved ($p=0.09$). Patients with a better WHO baseline performance status (0 or 1) had a higher response rate than those with a baseline performance status of 2 ($p=0.08$). The overall response rate was higher for patients over 50 years of age ($p=0.04$).

Duration of response for all responders was defined in the study protocols from the time of the first infusion to the time of progression; patients receiving further anticancer therapy, prior to the documentation of disease progression were censored. The median duration of response at the 100 mg/m² dose was 25 weeks among previously treated patients, and 29 weeks among previously untreated patients. **Comment:** *Note that by definition these*

response durations would include the time to first response. In addition, although all studies were initiated around the same time, the European trial (TAX223) had a cut-off date that was 8 weeks longer than for the US/Canadian trials.

Other efficacy endpoints included in the integrated summary, although not defined as protocol objectives were: time to progression (14 weeks for both previously treated and previously untreated patient groups), and survival (8 months for previously treated and 9 months for previously untreated patients).

Among the 88 previously treated patients, 37 were retrospectively defined in the integrated summary as platinum refractory since they developed progressive disease as the best response while receiving a platinum-containing regimen. (Note that the original protocols for the TAX270 and TAX271 trials did not define platinum-refractoriness.) A partial response rate of 13% was observed; the response rate was higher (30%) when only one organ was involved. All responders had visceral metastases, a WHO PFS of 1, and were > 50 years of age; 3 out 4 responders were female. The time to progression was 12 weeks and survival 7.4 months.

Although no Quality of Life questionnaire was utilized in these phase II studies, changes in analgesic requirement and tumor-related symptoms were to be monitored prospectively in the US trials. In addition, performance status was analyzed retrospectively for all trials.

Of 181 patients treated with docetaxel at the 100 mg/m² dose, there were 143 with performance status recorded at cycle 4, and 92 patients with performance status recorded at cycle 6. Performance scores for the majority of patients remained stable or improved. Seventeen of 120 patients taking analgesics at baseline and cycle 4 had improvement in analgesic requirement; 8 of these were responders.

8.4 Safety

8.41 Hematologic Toxicity

A total of 244 docetaxel-related serious adverse events were reported (see Table 39, 8.119.78). There were 33 deaths reported within 30 days of the last docetaxel infusion, 9 of which were drug-related. Neutropenia was reported for 231 evaluable patients, and was grade 3 or 4 in 89% of these. The median nadir of neutrophils was 0.2 x 10^3 mm^3 and the median days to nadir was 8. The median duration of grade 3 or 4 neutropenia was 7 days (range 1-16 days). Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 60 (24%) of patients. Sixteen of 41 episodes of infection (39%) were associated with grade 3 or 4 neutropenia. **Comment:** *The reviewer cannot reconcile this last figure with the study reports which state the incidence of infection with grade 3 or 4 neutropenia was 43-83%.*

Thrombocytopenia occurred in 5%; anemia was more frequent, occurring in 91%.

8.42 Non-Hematologic Toxicity

The following summary is based on evaluable patients treated at the 100 mg/m² dose.

The overall incidence of acute HSRs was 34% (64 patients), with 9% of patients having grade 3 reactions. The incidence and severity of HSRs were not decreased by the use of antihistamine/corticosteroid premedications.

Eight patients developed local skin reactions at the injection site.

Nausea was observed in 44% of patients, and was grade 3 or 4 in 5%. Vomiting was observed in 25%, grade 3 or 4 in 3%. Diarrhea was observed in 40%, grade 3 or 4 in 6%. Stomatitis occurred in 36%, and was grade 3 in 2%. Premedication had no effect on these toxicities.

Fluid retention (including peripheral, localized or generalized edema, pleural effusion, ascites, pericardial effusion, weight gain) was observed in 126 patients (51%), and was severe in 22 patients (9%). Twelve patients experienced weight gain, edema, and pleural effusion. The median cumulative dose to onset of fluid retention was 400 mg/m². **Use of premedication did not significantly reduce or delay the onset of fluid retention.** **Comment:** *The 9% incidence of severe reactions underestimates the number of patients whose treatment with docetaxel was compromised by fluid retention, as 12 patients discontinued treatment due to this toxicity, some with mild-moderate toxicities. It should also be noted that there was one toxic death in a patient developing pulmonary edema.*

Skin toxicities included erythema, pruritus, macular rash, swelling, papulae, desquamation, hyperpigmentation, dry skin and pain. The overall incidence was 67%, and was grade 3 or 4 in 8%; **premedication with anti-H1 antagonists was associated with the highest incidence (83%).** The overall incidence of nail changes was 29% (including discoloration, pain, and onycholysis). Alopecia occurred in 80% of patients.

The overall incidence of neurosensory toxicity was 55%, and was severe in 4%. The manifestations of this toxicity were paresthesias of hands and feet, dyesthesias, and burning pain. Neuromotor toxicity was observed in 23%, and was severe in 6.5%. Other types of neurotoxicity included constipation (4%), headache, mood and cerebellar changes (2% each). Asthenia was observed in 67%, and was severe in 11%. Premedication had no effect on neurotoxicity or asthenia.

Cardiac toxicity was manifested primarily as dysrythmia (13 patients). Seven patients had cardiac dysfunction, and 1 patient had ischemia. Hypo- or hypertension occurred in < 6%.

Myalgias were reported in 19%, arthralgias in 15%. Premedications had no effect.

Docetaxel-related elevations of SGOT and SGPT occurred in 28% and 23% of patients,

respectively. These were grade 1 or 2 primarily. Elevations of alkaline phosphatase were seen in 38%, and were primarily grade 1 or 2. Elevations of total bilirubin were seen in only 8%, but all were grade 2 or higher. Increases in creatinine were noted in 15%, and were primarily grade 1 or 2.

Since many more patients were treated at the initial planned dose of 100 mg/m² than at the initial planned dose of 75 mg/m² (238 vs 20 patients), no formal comparisons between the two groups can be made. The incidence of grade 4 neutropenia, febrile neutropenia, anemia, gastrintestinal, skin and neurotoxicity, asthenia, fluid retention, myalgias and arthralgias were higher at the 100 mg/m² dose. (See Tables 67 and 68, 8.119.106 - 8.119.107)

8.5 Japanese Studies

The TAX241, TAX284, and TAX290 studies enrolled 196 eligible patients with a median age of 67 (range 37-80 years) and a median WHO performance status of 1. The most common histologies seen were adenocarcinoma and squamous carcinoma. Sixty-one percent had stage IV disease and the most frequent site of metastasis was in lymph nodes. Docetaxel was administered at 60 mg/m² as a one hour continuous infusion.

The overall response rate (intent to treat analysis) was 21%, including 41 PRs. Response rates at individual sites were 17% in primary lesions and 19% in lymph nodes. The overall response rate among 163 patients previously untreated with chemotherapy was 27%, and 21% among 22 previously treated patients. **Comment:** *The reported response rates are surprisingly high, despite the lower dose used in these trials.*

Adverse reactions were graded according to Japanese Society for Cancer Therapy Guidelines and presented in Tables 76 and 77 (8.119.115 - 8.119.116). Neutropenia occurred in 185 patients, and was grade 3 or 4 in 87%. Thrombocytopenia was noted in 4% of patients; anemia occurred in 51% of patients, and was grade 3 in 12 patients. **Comment:** *The overall incidence of neutropenia, of grade 3 or 4 neutropenia, and of thrombocytopenia in the Japanese trials is identical to that reported for the high dose US/Canadian and EORTC trials described above; however, the incidence of anemia was lower in the Japanese trials.*

The most common non-hematologic toxicities among 193 patients were alopecia (79%), anorexia (59%), fatigue (45%), fever (39%), nausea and vomiting (38%), diarrhea (16%), skin rash (13%), and stomatitis (5%). The following toxicities occurred with a frequency of < 5%: arthralgia/myalgia/pain, peripheral neuropathy, edema, and allergy/shock. **Comment:** *With the exception of alopecia, fatigue, nausea and vomiting, the incidence of non-hematologic toxicities, including laboratory abnormalities, is much lower in the Japan experience. The spectrum of toxicities is similar, however, to that observed in the high dose studies conducted in other countries.*

9. Integrated Safety Summary

9.1 Program Overview

Volume 8.117 of the July 27, 1994, submission contains a summary of safety results for 8 phase I studies and 30 phase II studies with docetaxel as single agent chemotherapy for various tumor types, including metastatic breast cancer and metastatic non-small cell lung cancer (NSCLC). This information was also submitted on four diskettes in WordPerfect 6.0 for Windows on Septemb. , 1994.

Altogether, there were 1170 patients and 5167 treatment cycles evaluable for safety in US, Canadian, and European trials. The docetaxel dose level in 2918 cycles was 100 mg/m². In addition, there were 408 patients in 7 Japanese studies evaluable for safety but reported separately due to the lower recommended dose (60 mg/m²) used, and different methodology employed in the assessment and evaluability of response.

9.2 Phase I Studies

Of the seven phase I studies conducted (excluding Japan), 2 were considered pivotal, 4 were supportive, and 1 was a metabolism study. Of the 256 patients entered on these studies, 255 are evaluable for safety (1 patient is not due to loss of hospital chart). In the pivotal studies, docetaxel was administered at 100 mg/m² as a 1-2 hour (TAX001) or 1 hour infusion (TAX006). Two formulations were utilized: formulation #1 (15 mg/ml in 50% ethanol, 50% polysorbate 80) was administered to 217 patients; formulation #2 (40 mg/ml in polysorbate 80) was administered to 39 patients, including all 10 patients on the TAX006 study.

9.21 Patient Characteristics

The median age of all patients entered in the phase I trials was 55 years (range 22-78), with a male:female ratio of 0.4, and a median WHO performance status of 1. The most common tumor types were ovary (29%), breast (20%), colorectal (12%), and lung (9%). Prior anticancer therapy in these patients included : surgery in 86%, radiotherapy in 40%, chemotherapy in 91%, hormonotherapy in 23%, and immunotherapy in 8%. The median time between last chemotherapy and first infusion of docetaxel was 3.9 months.

In the phase I program, patients entered 15 initial planned dose levels ranging from 5 to 130 mg/m². Regimens were designed to give 1, 1-2, 2, 3, 6 or 24 hour infusions every 3 weeks, or daily 1 hour infusions for 5 days, repeated every 3 weeks, or 1 hour infusions on day 1 and day 8, repeated every 3 weeks. Out of a total of 1040 treatment cycles delivered, 157 cycles were given to 36 patients at the initial dose of 100 mg/m² as a 1-2 hour infusion on an every 3 week schedule.

9.22 Safety - Overall Phase I Experience

Adverse events leading to premature study discontinuation occurred in a total of 46 patients, including death in 22 patients. Only one death was considered to be drug-related. Unless otherwise indicated the following summary is an overview of toxicities experienced by 255 phase I patients evaluable for safety.

Hematologic Toxicity

Dose-dependent neutropenia was the primary dose-limiting toxicity in all regimens tested. In regimens involving one single administration every 3 weeks, neutropenia occurred in 79% of patients at the dose range of 55-70 mg/m², but in 98% of patients in the dose range of 95-105 mg/m². Grade IV neutropenia occurred in 30% of patients in the dose range of 55-70 mg/m², but in 89% of patients in the dose range of 95-105 mg/m². Among patients treated at the 95-105 mg/m² dose range (1-2 hour infusions), the median nadir of neutrophils was 0.2 x 10^3 mm³ and the median days to nadir was 8. The median duration of grade 4 neutropenia was 7 days.

Febrile neutropenia (fever $\geq$ 38°C with grade 3 or 4 neutropenia) occurred in 5% of patients at the dose range of 55-70 mg/m² and no patient developed infection. In the dose range of 95-105 mg/m², 15% of patients developed febrile neutropenia, and 5% developed infection. Overall, there were 24 infections, 19 of which (79%) were associated with grade 3 or 4 neutropenia.

Thrombocytopenia occurred in 13%, and was grade 4 in only 2 patients. Anemia was more frequent, occurring in 86%, but the incidence of grade 4 anemia was only 2%.

Non-Hematologic Toxicity

The following toxicities were found to be dose-related: skin toxicity, fluid retention, neurosensory, asthenia, digestive (including nausea/vomiting, diarrhea, mucous membrane disorder, anorexia), pain, and taste changes.

The overall incidence of acute HSRs was 16%, with 3% of patients having grade 3 reactions. All patients received docetaxel without premedications. Symptoms were primarily flushing, rash, pain in chest, back or abdomen, dyspnea and fever. Severe reactions were manifested by hypotension and/or bronchospasm. Reactions were usually acute, occurring within the first 10 minutes of the infusion. Although infusions were interrupted, they were generally resumed after premedication with steroids and/or antihistamines.

Nausea/vomiting was observed in 42% of patients, and was grade 3 in 2%. Diarrhea was observed in 32%, grade 3 or 4 in 5%. Mucous membrane disorder (including stomatitis) occurred in 32%. Anorexia occurred in 15%.

Cumulative fluid retention (including peripheral, localized or generalized edema, pleural effusion, ascites, pericardial effusion, weight gain) was observed in 66 patients (26%), and was grade 3 or 4 in 10 patients (4%).

Skin toxicities were of two major types: 1) maculpapular rash primarily on hands and feet within 1 week of treatment, generally resolving before the next dose, 2) less commonly, erythema followed by desquamation on hands, feet, palms and soles, occurring after several treament cycles and leading to interruption or discontinuation. Other toxicities included hyperpigmentation, dry skin and pain or burning. The overall incidence was 37%, and was grade 3 or 4 in 3%. The overall incidence of nail changes was 9% (including discoloration, pain, and onycholysis). Alopecia occurred in 55% of patients. **Comment:** *The incidence of skin toxicity and of alopecia for patients treated at the 95-105 mg/m² dose range (1-2 hour infusions) was 78%.*

The overall incidence of neurosensory toxicity was 28%, and was severe in 2%. The manifestations of this toxicity were paresthesias, decrease in deep tendon reflexes, and hypesthesias. Neuromotor toxicity was observed in 13%, and was severe in < 1%. Other types of neurotoxicity observed in less than 6% of patients included constipation, headache, anxiety, and cerebellar changes. Asthenia was observed in 20%, and was severe in < 1%. **Comment:** *The incidence of neurosensory and neuromotor toxicity for patients treated at the 95-105 mg/m² dose range (1-2 hour infusions) was 47 and 39%, respectively.*

Cardiac toxicity was manifested in 14% of patients as dysrythmia, changes in blood pressure or pericarditis. Myalgias were reported in 9%, arthralgias in 2%. Thirteen percent of patients developed local skin reactions at the injection site. Docetaxel-related elevations of liver enzymes and bilirubin occurred in 13% and 3% of patients, respectively. Conjunctivitis was reported in 5%, taste perversion in 8%, taste loss in 2%, pain in 11%, dypsnea in 7%, and cough in 5%.

The day 1 and day 8 regimen was associated with a higher incidence of skin toxicity (55%), fluid retention (55%), and asthenia (65%). Mucous membrane disorder (including stomatitis) was schedule-dependent as it was more frequent and severe with prolonged infusions (6 or 24 hours) or when infusions were repeated for 5 days. **Comment:** *Note that compared to the single dose regimens, the number of patients treated with other regimens is small: 39 for the daily x5 schedule and 40 patients for the day 1 and day 8 schedule.*

9.23 Pharmacokinetic Data

In the pivotal studies, TAX001 and TAX006, triphasic plasma clearance was observed in patients treated at the proposed dose and schedule (100 mg/m² over 1 hour). Plasma profiles were similar for both formulations 1 and 2. The TAX016 metabolism study revealed that docetaxel is rapidly and highly bound (98%) to plasma proteins. Seventy-five percent of the administered dose is recovered in feces, 5% in urine.

In the TAX001 study, dose escalation was continued until the MTD of 115 mg/m² was reached, the dose level at which all patients had grade 4 neutropenia. The recommended dose for phase II studies, 100 mg/m², was based on the incidence of neutropenia and of "very acceptable non-hematologic toxicity (no more than 5% incidence of severe/grade 3 toxicity except for alopecia". The choice of a 1 hour infusion was based on the observation of increased mucositis with prolonged infusions. As no major difference was observed between formulations in the incidence of neutropenia and skin toxicity, and the pharmacokinetic parameters were similar, the choice of formulation 2 was made so that the concentration of infused polysorbate 80 would be lowered.

9.24 Tumor Response

There were 8 PRs among 50 breast cancer patients, dosed from 60 to 115 mg/m², including all schedules, except the 24 hour infusion; there were 3 PRs among 23 lung cancer patients, dosed at 85-100 mg/m², as 1-2 hour infusions.

9.3 Phase II Studies - Overall

A total of 919 patients were registered in phase II studies in the US, Canada and Europe, of which 912 are evaluable for safety (7 patients were never treated). This includes 283 patients with breast cancer, 268 with NSCLC, and 361 with other tumor types. Patients in phase II studies received docetaxel at 100 mg/m² over 1 hour every 3 weeks in formulation 2 (40 mg/ml in polysorbate 80), except for 75 patients in the TAX280, TAX228, and TAX231 studies who received a starting dose of docetaxel at 75 mg/m².

9.31 Patient Characteristics

The median age of all patients entered in the phase II trials was 57 years (range 26-80), with a male:female ratio of 0.7, and a median WHO performance status of 1. The most common sites of involvement in patients were: lung (52%), lymph nodes (41%), liver (35%), and bone (23%). A single organ was involved in 27% of patients, the rest had 2 or more organs involved. Prior anticancer therapy included : surgery in 510 patients, radiotherapy in 122, chemotherapy in 135, radiotherapy + chemotherapy in 126. The median time between last chemotherapy and first infusion of docetaxel was 3 months for second line patients, but 27 months for first line patients (i.e., those having adjuvant or neo-adjuvant chemotherapy).

At the initial planned dose of 100 mg/m², 2720 of 3743 (73%) of cycles were given at 100 mg/m², 37 (1%) at 115 mg/m², and 983 (26%) at reduced doses. Treatment delays occurred in 294 patients (32%), and dose modifications in 309 patients (34%).

9.32 Safety Profile - Docetaxel at 100 mg/m²

Among the 912 patients, 449 patients (49.2%) presented adverse events, including toxic deaths. A total of 17 toxic deaths were reported, including 14 deaths due to neutropenic

infection or pneumonia or sepsis: 3 patients from study TAX224, 2 patients from study TAX223, 2 patients from study TAX269, and 7 patients from studies TAX221, TAX233, TAX231, TAX232, TAX270,TAX271, and TAX245 (one patient in each study). The other causes of toxic death were: 1 cardiac failure with pulmonary edema (TAX223), 1 right-sided hemiparesis and drowsiness (TAX222), and 1 gastro-intestinal hemorrhage due to thrombocytopenia in a patient with liver impairment (TAX266). In addition, there were 55 deaths on study, not related to docetaxel (42 due to progressive disease). There were 833 of 912 patients evaluable for safety at the 100 mg/m² docetaxel dose (excluding 4 patients who discontinued treatment during the first infusion due to an HSR).

Hematologic Toxicity

Among 795 patients evaluable for leukopenia (i.e. at least one blood count between day 2 and day 19 performed for at least 1 cycle), 773 patients (97%) developed leukopenia, which was grade 3-4 in 596 patients (75%). Neutropenia was observed in 767 out of 791 evaluable patients (97%), and was grade 3 or 4 in 724 patients (92%). The median nadir of neutrophils by patient was 0.2 x 10^3 mm^3 (range 0.0 - 25.2). The median time to nadir by patient was 8 days (range 1-35). The median duration of grade 3 or 4 neutropenia was 7 days (range: 0 - 17). The median time to recovery from grade 3 or 4 neutropenia to an absolute granulocyte count $\geq$ 1.5 x 10^3 mm^3 was 7 days.

Febrile neutropenia (fever $\geq$ 38°C with grade 3-4 neutropenia) was experienced by 185 of 893 patients (22%). Of 141 episodes of infection, 67 (48%) had concomitant grade 3 or 4 neutropenia. **Comment:** *This last figure seems low, given the 43-83% incidence of infection with grade 3 or 4 neutropenia given in study reports of pivotal trials.*

Thrombocytopenia was observed in 8% of patients, and 13 had an episode of hemorhage. Anemia occurred in 89% of patients and was < 8 g/dl in 10%.

Non-Hematologic Toxicity

Table 43, 8.117.81 - 8.117.87, represents all major drug-related non-hematologic toxicities, with and without premedications for evaluable patients dosed at 100 mg/m².

The overall incidence of acute HSRs was 31%, with 61 patients having grade 3 or 4 reactions. The lowest incidence of HSRs occurred among 315 patients who received docetaxel **without premedications**. Symptoms were primarily flushing, rash, pain, dyspnea and fever. Severe reactions were manifested by hypotension and/or bronchospasm. Most reactions occurred in the first 1 or 2 cycles.

Nausea and vomiting were observed in 45% and 28% of patients, respectively, and was

grade 3 or 4 in < 5%. Diarrhea was observed in 43%, grade 3 or 4 in 4%. Mucous membrane disorder (including stomatitis, pharyngitis, esophagitis, and proctitis) occurred in 43%, and graded severe in 3%. Premedications had no effect on gastro-intestinal toxicities.

Cumulative fluid retention was observed in 389 patients (47%), and was severe in 73 patients (9%). A total of 72 patients discontinued treatment due to fluid retention. Peripheral edema was the most common presentation, alone or in combination with pleural effusion, and/or weight gain. The median cumulative dose to onset of fluid retention was 400 mg/m², corresponding to 4 cycles of treatment; the median cumulative dose to treatment discontinuation was 1301 mg/m². **Comment:** *Note that of 72 patients withdrawn for this toxicity in the phase II program, 41 were from 3 breast cancer trials in Europe (TAX221, TAX237, and TAX280) in which investigators withdrew patients when fluid retention was observed. This suggests two possible clinical approaches to dealing with this problem: discontinue docetaxel when fluid retention develops, or continue docetaxel and treat the fluid retention as necessary.*

Premedication with anti-H1 antagonists appears to increase the overall incidence of fluid retention (to 61% in 171 patients). Use of corticosteroid premedication reduced the incidence of fluid retention to 33-37%, as compared to 40% in patients given no premedications. Use of corticosteroids also delayed the onset of fluid retention as compared to no medications although there was no difference between short and long regimens. **Comment:** *Many of the patients designated in the study report as ones receiving "short corticosteroids" or "long corticosteroids" were also given anti-H1 and/or anti-H2 antagonists. The reviewer finds it difficult to discern the true effect of corticosteroid prophylaxis, especially when antihistamines, which are thought to increase the incidence of fluid retention, are given concurrently.*

The overall incidence of skin toxicity was 65%, and was grade 3 or 4 in 7-9% of patients, regardless of the premedication regimen. **Premedication with anti-H1 antagonists appears to increase the overall incidence of skin toxicity (to 72% in 171 patients).** The overall incidence of nail changes was 43% (including discoloration, pain, and onycholysis). Severe nail changes occurred in 3%. Alopecia occurred in 83% of patients.

The overall incidence of neurosensory toxicity was 48%, and was severe in 4%. The manifestations of this toxicity were paresthesias, dysesthesias, and burning pain. Neuromotor toxicity was observed in 14%, and was severe in 4%. Other types of neurotoxicity observed in less than 6% of patients included constipation, headache, anxiety, and cerebellar changes. **An increased incidence of headache and constipation (12 and 10%, respectively) was observed with the use of "short corticosteroids"** (defined as "anti-H1 and/or anti-H2 and corticosteroids, at day 1 and/or day 1 only" or "corticosteroids only, at day 1 and/or day 1 only"). Asthenia was observed in 68%, and was severe in 11%.

Cardiac toxicity was manifested in 30 patients as dysrythmia, as changes in cardiac function in 5 patients, as ischemia in 7 patients, as changes in blood pressure in 61 patients, or as pericardial effusion/ pericarditis (not related to fluid retention) in 2 patients. Myalgias and arthralgias were reported in 12%. There were 51 patients (6%) who developed local toxicity at the injection site (phlebits, estravasation). Docetaxel-related elevations of SGOT and SGPT was reported in 33% and 26% of patients, and were mainly grade 1. Elevations of bilirubin occurred in 11%, all grade 2 or higher. Elevations of alkaline phosphatase occurred in 42%, and were grade 3 in 4%. Grade 1 increase in creatinine was seen in 11%.

9.33 Safety Profile - Docetaxel at 75 mg/m²

As noted above, there were 75 patients treated at the initial planned dose of docetaxel at 75 mg/m². No difference was seen in the incidence of leukopenia, neutropenia, grade 4 neutropenia, infections, thrombocytopenia, or anemia in patients treated at the lower dose. However, febrile neutropenia was less frequent among lower dose patients (12%), as compared to 22% in the 100 mg/m² dose group.

No formal conclusions can be drawn with regard to acute HSRs, fluid retention, skin and neurotoxicity, although the incidence of skin toxicity appeared to be reduced in the lower dose group (45% vs 64%).

9.34 Prognostic Factors

The odds of grade 4 neutropenia in female patients is 40% higher than in male patients; other factors associated with an increased odds of grade 4 neutropenia are higher dose, age over 65, and lower baseline neutrophil counts.

The incidence of neurosensory toxicity was higher in patients who received prior neurotoxic drugs, including cisplatin, vinblastine, vincristine, and vinorelbine (53%), as compared to patients who did not (44%). There was no difference in neuromotor toxicity between these two groups.

Fluid retention was more frequent in female patients (57%) as compared to male patients (36%). This analysis is confounded by the large number of female patients entered on breast cancer trials. Fluid retention was more frequent in patients under 50 years of age.

Asthenia and cardiac dysrhythmias were more frequent in patients over 65 years of age.

9.35 Clinical Benefit

Over 80% of 432 evaluable patients had a stable or improved PFS between baseline and cycle 4. Of 170 patients having analgesic usage recorded at baseline and cycle 4, 29 (17%) had

improvement in analgesic requirement. Sixteen of these patients were responders.

9.4 Phase II Studies: Breast Cancer

Section 7 reviews the safety profile for docetaxel as single agent therapy in metastatic breast cancer. Additional analyses were performed in the ISS as outlined below.

9.41 Safety Profile - Docetaxel at 75 mg/m²

Hematologic Toxicity

There were 55 patients treated at the initial planned dose of docetaxel at 75 mg/m². No difference was seen in the incidence of leukopenia, neutropenia, infection, or anemia in patients treated at the lower dose. However, grade 4 neutropenia and febrile neutropenia were less frequent among lower dose patients (80% and 11%), as compared to the 100 mg/m² dose group (92% and 30%). Thrombocytopenia was also less frequent (6% vs 13%).

Non-Hematologic Toxicity

The incidence of acute HSRs and of fluid retention was no different in the low dose group. However, gastrointestinal, skin and neurotoxicity, asthenia, myalgias and arthralgias were less frequent in the 75 mg/m² dose group.

9.42 Prognostic Factors

The risk of fluid retention increases by 13% for every additional 25 mg/m² in cumulative dose. The risk drops by 30% for every additional 1 g/dl of total serum protein at baseline.

9.5 Phase II Studies: Non-Small Cell Lung Cancer

Section 8 reviews the safety profile for docetaxel as single agent therapy in metastatic non-small cell lung cancer. Additional analyses were performed in the ISS as outlined below.

9.51 Prognostic Factors

The risk of fluid retention increases by 11% for every additional 25 mg/m² in cumulative dose. Patients who have liver metastases at baseline or patients who have already had a response appear more likely to develop fluid retention.

9.6 Phase II Studies: Comparison of Breast and Lung Studies

There were more toxic deaths in the NSCLC patients, primarily due to increased numbers of deaths from infection. More docetaxel-related adverse events lead to withdrawal from study among breast cancer patients.

The overall incidence of grade 3 or 4 neutropenia, febrile neutropenia, infection, thrombocytopenia, and anemia was higher among breast cancer patients. This may be due in part to the higher frequency of bone metastases in breast cancer patients (45% vs 17%), and to the greater proportion of breast cancer patients who were previously treated with chemotherapy (69% vs 33%).

Overall, there was no difference in non-hematologic toxicity between the two tumor types.

9.7 Japanese Studies

Phase I Study

Six dose levels of docetaxel were tested in 27 patients in a phase I study (10 - 90 mg/m²). Seventeen patients received a single dose, the remainder received consecutive cycles every 3-4 weeks, up to a maximum of 4. Docetaxel was administered as a 1-2 hour infusion. The median age was 65 (range 16-77 years) and the male:female ratio was 0.6. The most common histologies seen were NSCLC and ovarian carcinoma.

Dose-dependent neutropenia was the primary toxicity and was dose-limiting (3/3 patients receiving a single dose at 90 mg/m² and 5/6 receiving a single dose at 70 mg/m² had grade 4 neutropenia). The primary non-hematologic toxicities were anorexia, nausea, vomiting, fatigue, and alopecia. The MTD was fixed at 70 mg/m², and the recommended dose for phase II trials was 60 mg/m².

Phase II Studies: Breast and Lung Cancer

A total of 407 patients with breast or non-small cell lung cancer were entered on phase II trials, of which 381 were evaluable for safety. The median WHO performance status was 1 and the male:female ratio was 0.6. The most frequent sites of disease involved the primary tumor or metastases to lymph nodes. One-half had received prior chemotherapy. Docetaxel was administered at 60 mg/m² as a one hour continuous infusion.

Adverse reactions were graded according to Japanese Society for Cancer Therapy Guidelines. Neutropenia occurred in 366 patients, and was grade 3 or 4 in 87%. Thrombocytopenia was noted in 8% of patients; anemia occurred in 57% of patients, and was grade 3 or 4 in 23

patients. **Comment:** *The overall incidence of neutropenia, of grade 3 or 4 neutropenia, and of thrombocytopenia in the Japanese trials is identical to that reported for the high dose US/Canadian and EORTC trials described above; however, the incidence of anemia was lower in the Japanese trials.*

The most common non-hematologic toxicities were alopecia (83%), anorexia (64%), fatigue (55%), nausea and vomiting (49%), fever (41%), diarrhea (21%), skin rash (20%), stomatitis (12%), fluid retention (8%), pain/arthralgias/myalgias (8%), and peripheral neuropathy (7%). **Comment:** *With the exception of alopecia, nausea and vomiting, the incidence of non-hematologic toxicities, including laboratory abnormalities, is much lower in the Japan experience. The spectrum of toxicities is similar, however, to that observed in the high dose studies conducted in other countries.*

Safety Summary: Docetaxel 100 mg/m^2 over 1 hour every 3 weeks

I. Hematologic Toxicity

- Neutropenia was the dose-limiting toxicity and was dose-dependent.
- Neutropenia was severe but reversible and non-cumulative.
- Female sex, age over 65, lower baseline neutrophil counts, and higher dose increased the odds of grade 4 neutropenia. Metastatic breast cancer patients had an increased incidence of severe neutropenia, febrile neutropenia, infection, thrombocytopenia, and anemia: these patients were more likely to have bone metastases and previous chemotherapy than patients with other tumor types.
- Non-small cell lung cancer patients had an increased incidence of death from docetaxel-related infection; the incidence of infection in breast cancer patients was increased among those premedicated with "long" corticosteroids (with or without antihistamines).

II. Acute Non-Hematologic Toxicity

Acute Hypersensitivity Reactions

- Premedication had little positive impact on the incidence of acute HSRs.

Acute Gastrointestinal Toxicity (Nausea, Vomiting, Diarrhea)

- Dose-dependent toxicities
- Premedication had little positive impact on the incidence of acute GI toxicities.

Mucous Membrane Disorder (Stomatitis, Pharyngitis, Esophagitis, etc.)

- A schedule-dependent toxicity, more frequent and severe with prolonged infusions

Cardiac Toxicity

- Incidence was greater in patients over 65

III. Chronic Non-Hematologic Toxicity

Fluid Retention Syndrome

- Dose-dependent and cumulative toxicity with a median dose to onset of 400 mg/m²
- Female sex, age under 50, higher cumulative dose, lower baseline total serum protein, presence of liver metastases, and response to treatment increased the odds of fluid retention
- Antihistamines appeared to worsen fluid retention.
- "Long" corticosteroids (with or without antihistamines) delayed the onset and reduced the severity of fluid retention; additional evidence in support of this claim is forthcoming in RPR's safety update.

Skin Toxicity

- Dose-dependent toxicity
- Premedication had little positive impact on the incidence of skin toxicity; antihistamines appeared to worsen skin toxicity.

Neurotoxicity/Asthenia

- Neurosensory toxicity and asthenia were dose-dependent.
- Incidence of neurosensory (but not neuromotor) toxicity was higher in patients who received prior neurotoxic drugs (including cisplatin, vinblastine, vincristine, and vinorelbine)
- Incidence of asthenia was greater in patients over 65
- Incidence of headache and constipation was increased with use of "short" corticosteroids (with or without antihistamines)

10. Integrated Safety Summary - Updated Analysis

10.1 Program Overview

Volumes 9.1 - 9.12, submitted on November 7, 1994, contain a summary of safety results as of June 30, 1994 (US trials) or May 31, 1994 (EORTC-sponsored trials). Results are presented for 8 phase I studies and 32 phase II studies with docetaxel as single agent chemotherapy for various tumor types, including metastatic breast cancer and non-small cell lung cancer (NSCLC). Altogether, there were 1699 patients evaluable for safety, including 98 new patients: 10 from the TAX252 trial in ovarian cancer (US) and 88 from the TAX281 and TAX286 trials in breast cancer (Europe). Of these, 1010 patients were treated in phase II studies, 935 at the initial planned dose of 100 mg/m² and 75 at the initial planned dose of 75 mg/m².

10.2 Patient Characteristics - Docetaxel at 100 mg/m²

The median age of the 935 patients described above was 57 years (range 26-80), with a male:female ratio of 0.7, and a median WHO performance status of 1. The most common tumor types were breast (34%) and lung (27%). Only 26% of patients had one organ involved, the rest had $\geq$ 2 organs involved. Docetaxel was administered as second line therapy to 39% of patients. Out of a total of 4435 treatment cycles, 27% were given at a reduced dose. Dose reductions were due to hematologic toxicity (156 cycles), non-hematologic toxicity (163 cycles), or both (58 cycles). A treatment delay occurred in 34% of patients, involving 593 cycles. There were 75 deaths on study (42 due to disease progression).

10.3 Safety Profile - Docetaxel at 100 mg/m² and 75 mg/m²

Serious adverse events were reported in 50% of the patients enrolled in the phase II program, including 20 toxic deaths. Of these, 15 were due to neutropenic infection, pneumonia, or sepsis, 1 to cardiac failure with pulmonary edema, 1 to right-sided hemiparesis and drowsiness, 1 to supraventricular tachycardia, and 2 to gastrointestinal hemorrhage in the setting of thrombocytopenia and liver dysfunction.

Adverse events lead to treatment discontinuation in 201 patients: 60 of these patients experienced multiple events. The most frequent causes of treatment discontinuation were: fluid retention (80 patients), allergic reaction (14 patients), neurologic (9 patients), paresthesias and asthenia (8 patients each), and skin toxicity (6 patients).

10.31 Hematologic Toxicity - Docetaxel at 100 mg/m²

The incidence of hematologic toxicities in the updated database was similar to that reported in the original safety update, with 92% of evaluable patients experiencing grade 3 or 4 neutropenia.

The median neutrophil nadir, day to nadir, duration of nadir, and time to recovery were also similar. Febrile neutropenia (fever $\geq$ 38°C, with grade 3 or 4 neutropenia) occurred in 25% of patients, and infection in 20%. The incidence of thrombocytopenia (8%) and of anemia (90%) was also similar. (See Review Section 9.32)

10.32 Non-Hematologic Toxicity - Docetaxel at 100 mg/m²

Table 13A and B (9.1.29 - 9.1.30) summarizes all major docetaxel-related non-hematologic toxicities, regardless of the type of premedication used. No significant change in incidence or severity was observed as compared to the original database. (See Review Section 9.32).

Fluid Retention

In the updated safety summary, 479 of 931 evaluable patients (52%) treated with docetaxel at 100 mg/m² experienced fluid retention, regardless of premedication. Of these, 90 patients (10%) had severe reactions. These findings are similar to those reported in the original Integrated Safety Summary (overall incidence of 47%, severe reactions 9%, 8.117.94). Globally, weight gain was correlated with the appearance of fluid retention.

- **Analysis of the 5-day Dexamethasone Premedication Regimen**

As requested by FDA at the 30-day post-submission teleconference, RPR submitted a retrospective analysis of the efficacy of the 5-day dexamethasone premedication regimen in support of their claim that such pretreatment could ameliorate the incidence and severity of fluid retention associated with docetaxel treatment at 100 mg/m² every 3 weeks. Table 16 (9.1.36) shows that there were 63 patients (32 with breast cancer and 31 with NSCLC) treated in US trials that had been amended to permit the use of dexamethasone 8 mg bid PO for 5 days. Among these, 59 also received concomitant anti-H1 antagonists and 4 received anti-H2 antagonists. Sixty patients actually received premedication from day-1 to day 4 of the docetaxel infusion (the recommended schedule for the dexamethasone in the proposed package insert).

Overall, the incidence of fluid retention with 5-day dexamethasone premedication was 43%, with severe reactions in 6%). There was no difference among premedicated breast cancer and NSCLC patients in the incidence and severity of fluid retention. The median cumulative dose to onset of fluid retention was 508 mg/m². Only one patient withdrew from treatment due to fluid retention.

These results are compared to 118 patients (60 with breast cancer and 58 with NSCLC) from 11 studies who never received premedication: the overall incidence was 61% (77% for breast cancer and 45% for NSCLC patients). Severe reactions were observed in 13% overall, in 20% of breast cancer patients and 5% of NSCLC patients. The difference between the two tumor types could be explained by the higher number of cycles given to the breast cancer patients (a

median of 5 cycles/breast cancer patient vs 4 cycles/NSCLC patient). The median cumulative dose to onset of fluid retention was 395 mg/m². Twenty-five patients (35%) withdrew from treament due to fluid retention.

Comment: *The overall incidence of fluid retention was reported as 40%, severe in 7%, for 315 patients treated at docetaxel 100 mg/m² without premedication in the entire phase II program (Table 47B, original ISS). When breast cancer patients are looked at separately (60 patients, Table 74B, original ISS and reiterated in Table 17 of the updated safety summary) fluid retention appears more frequent and severe without premedication as compared to the NSCLC patients (58 patients, Table 102B, original ISS and reiterated in Table 17 of the updated safety summary). Note that in addition to the higher cumulative dose given in breast cancer, these patients had other prognostic indicators presumed to be related to the development of fluid retention, namely, female sex, younger age, higher incidence of liver metastases, and higher response rates to treatment. The benefit of the 5-day dexamethasone regimen may not be simply for breast cancer patients but for any patient with this cluster of prognostic features, regardless of tumor type. The NSCLC patients do as well with no premedication as with the 5-day regimen.*

FLUID RETENTION BY PATIENT (100 mg/m²)

	No Premedication		5-Day Dexamethasone	
Patient Type	Overall Incidence	Severe	Overall Incidence	Severe
All Phase II	40% (126/315)	7% (21/315)	-	-
Breast Cancer	77% (46/60)	20% (12/60)	43% (14/32)	6% (2/32)
NSCLC	45% (26/58)	5% (3/58)	42% (13/31)	6% (2/31)

Tables 47B, 74B, and 102B, Integrated Summary of Safety, 7/27/94;
Tables 16 and 17, Safety Update Report, 11/7/94

Next, RPR reported on 115 patients from 3 studies that were never amended to allow premedication were analyzed (TAX221, TAX237, and TAX223). The overall incidence in this group ("no premedication planned") was 64%, and severe reactions were noted in 14% of patients. Again, the breast cancer patients fared worse than the NSCLC patients. The median cumulative dose to onset of fluid retention was 399 mg/m².

Comment: *Although the number of patients that actually received the proposed 5-day*

dexamethasone premedication regimen is small, and the onset of fluid retention is delayed by only one treatment cycle, most patients developing this toxicity while receiving this premedication could continue docetaxel treatment. This kind of information is crucial to the recommendation of this regimen in the proposed package insert. In light of these findings, the reviewer suggests that the package insert be amended to reflect the results for the 63 patients (43% overall incidence, 6% severe) that actually received the 5-day course of dexamethasone, rather than the 82 patients that received "type 3" premedications (see 2.1.22).

Finally, two new studies (TAX286 and TAX281) in breast cancer patients mandated premedication with a triple-drug regimen (corticosteroids, anti-H1 and anti-H2 antagonists) given prior to docetaxel. These patients fared no better (perhaps worse) than those given no premedications (see below).

Comment: *The reviewer remains concerned over the possible harmful effects of antihistamines with respect to the incidence and severity of fluid retention (see 8.117.95). Note that the majority of the 63 patients on the 5-day dexamethasone regimen also received anti-H1 antagonists. Would they have fared better with steroids alone? The reviewer suggests prospective evaluation of the 5-day dexamethasone regimen (with and without antihistamines) in ongoing and/or future trials, so that its benefits and risks can be fully evaluated.*

- **TAX265: Randomized Premedication: Cetirizine + Methylprednisolone versus Cetirizine alone**

The TAX265 trial, conducted by Dr. M. Piccart of the EORTC Breast Group Phase II Working Party, opened on November 10, 1992 and is ongoing. It is a phase II trial evaluating docetaxel as second line treatment for metastatic breast cancer. Docetaxel 50 mg/m² is given on day 1 and day 8 every 3 weeks. Patients are randomized to receive the anti-H1 antagonist cetirizine chlorhydrate 10 mg with or without methylprednisolone 40 mg on d-1, d1, d2, and d7, d8, and d9 of each treatment cycle. An interim analysis is presented on 70 patients 35 in each of the two premedication regimens (9.11.193 - 9.11.390). The two patient groups were well balanced in terms of baseline characteristics, and were fundamentally similar to patients entered on the TAX221 EORTC-sponsored trial (i.e., no definition of anthracycline-resistance was specified). While 56% of treatment cycles given with steroids delivered full dose docetaxel, only 37% of cycles given without steroids delivered full doses. "Reduced cycles" were given as follows (in decreasing frequncy): 40 mg/m² on day 1 and day 8, 50 mg/m² on day 1 only, or 40 mg/m² on day 1 only. (The original protocol for this trial was not submitted for review.)

The addition of methylprednisolone to the premedication regimen prolonged the onset of edema by 5 weeks, and of pleural effusion by 6 weeks. Consequently, the median

cumulative dose to onset of these toxicities was higher in the group receiving steroids (550 vs. 298 mg/m² for edema, 498 vs 296 mg/m² for pleural effusion). Among 20 patients withdrawing treatment due to toxicity, fluid retention was the reason in 1/8 patients treated with steroids, and in all 12 patients not premedicated with steroids. The median cumulative dose for these 12 patients at off study was only 375 mg/m².

Comment: *Note that the schedule in this trial, day 1 and day 8 every 3 weeks is not that which was used in pivotal trials or is proposed in RPR's package insert. In addition, in the phase I program, this regimen was associated with a higher incidence of fluid retention than single dose regimens of docetaxel. Again, the most impressive benefit of corticosteroid premedication is that more patients could continue therapy despite the development of fluid retention. Given that the antihistamines may be exacerbating fluid retention, one wonders if the steroid effect was diminished by their inclusion. Based on these encouraging preliminary results, premedication with corticosteroids seems warranted. At present, it remains unclear as to what the optimum length of corticosteroid treatment should be: what is the advantage of a 5-day over a 3-day regimen? What is the compliance rate among patients on a 5-day course vs. a 3-day course?*

- **Pathophysiology: TAX029**

The TAX029 trial, conducted by Dr. G. Lagrue of France, opened on January 4, 1994, and is ongoing. It is a phase I/II trial evaluating the pathophysiology of edema in patients with advanced breast or ovarian cancer who are receiving docetaxel at 100 mg/m² every 3 weeks without premedication, diuretics, or calcium antagonists. In case of severe fluid retention that could lead to docetaxel discontinuation, symptomatic treatment with Diosmine-Hesperidine (Daflon 500), 2 gm/day could be prescribed. Note that the docetaxel was provided as a solution of 40 mg/ml in polysorbate, but the solvent contained ethylacohol 95%/water 13/87 w/w. **Comment:** *The solvent typically used in pivotal trials was 5% dextrose or 0.9% saline, presumably free of ethylalcohol. Physiologic alterations noted in this trial should take into account the presence of ethylalcohol in the excipient.*

An interim report on the first 15 evaluable patients who received at least 4 cycles was submitted (9.11.117 - 9.11.175). Twelve of the 15 patients have developed fluid retention, and 5 of these have discontinued treatment. **Comment:** *An incidence of fluid retention in 80% is much higher than the overall incidence of 40% in 315 patients given no premedication reported in Table 47B, ISS).*

Preliminary results from the following tests were presented: capillary filtration test (using ^{99m}Tc-albumin), lymphatic oscillations, and microcirculation tests (lower extremity volumetry, laser doppler, periungueal capillaroscopy). The investigators postulate that fluid retention develops by the following process: after 2 cycles of docetaxel, excessive transcapillary filtration of proteins leads to an abnormal retention of albumin within the interstitial space;

between the second and fourth cycle, signs of lymphatic failure are notable; and after the fifth cycle, lymphatic drainage is unequivocally impaired. Five patients premedicated with Daflon showed decreased albumin retention. **The investigators propose the use of flavonoids as premedication, such as Diosmine-Hesperidine, beginning at cycle 1, with increasing doses at cycle 4 as necessary. In addition, treatment with Benzopyrones, derivatives of coumarin, that lyse proteins and facilitate their elimination by the lymphatic system, or manual lymphdrainage may also be beneficial. Comment:** *These results are very preliminary. To the best of the reviewer's knowledge, the proposed premedications are not widely used by US physicians at the present time.*

- **Pathophysiology: TAX248**

The TAX248 trial, sponsored by the EORTC Clinical Screening Cooperative Group, opened on April 8, 1992 and is ongoing. It is a phase II trial evaluating docetaxel as second or third line treatment for advanced ovarian cancer, recurrent and/or refractory to platinum. As of June 30, 1994, 138 patients have been registered and treated with docetaxel at 100 mg/m² every 3 weeks without premedication. A preliminary report of immunologic findings in eight patients is presented (9.11.176 - 9.11.192).

Eight patients who had received a minimum of 2 cycles were selected for further immunologic evaluation, including assay of NK/LAK cell populations, and of IL-2, IL-2 receptor, interferon-γ, and TNF levels. Lymphocyte subpopulations were assayed by flow cytometry after FICOLL separation. Cytokine assays were performed using commercially available ELISA kits. Treatment with docetaxel did not alter circulating levels of IL-2, IL-2 receptor, interferon-γ, and TNF in 8 patients with ovarian cancer. However, 3 patients had normal levels of circulating NK/LAK cells at baseline (8%), which rose to a maximum of 21% at 1 hour after the first infusion. Seven patients had elevated levels (25%) at the start of cycles 2-6, which rose even further (to 34%) at 1 hour after infusion. **This latter finding suggests that circulating lymphocytes with the NK/LAK phenotype are elevated both at the time of infusion and chronically during docetaxel treatment. The investigators postulate that docetaxel-related capillary hyperpermeability (see TAX029 trial) may be mediated by NK/LAK cells which are known to be directly toxic to capillary endothelial cells. Comment:** *Although these results are preliminary, they are intriguing. Evaluation of additional patients is warranted.*

- **Updated Cox Regression: Fluid Retention**

Conclusions regarding prognostic factors for the development of fluid retention remain essentially unchanged from the original Integrated Safety Summary.

Skin Toxicity

The overall incidence and severity of skin toxicity was not reduced in the 63 patients noted above premedicated with a 5-day course of dexamethasone (65% overall, 8% with grade 3-4 toxicity), as compared to patients who were not premedicated (118 patients) or to patients for whom no premedication was planned (115 patients).

In the TAX265 trial, the time to onset and the cumulative dose to onset of skin toxicity was not affected by the addition of a 3-day course of methylprednisolone to the anti-H1 antagonist, cetirizine.

Comment: *These findings are consistent with conclusions drawn in the original Integrated Safety Summary.*

Hypersensitivity Reactions

The sponsor performed a retrospective analysis of the incidence and severity of acute HSR's depending upon the following types of premedication at cycle 1: none, antihistamines only, corticosteroids (and/or antihistamines) given at day-1 or day 1 of the infusion. Overall, the incidence of acute HSR's was not affected by premedication of any type. Grade 3-4 reactions occurred in 2-7% of patients regardless of premedication, except for patients receiving corticosteroids on day-1 (no grade 3-4 reactions were noted). **Comment:** *These findings are consistent with conclusions drawn in the original Integrated Safety Summary.*

10.5 Update - Efficacy of Docetaxel in Metastatic Breast Cancer

The sponsor has provided an update of the duration of response, time to progression and survival for patients with metastatic breast cancer treated in three pivotal trials (TAX233, TAX267, and TAX221) and in four supportive trials (TAX266, TAX228, TAX237, and TAX280) using new cut-off dates: May 31, 1994 for European studies and June 30, 1994 for US studies.

In addition, efficacy data for two new supportive trials, TAX281 and TAX286, which were not included in the original NDA submission (July 27, 1994), is submitted, with a cut-off date of May 31, 1994.

The median follow-up time increased to 18 months for previously treated patients (at 100 mg/m^2) and 15 weeks for the subset of anthracycline-resistant patients. No difference between the original and updated analysis was observed in the median duration of response among the different subgroups. The median duration of response was 28 weeks (range 3+ to 76 weeks) for the previously treated patients (at 100 mg/m^2) and 27 weeks (range 9 to 76

weeks) for the anthracycline-resistant patients. Twelve of 54 responders (22%) in the previously treated group were censored, 8 due to further anticancer therapy and 4 due to lack of progression at the new cut-off date. Five of 40 responders (13%) in the anthracycline-resistant group were censored, 1 due to further anticancer therapy and 4 due to lack of progression at the new cut-off date.

No significant difference was observed in the median time to progression using the new cut-off date. For previously treated patients, the median time to progression was 20 weeks (20/111 patients censored, 15 due to further anticancer therapy and 5 due to lack of progression at the new cut-off date). For anthracycline-resistant patients, the median time to progression was 19 weeks (9/83 patients censored, 4 due to further anticancer therapy and 5 due to lack of progression at the new cut-off date).

No significant difference was observed in median survival using the new cut-off date. For previously treated patients, the median survival was 11 months and for anthracycline-resistant patients, the median survival was 10 months (range 0-25 months for both groups). At the new cut-off date, 71% of patients had died in these groups.

Comments: *Note that "anthracycline-resistant" here includes patients who were mitoxantrone-resistant: only 60 patients in the pivotal trials were actually resistant to doxorubicin. Time to disease progression and survival were not protocol-defined objectives in these trials. While the survival data are encouraging, caution should be applied in comparing a median survival of 11 months in 111 patients in phase II studies of docetaxel with 11.7 months in 235 patients in a phase III trial of paclitaxel.*

10.51 TAX286 Trial

A comprehensive study report was submitted for this phase II trial in anthracycline-resistant metastatic breast cancer patients in support of the proposed indication for docetaxel as second line therapy in breast cancer (9.12.138 - 9.12.268). The protocol and electronic data were submitted for review on November 18, 1994.

This study was conducted in 13 centers in Europe (Dr. M. Marty, Study Chairman) between June 14, 1993 and January 18, 1994. The eligibility criteria for this trial were stricter than those for the TAX233 and TAX267 trials conducted in anthracycline-resistant patients: 1) patients resistant to mitoxantrone were excluded, 2) patients must have had stable disease after 4 cycles of first line anthracycline-containing therapy for metastatic disease or metastatic progression on adjuvant or first line therapy, and 3) patients dosed with $\geq$ 550 mg/m^2 of doxorubicin or $\geq$ 900 mg/m^2 of epirubicin were required to have an LVEF of 50% or greater. All patients were scheduled to receive docetaxel 100 mg/m^2 as a one hour infusion every 3 weeks. Routine premedication with methylprednisolone 32 mg, cetirizine 10 mg, and ketotifen 1 mg, 12 and 3 hours before docetaxel treatment was mandated. Dose

modifications, efficacy and safety assessments were carried out as in the TAX221 trial. The database was frozen on October 13, 1994.

Patient Eligibility

Fifty-two patients were registered, but one was not treated due to elevated liver function tests. Ten patients were considered ineligible and four non-evaluable for response. Thus, 51 patients were evaluable for safety and 38 for efficacy. Of the 51 patients, 30 withdrew for disease progression, 11 withdrew for toxicity, and 5 died (2 to toxicity). Fluid retention alone or in combination with other toxicities lead to treatment discontinuation in 7 patients (14%), 3 of which were PRs.

Patient Characteristics

The median age was 47 years (range 27-72 years), and the median baseline WHO PFS was 1.0. A median time of 25 months (range 0.3-316) separated the time of diagnosis and study entry. The most common tumor histology was infiltrating duct carcinoma. Fifty patients had metastatic disease at entry; nearly 80% of patients had 2 or more organs involved. Liver involvement was present in 43% of patients. The median number of prior chemotherapy regimens was 2 (range 1 to 3): the median time between last chemotherapy and first infusion of docetaxel was 1.4 months (range 0.7 - 9.7 months). Twenty five patients had progressive disease as the best response to first line therapy and 5 relapsed while on anthracycline adjuvant therapy (so-called anthracycline-refractory patients). A total of 258 treatment cycles were delivered, 209 (81%) of which were at the 100 mg/m² dose. The median number of cycles given was 5 (range 1-12); the median relative dose intensity was 0.95 (range 0.66-1.02). Dose delays or dose modifications were required in 16 patients (31%). Treatment delays were due primarily to non-drug related reasons, while dose modifications were frequently due to hematologic toxicity.

Efficacy Results

- **Tumor Response Rate**

Among the 52 patients entered on this trial and included in the intent to treat analysis, there were 15 PRs and no CRs, with an overall response rate of 29% (CI= 18%; 44%). High response rates were observed in breast lesions (56%), skin (55%), and lymph nodes (44%). Response rates in liver and lung were much lower (14% and 22%). A response rate of 33% was noted in 30 anthracycline-refractory patients (having progressed as the best response to prior anthracyclines for advanced disease or relapsed on adjuvant therapy). A higher response rate was observed in older patients than younger patients (58% for ages 50-65 years vs. 23% for ages 35-49 years). **Comment:** *Tumor responses were confirmed by review of eletronic data installed in Paradox 5.0 for Windows files on 11/18/94 and are summarized in*

*the table below. Tumor sites in bold typeface had complete regression; sites followed by an * had major regressions (75% or better). All patients had at least one bidimensionally measurable lesion at baseline that met the protocol-defined size requirements (at least one diameter ≥ 2 cm on CT or ultrasound; palpable lesions or lung lesions on chest xray could be ≥ 1 cm) except for patients Patients had a major response in a lesion ≥ 5 cm (in skin and breast).*

RESPONSES (ITT) - TAX286

Investigator/Patient Number	Sites of Response (Bidimensional Lesions)	Response Duration (weeks)
FR00194:	**Skin**	18
	Lymph nodes (1, 2)	14
	Liver (1, 2*, 3)	27
FR00010:	Liver *	24
	Breast, lung (1*, 2)	22
FR00007:	Breast*, lymph node, skin (1, 2, 3)	22
	Breast (1*, 2), lymph node*	19
FR00279:	**Skin (5)**	24
	Lymph node (1*, 2, 3), skin (1*, 2*, 3, 4, 5), breast, chest wall*	25
FR00201:	Breast, lymph node (1*, 2)	23
FR00284:	**Lymph node (3)**	12+
FR00011:	**Skin, breast***	28+
BE00063:	**Lymph node (3), skin**	33
GB00148:	**Breast***	27+
CH0002:	**Lymph node**	18+

Comment: *RPR pools all the anthracycline/anthracenedione-resistant patients treated on the TAX233 and TAX267 trial with the 51 patients on this trial and reports an overall response*

rate of 41% (CI=33%; 49%) for a total of 134 patients (Table 10, Study Update, Metastatic Breast Cancer). Note that this patient population is fairly heterogenous with respect to prior response to doxorubicin or mitoxantrone. Perhaps a more valid observation can be made for the subset of anthracycline-refractory patients who can be rigorously defined, albeit retrospectively, and who represent the worst prognosis. In this group, the overall response rate was 35% (22/63 patients from TAX233, TAX267 and TAX286), including 2 CRs and 20 PRs (see the original Integrated Summary for Metastatic Breast Cancer, 8.118.59).

- **Response Duration**

The median duration of response in all responding patients (intent to treat analysis) was 24 weeks (range 12+ to 33 weeks). **Four of 15 responders were censored for this analysis, one due to further hormonotherapy, and three due to lack of documentation of progression at the cut-off date. Comment:** *The reviewer agrees with RPR's calculation of response durations in this trial.*

- **Other Endpoints**

The median time to first response was 20 weeks (range 1+ to 23+), although this value is not accurate due to the large number of censored patients (36 patients). The median time to progression was 16 weeks (range 1+ to 39 weeks). **Nine of 51 patients were censored for this analysis: 3 due to further anticancer therapy and 6 due to lack of documentation of progression at the cut-off date.** The median survival was 10 months (range 0 to 11+ months). As of May 31, 1994, 19 patients had died and 32 were alive.

- **Quality of Life Assessments**

The electronic data confirms that there were 38 patients with WHO PFS recorded at baseline and at cycle 4 and 22 with PFS recorded at baseline and at cycle 6. The majority of patients had a stable PFS, with only 1 patient reported as having declined from 0 to 3 (patient .

Safety Results

Out of 51 patients evaluable for safety, the most frequent adverse events were: leukopenia, neutropenia and anemia (all patients), asthenia (40 patients), neurosensory (33 patients), alopecia (32 patients), fluid retention (30 patients), fever (21 patients), pain (20 patients), skin toxicity (19 patients), nausea (18 patients), diarrhea and nail changes (17 patients each), stomatitis (15 patients), infection (11 patients), pulmonary (10 patients), and vomiting (9 patients). The most frequent serious adverse events were febrile neutropenia (12 patients) and 7 episodes of infection, including 1 death due to septic shock.

- **Hematologic Toxicity**

Leukopenia and neutropenia were observed in all treated patients: 98% had grade 3 or 4 neutropenia. The incidence of neutropenia was not affected by the number of prior chemotherapy regimens, the time elapsed between the end of prior chemotherapy, or dose level. The median neutrophil nadir was 0.1 x 10^3 /mm^3 (range 0.0-1.5). The median day to nadir of neutrophils was 9 days; the median duration of grade 4 neutropenia was 7 days (range 1-14 days). Only one cycle did not show recovery by day 22 $\pm$ 3.

Thrombocytopenia was noted in only 3 patients, although grade 4 toxicity was noted in 1 patient with tumor-related liver failure and markedly elevated bilirubin and SGOT levels (patient . Anemia was observed in all patients, and was grade 3 or 4 in only 4 patients. The median nadir of hemoglobin was 10.0 g/dl (range 5.2-11.7), with a median day to nadir of 8 days. In this trial, 23 patients had anemia at entry; 3 patients required transfusions.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 16 patients (31%) resulting in hospitaliz .tion in 12. Eighteen episodes of infection occurred in 11 patients: 17 of these episodes (94%) were associated with grade 3 or 4 neutropenia, including one toxic death.

- **Non-Hematologic Toxicity**

Among 51 treated patients, only 7 had acute HSR's, all grade 1. These reactions were manifested by facial rash or flushing, hypertension, or tachycardia. Only two infusions were temporarily interrupted. No patient discontinued treatment because of an HSR.

Nausea and vomiting occurred in 35% and 18% of patients respectively. All reactions were grade 1 or 2. Diarrhea occurred in 33% of patients, but was grade 3-4 in three patients. Stomatitis occurred in 29% of patients and was grade 1 or 2 only, except for the one patient with tumor-related liver failure (patient).

Thirty-three patients experienced neurosensory toxicity. Two cases of severe peripheral neuropathy contributed to treatment withdrawal. Three patients experienced neurosensory and neuromotor toxicity: two of these discontinued treatment. Two patients experienced anxiety or "nervous excitation" on the day of treatment. Myalgias were noted in 9 and arthralgias in 3 patients. Asthenia was noted in 78% and was severe in 6 patients. Among patients with asthenia concomitant neurosensory toxicity was reported in 22, neuromotor toxicity in 2, and fluid retention in 16.

Fluid retention was noted in 30 patients (58%), and was severe in 4 (8%). Seven patients discontinued treatment due to fluid retention, 3 of these had severe reactions. (Thus, a total of 8 patients had treatment compromised by this toxicity.) The median cumulative dose to

onset of fluid retention was 401 mg/m². The cumulative dose in the 7 patients who withdrew treatment ranged from 394 to 600 mg/m². **Comment:** ***The incidence and severity of fluid retention reported with this triple-drug premedication regimen is intermediate between no premedication and the 5-day dexamethasone regimen (see table above).***

Skin toxicity was noted in 37%, but was grade 3-4 in only 3 patients. One patient had grade 4 desquamation of hands and feet with angioedema in cycle 2. Seventeen patients (33%) had mild to moderate nail changes. Alopecia was reported in 63% of patients.

There were elevations of SGOT and SGPT in 56% and 47% of patients: none were grade 4. Total bilirubin was increased in 5 patients, grade 4 in two patients with progressive liver metastases. Alkaline phosphatase was elevated in 42%. Hypoalbuminemia was noted in 42%, but only 6 patients had albumin levels < 3 g/dl. Serum creatinine elevations in two patients were associated with hemorrhage and piroxicam intake.

10.52 TAX281 Trial

A comprehensive study report was submitted for this phase II trial in previously untreated metastatic or locally advanced breast cancer patients in support of the proposed indication for docetaxel as second line therapy in breast cancer (9.12.1 - 9.12.137). At the time of this writing, no primary data or statistical tables had been submitted for review. The protocol was submitted on November 18, 1994.

This study was conducted in 13 centers of the EORTC Clinical Screening Cooperative Group (Dr. P. Fumoleau, Study Chairman) between August 17, 1993 and January 7, 1994. The eligibility criteria for this trial were similar to those for first line patients entered on the TAX221 trial: patients may not have had prior chemotherapy for advanced disease. All patients were scheduled to receive docetaxel 100 mg/m² as a one hour infusion every 3 weeks. Routine premedication with prednisone or prednisolone 130 mg orally, 12 and 6 hours prior to docetaxel, diphenhydramine 50 mg or dexchlorpheniramine 5 mg IV 30 minutes prior, and ranitidine 50 mg or cimetidine 300 mg IV 30 minutes before docetaxel treatment was mandated. Dose modifications, efficacy and safety assessments were carried out as in the TAX221 trial. The study follow-up cut-off date was May 31, 1994.

Patient Eligibility

Thirty-seven patients were registered: all patients were considered eligible and evaluable for response and safety. Of the 37 patients, 6 withdrew for disease progression, 18 withdrew for toxicity, and 3 died (due to progression). **Fluid retention lead to treatment discontinuation in 16 patients (43%), 13 of which were responders.**

Patient Characteristics

The median age was 48 years (range 29-65 years), and the median baseline WHO PFS was 1.0. A median time of 36 months (range 0.2-168) separated the time of diagnosis and study entry. The most common tumor histology was infiltrating duct carcinoma. Thirty-six patients had metastatic disease at entry; nearly 80% of patients had 2 or more organs involved. Liver involvement was present in 41% of patients. Prior chemotherapy as adjuvant or neo-adjuvant treatment had been given to 24 patients, 21 of which had exposure to anthracyclines. The median time between last chemotherapy and first infusion of docetaxel was 32 months (range 13-143 months). A total of 200 treatment cycles were delivered, 179 (90%) of which were at the 100 mg/m² dose. The median number of cycles given was 5 (range 1-10); the median relative dose intensity was > 0.96. Dose delays or dose modifications were required in 6 and 7 patients, respectively. Treatment delays were due primarily to non-drug related reasons, while dose modifications were frequently due to hematologic toxicity.

Efficacy Results

- **Tumor Response Rate**

Among the 37 patients there were 23 PRs and 2 CRs, with an overall response rate of 68% (CI= 50%; 82%, intent to treat analysis). High response rates were observed in all sites except lung: breast lesions (67%), skin (100%), lymph nodes (79%), liver (77%), and lung (0%). The complete responses were seen in patients with skin or lymph node involvement only. **Comment:** *The overall response rate here is the highest reported in first line breast cancer. Among 117 previously untreated patients receiving docetaxel at 100 mg/m² as initial therapy, the overall response rates were 46% (11 patients, TAX221), 54% (37 patients, TAX266), 54% (35 patients, TAX228), and 65% (34 patients, TAX237).*

- **Response Duration**

The median duration of response in all responding patients (intent to treat analysis) was not reached. **Eighteen of 25 responders were censored for this analysis, three due to further therapy, and 15 due to lack of documentation of progression at the cut-off date.**

- **Other Endpoints**

The median time to first response was 7 weeks (range 1+ to 22+). The median time to progression was 31 weeks (range 1 to 36+ weeks). **Twenty-one of 37 patients were censored for this analysis: 5 due to further anticancer therapy and 16 due to lack of documentation of progression at the cut-off date.** The median survival had not been reached: the median follow-up was only 7 months. As of May 31, 1994, 6 patients had died

and 31 were alive.

- **Quality of Life Assessments**

The study report does not indicate how many patients had WHO PFS recorded at baseline and at cycle 4 or 6, however, the majority of patients had a stable PFS during the trial.

Safety Results

Out of 37 patients evaluable for safety, the most frequent adverse events were: leukopenia, neutropenia, and alopecia (36 patients each), anemia (34 patients), fluid retention (33 patients), neurosensory (30 patients), asthenia (27 patients), skin toxicity and nausea (18 patients each), diarrhea (15 patients), stomatitis (14 patients), and vomiting (10 patients). The most frequent serious adverse event was febrile neutropenia (6 patients). There were no toxic deaths.

- **Hematologic Toxicity**

Leukopenia and neutropenia were observed in 36 patients: 97% had grade 3 or 4 neutropenia. The incidence of neutropenia was not affected by prior chemotherapy or dose level. The median neutrophil nadir was 0.1 x 10^3 /mm^3 (range 0.0-3.3). The median day to nadir of neutrophils was 9 days; the median duration of grade 4 neutropenia was 6 days (range 2-14 days). No cycle failed to show recovery by day 22 $\pm$ 3.

Thrombocytopenia was noted in only 2 patients, although grade 3 toxicity was noted in 1 patient with multiple liver metastases and altered docetaxel clearance (patient
Anemia was observed in 34 patients, and was grade 3 in only 2 patients.

Febrile neutropenia (fever > 38°C with grade 3 or 4 neutropenia) occurred in 13 patients (35%). Seven episodes of infection occurred in 6 patients.

- **Non-Hematologic Toxicity**

Among 37 treated patients, only 7 had acute HSR's, all grade 1. These reactions were manifested by flushing, hypertension, or dyspnea. Only three infusions were temporarily interrupted. No patient discontinued treatment because of an HSR.

Nausea and vomiting occurred in 49% and 27% of patients respectively. All reactions were grade 1 or 2. Diarrhea occurred in 41% of patients, and was grade 1 or 2 only. Stomatitis occurred in 38% of patients and was grade 3 in 2 patients.

Thirty patients experienced grade 1 or 2 neurosensory toxicity. One of these also developed grade 1 neuromotor toxicity. Mild to moderate asthenia was noted in 27 patients.

Fluid retention was noted in 33 patients (89%), and was severe in 4 (11%). Sixteen patients discontinued treatment due to fluid retention, 4 of these had severe reactions. The median cumulative dose to onset of fluid retention was 301 mg/m². The median cumulative dose in patients who withdrew treatment was 698 mg/m² (range 98+ to 995). **Comment:** *The incidence and severity of fluid retention reported with this triple-drug premedication regimen is no better than that reported for no premedication in the TAX237 and TAX280 trials conducted by the same group of investigators.*

Skin toxicity was noted in 49% but was grade 1 or 2, except for one patient who had a serious local reaction, considered initially to be erysipelas. Twenty-four patients (65%) had mild to moderate nail changes. Alopecia was universal.

There were elevations of SGOT and SGPT in 38% and 27% of patients: none were grade 3 or 4. Total bilirubin was increased in 2 patients, grade 1 or 2 only. Hypoalbuminemia was noted in 27%. Grade 1 creatinine elevations in five patients and grade 3 hypomagnesemia was noted in 2 patients.

10.6 Update - Efficacy of Docetaxel in Metastatic Non-Small Cell Lung Cancer

The sponsor has provided an update of the duration of response, time to progression and survival for patients with metastatic non-small cell lung cancer treated with docetaxel as first line (TAX223, TAX231, TAX232, and TAX269) and second line therapy (TAX270 and TAX271) using new cut-off dates: May 31, 1994 for European studies and June 30, 1994 for US studies.

The median follow-up time increased to 21 months for previously untreated patients and 18 months for previously treated patients (all treated at the initial dose of 100 mg/m²). No difference between the original and updated analysis was observed in the median duration of response: 25 weeks (range 9.6 to 82+ weeks) for the previously untreated patients and 29 weeks (range 18-77 weeks) for the previously treated patients. Eleven of 43 responders (26%) in the previously untreated group were censored, 4 due to further anticancer therapy and 7 due to lack of progression at the new cut-off date. One of 15 responders (7%) in the previously treated group was censored due to lack of progression at the new cut-off date.

No difference was observed in the median time to progression using the new cut-off date. For previously untreated patients, the median time to progression was 14 weeks (28/160 patients censored, 16 due to further anticancer therapy and 12 due to lack of progression at the new cut-off date). For previously-treated patients, the median time to progression was also 14 weeks (9/88 patients censored, 1 due to further anticancer therapy and 8 due to lack

of progression at the new cut-off date).

No significant difference was observed in median survival using the new cut-off date. For previously untreated patients, the median survival was 9 months (range 0-23 months). For previously treated patients, the median survival was also 9 months (range 0-23 months). At the new cut-off date, 61% and 73% of patients had died in these groups.

Comment: *All but one patient in the second line therapy trials (TAX270 and TAX271) failed to respond to cisplatin and/or carboplatin. Hence, "previously treated" here is synonymous with "platinum failure".*

11. Oncology Drugs Advisory Committee Meeting - December 13, 1994

The Oncology Drugs Advisory Committee reviewed NDA #20,449 [Taxotere® (docetaxel) for injection concentrate] for the treatment of "patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed; prior therapy should have included an anthracycline unless clinically contraindicated; and for the treatment of "patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy". Dr. Charles Schiffer, Professor of Medicine and Oncology, University of Maryland Cancer Center, presided. Primary discussants were: Dr. James Ingle, Professor of Oncology, Mayo Clinic, for breast cancer; and Dr. Paul Bunn, Director, University of Colorado Cancer Center, for lung cancer.

Question 1a: Given the high response rate, reasonable response duration, performance status and pain data, and constellation of hematologic and non-hematologic toxicities, is Taxotere approvable for the treatment of "patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed"?

Committee members expressed interest in Taxotere as a single agent in the treatment of metastatic breast cancer given the response rates in previously treated patients, the majority of whom were rigorously defined as anthracycline-resistant prior to study entry (overall response rate in 163 patients was 42%, 95% CI = 35; 50). Tumor response data had been confirmed by an independent review panel as well as by this reviewer. However, the following reservations were also voiced:

The four pivotal trials in breast cancer were phase II in design: response rates typically decline when a given agent is tested in randomized clinical trials, with the participation of multiple centers and inclusion of larger numbers of patients, many of whom are not the "best" patients. It was pointed out that for the two US trials (TAX233 and TAX267), most of the patients were entered and treated at a single site (MD Anderson and San Antonio, respectively), even though other sites also participated.

The number of durable complete responders was low: there were only four CRs lasting 6, 6, 7, and 12 months.

Quality of life data were sketchy due the small numbers of patients evaluable for analgesic use and tumor-related symptoms at baseline and subsequent cycles. Furthermore, efforts to correlate symptom improvement and objective response were hampered by the onset of cumulative toxicity, fluid retention in particular, developing in later cycles among responders.

Finally, members summarized the Taxol NDA applications that were reviewed previously. The clinical experience with Taxol included not only phase II trials, but also a randomized

dose-response trial in breast cancer in which patients on the high dose arm showed a superior time to disease progression than those on the low dose arm. In addition, the NCI Treatment Referral Center program provided comprehensive supportive efficacy and safety data on several hundred patients with ovarian and breast cancer.

Members were concerned with the high degree of hematologic toxicity experienced with Taxotere: especially the 25% overall incidence of febrile neutropenia and 15 (of 20) toxic deaths related to neutropenic infection. These figures were believed to be unacceptably high in good performance status patients many of whom were treated at major US cancer centers.

There was also great concern over the array of non-hematologic toxicities experienced among (1010) patients evaluable for safety in the phase II Taxotere program, including: hypersensitivity reactions (overall 31%, grade 3-4 in 7%), nausea, vomiting and diarrhea (overall 28-45%, grade 3-4 in 12%), mucositis (overall 41%, grade 3-4 in 6%), neurosensory toxicity (overall 48%, grade 3 in 4%), skin toxicity (overall 64%, grade 3-4 in 8%), asthenia (overall 68%, severe in 11%), and fluid retention (overall 52%, severe in 10%). In particular, skin toxicity, asthenia, and fluid retention were not reported toxicities with Taxol. The question of whether too high a dose was chosen for the phase II Taxotere program was also raised.

Comment: *The incidence of toxicities among 402 patients treated with Taxol as reported in the package insert are: grade 3-4 neutropenia (92%), infections (35%), 5 septic deaths; hypersensitivity reactions with premedications (overall 41%, severe in 2%); nausea and vomiting (59%), diarrhea (43%), mucositis (39%); peripheral neuropathy (overall 62%, severe in 4%).*

The Committee's first vote on Dr. Ingle's motion against approval was: 3 yes, 5 no.

The discussion then focused on whether the sponsor should seek conditional approval for Taxotere in metastatic breast cancer, under the accelerated approval mechanism. This allows marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is likely to predict clinical benefit (CFR 314, Subpart H).

Dr. Bunn stated that approval using this mechanism would be contingent upon the demonstration of net clinical benefit in phase III randomized trials. At a minimum, the TAX311 trial comparing Taxol and Taxotere in previously treated metastatic breast cancer should be submitted for review. Preferably, results from all three ongoing phase III trials in breast cancer should be reviewed. However, as these trials were only recently opened to accrual, it could be 3 years before ODAC members would be in a position to analyze them. To some, this period of time seemed fairly long, especially if these trials ultimately failed to demonstrate net clinical benefit. Dr. Omura recommended that the sponsor also evaluate the

safety and efficacy of Taxotere in Taxol-resistant patients, as this would represent an important advance in the treatment of metastatic breast cancer.

The Committee's vote on (conditional) accelerated approval was: 4 yes, 4 no.

Comment: *At the pre-NDA meeting held with the sponsor on May 13, 1993, the Agency indicated that accelerated approval based on the phase II data submitted does not seem likely.*

The Committee's vote on the question as phrased above, for approval was 0 yes, 6 no, with 2 abstaining. This is the final vote on approval, evolving from extensive discussion and concerns regarding toxicity.

Question 1b: Should the labeling state that "prior therapy should have included an anthracycline unless clinically contraindicated"?

The Committee's vote was 8 yes, 0 no, if Taxotere was approved.

Question 2a: Is Taxotere approvable for the treatment of "patients with locally advanced and metastatic non-small cell lung cancer after failure of platinum-based chemotherapy"?

All the comments made in response to Question 1a apply here as well, with one notable exception: the overall response rate in two phase II trials for 88 previously treated patients with non-small cell lung cancer was 17% (95% CI = 9; 25). This result was comparable to other agents already available for treatment of this disease.

The Committee's vote was 8 against approval, 0 for approval.

Question 2b: If not, what additional studies should be performed?

Dr. Bunn eloquently addressed the need for randomized, controlled phase III trials in lung cancer. In previously untreated patients with advanced non-small cell lung cancer he suggested that comparisons of Taxotere versus Navelbine or Taxotere/Cisplatin versus Navelbine/Cisplatin would be valuable. In resectable patients, one could compare two cycles of Taxotere pre- and post-operatively versus surgery alone. In small cell lung cancer patients, a useful comparison might be Cisplatin/Etoposide/Taxotere versus Cisplatin/Etoposide. Dr. Bunn also felt strongly that phase III multicenter trials in lung cancer should take no more than a year to accrue patients.

Question 3a: Is recommendation of a 5-day Dexamethasone premedication regimen justified?

No rationale was ever provided by the sponsor for the selection of this premedication regimen over other agents and schedules used. Thus, there was great concern that its use represented part of a "learning curve" on the part of treating investigators, rather than a well-tested safeguard against a serious cumulative toxicity (i.e., fluid retention) that often lead to treatment discontinuations among responders.

The argument in favor of this regimen was also weakened by evidence of selective benefit in breast cancer patients but not lung cancer patients. Dr. Omura questioned what the tolerability of 5 days of oral corticosteroids taken every 3 weeks might be in patients with metastatic cancer. Finally, there was some concern that use of this regimen in breast cancer patients may confound the response rate to Taxotere.

The sponsor indicated that trials are ongoing that may supply data to answer this question. In particular, all patients entered on the phase III trials in breast and non-small cell lung cancer will be premedicated with the 5-day Dexamethasone premedication regimen.

Comment: *The reviewer is not aware of any ongoing or proposed controlled, randomized trial evaluating the need for premedication for fluid retention. This recommendation was made by the Agency at the pre-NDA meeting with the sponsor held on May 13, 1993.*

An interim analysis of the EORTC-sponsored TAX265 trial was included in the Updated Safety Report (see Review Section 10.32). To date, 70 patients have been randomized to receive the anti-H1 antagonist cetirizine chlorhydrate with or without methylprednisolone. Since the Taxotere infusion schedule on this trial is day 1 and day 8, the premedications are given on days: d-1, d1, d2, and d7, d8, and d9. Thus far, one patient pretreated with steroids has withdrawn for fluid retention as compared to twelve patients not premdicated with steroids.

12. Recommended Regulatory Action

NDA #20,449 [Taxotere® (docetaxel) for injection concentrate] for the treatment of "patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed; prior therapy should have included an anthracycline unless clinically contraindicated; and for the treatment of "patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy" is not approvable. The proposed labeling text (2.1.2 - 2.1.102) will not be reviewed.

Julie Beitz MD 12-16-94

Julie Beitz, MD Date

Robert L. Justice M.D 10/23/95

Robert Justice, MD Date

cc:
NDA # 20,449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

TAXOTERE® (Docetaxel) for Injection Concentrate

Amendment to NDA # 20-449

Table of Contents

1. Specific Safety Analysis: 1/18/95

1.1 Introduction

Volumes 7.1 - 7.2, submitted on January 18, 1995, contain Rhone-Poulenc Rorer's specific safety analysis which is intended to rebut some of the arguments expressed by ODAC members at the December 13, 1994 Meeting. This analysis was presented informally at a meeting the Agency held with the sponsor on December 20, 1994. This submission also contained RPR's responses to the Agency's letter dated November 18, 1994, that requested additional data relevant to the Chemistry, Manufacturing and Controls Section of the original NDA. The Appendix contained summations of preclinical studies carried out to unveil possible hyperpermeability effects and their mechanisms; these studies were relevant to specific Pharm/Tox questions. The sponsor expects this submission will extend the NDA review date by a minimum of 90 days. During this period the sponsor will submit safety data on additional patients from ongoing studies.

1.2 Patient Characteristics - Docetaxel at 100 mg/m² and 75 mg/m²

Results are presented for 26 phase II studies with docetaxel as single agent chemotherapy for various tumor types, excluding the Japanese experience (6 phase II trials conducted at the 60 mg/m² dose). Altogether, there were 1010 patients treated in these studies, 935 at the initial planned dose of 100 mg/m² and 75 at the initial planned dose of 75 mg/m². These results are identical to those reported previously in the Updated Integrated Safety Summary (11/7/94) and discussed at the Oncology Drugs Advisory Committee Meeting on December, 1994.

In brief, the median age of the 935 patients was 57 years (range 26-80), with a male:female ratio of 0.7, and a median WHO performance status of 1. The most common tumor types were breast (34%) and lung (27%). Only 26% of patients had one organ involved, the rest had $\geq$ 2 organs involved. Docetaxel was administered as second line therapy to 39% of patients. Out of a total of 4435 treatment cycles planned at the initial dose of 100 mg/m², 27% of cycles (1183) were given at a reduced dose (Table 4, 1/18/95 submission, attached). The accompanying text, however, indicates that dose modifications occurred in 35% of patients during 412 cycles (due to hematologic and/or non-hematologic toxicities). A treatment delay of > 3 days occurred in 34% of patients, involving 593 cycles.

Comment: *There is an apparent discrepancy in number of cycles in phase II studies requiring dose modification: 1183 cycles in Table 4 vs 412 cycles in the text. Previous submissions support a number greater than 412. For example, among 228 metastatic breast cancer patients receiving a total of 1235 cycles at the initial planned dose of 100 mg/m², 443 cycles were dosed at 75 or 55 mg/m² (Table 15, 8.118.44, Integrated Summary, Breast Cancer). Similarly, among 248 metastatic NSCLC patients receiving a total of 1163 cycles at the initial planned dose of 100 mg/m², 278 cycles were dosed at 75 mg/m² or less (Table 16, 8.119.42, Integrated Summary, NSCLC).*

1.3 Specific Safety Results - Docetaxel at 100 mg/m² and 75 mg/m²

1.31 Toxic Deaths

Serious adverse events were reported in 50% of the patients enrolled in the phase II program. There were 75 deaths on study, including 20 toxic deaths. Thus, the overall toxic death rate was 2% (20/1010). There were 15 deaths due to neutropenic infection, pneumonia, or sepsis, including 3 deaths in breast cancer studies, 8 in NSCLC studies, and 4 in other tumor types. Thus, the rate of septic deaths observed in phase II docetaxel studies was 1.5% (15/1010 patients). The remaining 5 toxic deaths were: 1 to cardiac failure with pulmonary edema, 1 to cerebrovascular accident with right-sided hemiparesis and drowsiness, 1 to supraventricular tachycardia with dehydration and hypotension, and 2 to gastrointestinal hemorrhage in the setting of thrombocytopenia and liver dysfunction (both in breast cancer patients).

Among breast cancer patients treated at the initial planned docetaxel dose of 100 mg/m², the rate of toxic deaths was 1.6% (5/316), and 0.9% for septic deaths (3/316 patients). The sponsor concluded that these findings were comparable to that reported for paclitaxel in the package insert: septic death rate of 1% among 812 advanced ovarian and breast cancer patients. Note that doses of paclitaxel in these phase 2 studies ranged from 135 to 300 mg/m² administered over 3 or 24 hours. G-CSF support was used in four studies.

Comments:

1) There have been thirteen additional patient deaths "possibly" or "probably" related to docetaxel that have been reported under IND since January 1, 1995. Six deaths occurred during a 5 week period between 1/19/95 and 2/23/95. Six deaths occurred in patients with breast cancer (indicated in bold typeface). See Appendix for a brief description of deaths reported. Briefly, these were:
TAX020: cardiac arrest
TXB201: dyspnea and hemoptysis
TAX301: edema and jaundice
TAX264: GI bleeding
TAX-SI-002: dyspnea and cardiac pain, with grade 4 neutropenia
TAX-SI-002: severe diarrhea with grade 4 neutropenia
TAX-V-298: sepsis complicated by febrile neutropenia and a CVA
TAX-Compassionate Use: "unexplained death" with neutropenia, diarrhea, and mucositis
TAX-V-238: "unexplained death" associated with grade 4 neutropenia and asthenia
TAX-V-216: "unexplained death"
TAX-SI-001: "unexplained death"
TAX-EAP: intracerebral event and metastatic breast cancer
TAX-V-301: "unexplained death"

In addition, there have been two patient deaths related to docetaxel reported under IND #

1 patient with myopathy, pleural and pericardial effusions and tumor progression [ECOG-1293], 1 patient who developed rapidly progressive liver failure without evidence of liver metastases [CALGB-9256].

2) Regarding toxic deaths associated with paclitaxel treatment, infusion rate has a greater impact on myelosuppression than dose. For example, in the phase III multicenter trial conducted in 471 previously treated metastatic breast cancer patients randomized to receive paclitaxel at a dose of either 175 or 135 mg/m² as a 3-hour infusion, there was only one septic death reported (septic death rate 0.2%, Bristol-Myers Squibb, NDA # 20-262). Review of patient characteristics in this trial revealed that 60% had symptomatic disease, 73% had visceral metastases, 67% had received prior anthracyclines, and 23% had anthracycline-resistant disease.

Reviewer's Conclusions:

1) In the absence of a randomized comparison between docetaxel and paclitaxel, it is problematic to directly compare treatment-related septic death rates for these two agents in analogous patient populations. In the literature, paclitaxel doses have typically ranged from 135-250 mg/m²; myelosuppression was more pronounced in trials using 24-hour infusions as compared to 3-hour infusions. Use of G-CSF in some trials may shorten the duration of paclitaxel-induced neutropenia.[1]

2) A fair comparison of these two agents assumes that one knows what paclitaxel dose and schedule is most comparable to docetaxel 100 mg/m² over 1 hour. This is as yet unknown.

3) Given the data submitted in the paclitaxel NDA quoted above, the septic death rate for previously treated metastatic breast cancer patients appears to be lower for paclitaxel given as a 3-hour infusion than for docetaxel dosed at 100 mg/m² over 1 hour (0.2% vs 0.9%).

1. Oneto N, Canetta R, Winograd B, Catane R, Dougan M, Grechko J, Burroughs J, Rozencweig M: Overview of Taxol Safety. J NCI Monographs, No. 15, 1993, pp 131-139.

1.32 Hematologic Toxicity - Docetaxel at 100 mg/m²

Grade 3 or 4 neutropenia was experienced by 92% of evaluable patients. The median neutrophil nadir by cycle was 0.4 x 10^3/mm³, the median time to nadir was 8 days, and the median time to recovery from nadir was 7 days. Febrile neutropenia (rever > 38°C, with grade 3 or 4 neutropenia) occurred in 24% of patients, involving 237 cycles. Infection of any severity was observed in 20% of evaluable patients (187/931), involving 310 cycles. Grade 3 or 4 infections occurred in 28% of patients developing infections (53/187), involving 83 cycles. Febrile neutropenia with documented infection occurred in 18 cycles.

Comments: *Note the following discrepancies in the data presented in this report as compared*

to the Updated ISS (pages 9.1.26 to 9.1.27, 11/7/94). Some or all of the discrepancies may be due to the use of a different denominator for number of treatment cycles. Table 12, 9.1.27, used the number of cycles planned at the 100 mg/m² dose (i.e., 4431 cycles), whereas Tables 6 and 7 of this report used the number of cycles actually dosed at 100 mg/m² (i.e., 3214 cycles). With the exception of infection rate by cycle (item 2 below) there does not appear to be much difference in the outcomes of the two different analyses.

1. *The number of patients with febrile neutropenia is now reported as 224 (Table 6, 1/18/95 submission, attached), compared to 236 on page 9.1.26. Total N=931 patients in both instances.*

2. *The incidence of febrile neutropenia by cycle is either 314/4431 (7%) or 237/3214 (7.4%). The incidence of infection by cycle is either 250/4431 (5.6%) or 310/3214 (9.8%).*

3. *The number of cycles with febrile neutropenia and documented infection is now reported as 18, compared to 28 on page 9.1.27.*

4. *The number of cycles with febrile neutropenia and grade 3 or 4 infections is now reported as 5, compared to 7 on page 9.1.27.*

This report states that "Febrile neutropenia with documented infection occurred in 18 (0.6%) of the cycles. Only five of these infectious episodes were of grade III or IV severity."

Comment:

1) The incidence of clinically significant infections may be underestimated by this statement, given the figures RPR provided previously in the individual study reports (see below). For example, 45 of 56 infectious episodes occurring among 133 anthracycline-resistant patients enrolled in three pivotal trials were complicated by grade 3 or 4 neutropenia (see shaded area). Among 88 previously treated patients with NSCLC enrolled in two pivotal trials (TAX270 and TAX271), 12 of 21 infectious episodes were associated with grade 3 or 4 neutropenia.

2) While it is important to focus on the handful of life-threatening infections, it is equally important to determine how many patients are placed at risk of grade 3 or 4 neutropenia while on docetaxel treatment. In addition, the morbidity of infection associated with grade 3 or 4 neutropenia cannot be ignored (antibiotic usage, hospitalization, treatment delays, etc.).

Overview - Anthracycline-Resistant Breast Cancer Patients - Docetaxel 100 mg/m²

Endpoint	TAX233 *n=41*	TAX267 *n=41*	TAX286 *n=51*	Overall *n=133*
Neutropenia, Grade 3/4 (% of patients)	92	100	98	97
Febrile Neutropenia (% of patients)	32	37	31	33
Febrile Neutropenia (% of cycles)	6.6	10.2	8.5	8.4
Infection Rate (% of patients)	37	24	22	28
[redacted]				

• *Includes one septic death*

- **Paclitaxel Experience**

The sponsor argues that given the different conventions used in docetaxel and paclitaxel studies to define febrile neutropenia, the "comparative hematologic toxicity/safety of the two compounds is better assessed by the infection rate". The infection rates for paclitaxel were quoted as follows: 30% for 812 ovarian and breast cancer patients included in the package insert, 23% for 229 patients with breast cancer treated with 175 mg/m² as a 3-hour infusion, and 37% for breast cancer patients treated with 135-175 mg/m² as a 24-hour infusion.

Comment: *Returning to the data from the randomized phase III paclitaxel trial in metastatic breast cancer, the package insert reports a 23% and 15% infection rate for the 175 and 135 mg/m² arms (both 3-hour infusions), and a 2% febrile neutropenia rate for both. In the NDA submitted by only 5% of all treatment courses (60/1141) were complicated by febrile episodes. For 24 of these episodes there was insufficient data to make an association between fever and neutrophil counts; in the remaining 36 episodes, only 4 were associated with grade 4 neutropenia.*

Reviewer's Conclusions:

1) Again, in the absence of a randomized comparison between docetaxel and paclitaxel, it is problematic to directly compare treatment-related febrile neutropenia and infection rates for these two agents in analogous patient populations.

2) The data quoted for breast cancer patients from the NDA and

package insert suggest that febrile neutropenia rates may be lower for paclitaxel when given as a 3-hour infusion than for docetaxel dosed at 100 mg/m² over 1 hour (i.e., 2% [paclitaxel] vs 24% [docetaxel, overall] or 33% [docetaxel, anthracycline-resistant patients]).

*3) On the other hand, **overall infection rates appear to be similar for these two agents** (15-23% [paclitaxel] vs 20% [docetaxel, overall] or 28% [docetaxel, anthracycline-resistant patients]).*

1.33 Fluid Retention - Docetaxel at 100 mg/m²

In the phase II program, adverse events lead to treatment discontinuation in 201 patients: the most frequent reason for treatment withdrawal was fluid retention involving 80 patients.

In the Updated ISS, 479 of 931 evaluable patients (52%) treated with docetaxel at 100 mg/m² experienced fluid retention, regardless of premedication. Of these, 90 patients (10%) had severe reactions. Fluid retention was characterized as edema only in 32% of patients, in 21% as edema and pleural effusion, in 15% as edema, pleural effusion, and weight gain, in 15% as edema and weight gain, in 4% as pleural effusion only, and in 12% as other symptoms.

The severity grading for edema and effusions is summarized in the table below. Note that symptomatic fluid retention refers to moderate or severe events. **Comment:** *It is not known when this grading scale was adopted and for which clinical trials.*

Severity Grading	Edema	Effusion
Mild	Asymptomatic and/or very well tolerated and/or dependent in evening only	Asymptomatic No intervention required
Moderate	Pronounced and well tolerated and/or dependent entire day	Exertional dyspnea and/or chest pain and/or EKG changes and/or abdominal distention Drainage may be required
Severe	Pronounced and not well tolerated and/or generalized anasarca	Drainage urgently required: dyspnea at rest and/or tamponade and/or pronounced abdominal distention

- **Pathophysiology: TAX029**

The TAX029 trial is a phase I/II trial evaluating the pathophysiology of edema in patients with

advanced breast or ovarian cancer who are receiving docetaxel at 100 mg/m² every 3 weeks without premedication, diuretics, or calcium antagonists. In case of severe fluid retention that could lead to docetaxel discontinuation, symptomatic treatment with Diosmine-Hesperidine (Daflon 500), 2 gm/day could be prescribed. Note that the docetaxel was provided as a solution of 40 mg/ml in polysorbate, but the solvent contained ethylalcohol 95%/water 13/87 w/w. **Comment:** ***The solvent typically used in pivotal trials was 5% dextrose or 0.9% saline, presumably free of ethylalcohol. Physiologic alterations noted in this trial should take into account the presence of ethylalcohol in the excipient.***

An interim report on the first 15 evaluable patients who received at least 4 cycles was submitted previously (9.11.117 - 9.11.175) and in this report. Twelve of the 15 patients developed fluid retention, and 5 of these discontinued treatment. **Comment:** ***An 80% incidence of fluid retention is twice the overall incidence of 40% in 315 patients given no premedication as reported in Table 47B, ISS).***

The sponsor postulates that fluid retention develops by the following process: after 2 cycles of docetaxel, excessive transcapillary filtration of proteins leads to an abnormal retention of albumin within the interstitial space; between the second and fourth cycle, signs of lymphatic failure are notable; and after the fifth cycle, lymphatic drainage is unequivocally impaired. Five patients premedicated with Daflon showed decreased albumin retention. **Use of flavonoids as premedication has been proposed, beginning at cycle 1, with increasing doses at cycle 4 as necessary. In addition, treatment with Benzopyrones, derivatives of coumarin, that lyse proteins and facilitate their elimination by the lymphatic system, or manual lymph drainage has been suggested.**

- **Pathophysiology: TAX248**

The TAX248 trial is a phase II trial evaluating docetaxel as second or third line treatment for advanced ovarian cancer, recurrent and/or refractory to platinum. A preliminary report of immunologic findings in eight patients was presented previously (9.11.176 - 9.11.192) and in this report.

Eight patients who had received a minimum of 2 cycles were selected for further immunologic evaluation. Treatment with docetaxel did not alter circulating levels of IL-2, IL-2 receptor, interferon-γ, and TNF in any of the patients. However, 3 patients had normal levels of circulating NK/LAK cells at baseline, which rose to a maximum at 1 hour after the first infusion. Seven patients had elevated levels at the start of cycles 2-6, which rose even further at 1 hour after infusion. This latter finding suggested that circulating lymphocytes with the NK/LAK phenotype are elevated both at the time of infusion and chronically during docetaxel treatment. **The sponsor postulates that docetaxel-related capillary hyperpermeability may be mediated by NK/LAK cells which are known to be directly toxic to capillary endothelial cells. Comment:** ***Although these results are preliminary, they are intriguing. Evaluation of additional patients is warranted.***

- **Premedication Regimens in Original NDA Submission**

Thirteen of 24 phase II studies at the initial planned dose of 100 mg/m² were amended to allow premedication for enrolled and new patients. Premedications were added to reduce the incidence of acute hypersensitivity reactions and fluid retention. There were 315 patients who did not receive any premedication in any cycle; 171 patients who received anti-H1 and/or anti-H2 antagonists only, 60 patients who received short-term corticosteroids $\leq$ 2 days with or without anti-H1 or anti-H2 antagonists, and 82 patients who received long-term corticosteroids > 2 days with or without anti-H1 or anti-H2 antagonists. Compared to no premedication, long-term corticosteroids was associated with a significant reduction in the overall incidence of fluid retention (33% vs 40%, $p=0.06$) and in its severity (2% vs 7%, $p=0.03$). Comment: *Note that this is a retrospective analysis in patients culled from many different studies. The long-term corticosteroid group also received antihistamines. Since the antihistamine group fared the worse (overall incidence, 61%, severe fluid retention, 15%), this would suggest that future premedication regimens avoid the use of antihistamines.*

- **Analysis of the 5-day Dexamethasone Premedication Regimen**

As requested by FDA at the 30-day post-submission teleconference, RPR submitted a retrospective analysis of the efficacy of the 5-day dexamethasone premedication regimen in support of their claim that such pretreatment could ameliorate the incidence and severity of fluid retention associated with docetaxel treatment at 100 mg/m² every 3 weeks. Table 16 (Updated ISS, 9.1.36) was reiterated in Tables 12, 13, and 14 of the 3/9/95 report; additional information (Table 11, ODAC Briefing Document, 6/8/95) has been incorporated below.

FLUID RETENTION BY PATIENT (100 mg/m²)

	No Premedication (N=118)		5-Day Dexamethasone (N=63)	
Patient Type	Overall Incidence	Severe	Overall Incidence	Severe
Breast Cancer	77% (46/60)	20% (12/60)	44% (14/32)	6% (2/32)
NSCLC	45% (26/58)	5% (3/58)	42% (13/31)	6% (2/31)

Tables 47B, 74B, and 102B, Integrated Summary of Safety, 7/27/94;
Tables 16 and 17, Updated ISS, 11/7/94

There were 63 patients (32 with breast cancer and 31 with NSCLC) treated in 5 US trials that had been amended to permit the use of dexamethasone 8 mg bid PO for 5 days. Among these,

59 also received concomitant anti-H1 antagonists and 4 received anti-H2 antagonists. Sixty patients actually received premedication from day-1 to day 4 of the docetaxel infusion. Overall, the incidence of fluid retention in the 63 patients given the 5-day dexamethasone premedication was 43%, with severe reactions in 6%. Among the 32 breast cancer patients, the incidence of fluid retention was 44%, with moderate reactions in 19% and severe reactions in 6%. Only one breast cancer patient (1/32 or 3%) withdrew from treatment due to fluid retention. There were no treatment withdrawals for fluid retention among the NSCLC patients.

These results are compared to 118 patients (60 with breast cancer and 58 with NSCLC) from 11 studies who never received premedication: the overall incidence was 61% (77% for breast cancer and 45% for NSCLC patients). Severe reactions were observed in 13% overall, in 20% of breast cancer patients, and 5% of NSCLC patients. RPR suggests that the difference between the two tumor types may be explained by the higher number of cycles given to the breast cancer patients (a median of 5 cycles/breast cancer patient vs 4 cycles/NSCLC patient). Nineteen breast cancer patients (19/60 or 32%) and 6 NSCLC patients (6/58 or 10%) withdrew from treament due to fluid retention.

Comments: *The table below summarizes the severity of fluid retention in patients with toxicity in the various subgroups in the phase II program.*

Severity of Fluid Retention

Fluid Retention	No Premedication (N=315)[a]	No Premedication (N=118)[b]	Long-term Corticosteroids (N=82)[a]	Dexamethasone 5 days (N=63)[b]
# Patients with Toxicity	126	72	27	27
Mild	37%	32%	44%	41%
Moderate	46%	46%	48%	44%
Severe	17%	21%	8%	15%
Symptomatic	63%	67%	56%	59%
Dose to Onset: Mod/Sev Tox (mg/m^2)	NA	490 (Breast) 548 (NSCLC)	NA	746 (Breast) 797 (NSCLC)

[a] *Original ISS, Table 47B; Table 11, Specific Safety Analysis, 1/23/95*
[b] *Table 7 of the Updated ISS, 11/7/94; Tables 13-14, Specific Safety Analysis, 1/23/95*

1) Overall, the incidence of moderate to severe events was 60% among patients developing fluid retention, regardless of premedication.

2) For the 60 breast cancer patients given no premedication (out of the 118 above), 46 developed fluid retention, and 67% of these were symptomatic cases. For the 32 breast cancer patients given 5-days dexamethasone (out of the 63), 14 developed fluid retention, and 57% of these were symptomatic cases. There was, however, a shift of cases from severe to mild with use of the 5-days of corticosteroid. See Section 2.33 for further details.

3) The cumulative dose to treatment withdrawal for the 118 patients not given premedication was 552 mg/m², suggesting that patients discontinued treatment shortly after the onset of moderate to severe fluid retention.

4) Among the 118 patients not given premedication, fluid retention in the breast cancer group was more frequent and severe than in the NSCLC group. NSCLC patients appear to do as well without premedication as with the 5-day regimen, at least in terms of overall incidence and severity of reactions. If fluid retention is cytokine-mediated, then should not corticosteroids work regardless of tumor type?

5) Although substantial numbers of patients receiving the proposed 5-day dexamethasone premedication regimen still developed fluid retention, the onset of moderate fluid retention is delayed by 2-3 treatment cycles, and all but one symptomatic patient receiving this premedication could continue docetaxel treatment for an unspecified period of time. No specific clinical information is provided regarding the morbidity of symptomatic fluid retention in patients for the period of continued treatment and following treatment withdrawal (e.g., supportive care measures required, performance status and other quality of life measures). Is there net clinical benefit to those patients who continue docetaxel therapy after the onset of symptomatic fluid retention?

6) At the FDA's request, RPR has submitted (July 21, 1995) an analysis of the impact of corticosteroid premedication on response rate in breast cancer patients. Use of short-term or 5-day corticosteroids did not affect response rates in first or second line patients. See Appendix for further details.

7) At the FDA's request, RPR has submitted (July 21, 1995) an analysis of the impact of corticosteroid premedication on docetaxel clearance, AUC, and clearance prediction error (mean SD). Use of corticosteroids did not alter docetaxel clearance or systemic exposure (AUC). These findings are consistent with those observed clinically in item (6).

- **Reversibility of Fluid Retention**

In the absence of routine premedication, the median time to disappearance of fluid retention from the last infusion was 18 weeks (range 3-29 weeks) for patients dosed at 75 mg/m² (TAX280). The median time to disappearance of fluid retention from the last infusion was 25 weeks (range 3-60 weeks) for patients dosed at 100 mg/m² (TAX237). RPR states that the fluid retention was reversible, independent of any symptomatic treatment. See Section 2.33, for further details on the duration of fluid retention.

- **Paclitaxel Experience**

In the package insert, edema was reported in 21% of 812 patients treated with paclitaxel, and was severe in 1%. No patient required treatment discontinuation. Edema was commonly focal and disease-related. All patients had received premedication with oral corticosteroids 12 and 6 hours before paclitaxel, diphenhydramine 50 mg IV 30-60 minutes prior, and cimetidine 300 mg or ranitidine 50 mg IV 30-60 minutes prior to paclitaxel to prevent acute HSRs.
Comment: *Literature searches to date have failed to demonstrate an incidence of fluid retention/edema associated with paclitaxel that approaches the incidence observed with docetaxel. Moreover, fluid retention has not been observed in protocols utilizing repetitive high-dose paclitaxel (300 mg/m² x 2 cycles) for peripheral stem cell mobilization in ovarian cancer patients (Dr. David Spriggs, MSKCC, presentation at GOG Meeting, 2/95).*

1.34 Performance Status

At baseline, the ECOG performance status of 83 patients enrolled in two pivotal breast cancer docetaxel trials (TAX267 and TAX233) was: PS0, 21%; PS1, 61%, and PS2, 18%. In the pivotal phase III trial of paclitaxel in breast cancer reported in NDA # 20-262, the baseline performance status in 471 patients was: PS0, 40%; PS1, 44%, and PS2, 16%.
Comment: *RPR argues that patients on docetaxel had a worse performance status at baseline than those on paclitaxel. On the other hand, one could argue that > 80% of patients on either drug had a PS of 0 or 1, and < 20% a PS2. Thus, it is difficult to determine if there was a meaningful difference in baseline performance status in these patient populations. The more critical question relates to how PS evolved on treatment with either docetaxel or paclitaxel.*

1.35 Multicenter Nature of Taxotere Clinical Trials

The safety data reported in this NDA were derived from patients treated at > 180 sites in Europe, Canada, and the US. Overall, 73% of patients were enrolled in multicenter trials.

Comment: *The reviewer acknowledges the multicenter nature of the clinical trials presented in this NDA. The concern of ODAC members was centered on the fact that patients on two of the pivotal trials in breast cancer (TAX267 and TAX233), and on both pivotal trials in NSCLC*

(TAX270 and TAX271) were treated primarily at a single institution (i.e., MD Anderson or San Antonio). With regard to safety, Drs. Schiffer and Bunn were concerned with the toxicity of docetaxel in patients with low performance status (e.g., PS2 and higher) who might receive this drug from community physicians who, in turn, would not be familiar with or might not recognize complications in a timely fashion. Had patients in pivotal trials been enrolled in equal numbers at all participating sites, i.e., at major cancer centers and in community-based practices, there would have been greater generalizability to the "real" world.

1.4 Safety Analysis to be Provided in March 1995

A specific analysis of the five major issues raised by ODAC members will be provided for patients in the following ongoing docetaxel studies:

Phase II and III breast cancer studies
TAX265 - evaluating a d1, d8 docetaxel schedule with or without a 3-day corticosteroid premedication regimen
Phase II studies in solid tumors conducted by NCI
Phase II studies in solid tumors conducted by NCI-Canada.

1.5 Sponsor's Conclusions

The rates of septic death and infections with docetaxel and paclitaxel are not substantially different. The higher incidence of febrile neutropenia reported for docetaxel may be due to a more comprehensive and strict definition.

The 5-day corticosteroid premedication significantly reduced the incidence of clinically relevant fluid retention leading to treatment discontinuation. Fluid retention may be managed with symptomatic therapy and is reversible.

The majority of patients on docetaxel trials were symptomatic at baseline.

The majority of patients on docetaxel trials were enrolled by multicentric/cooperative groups.

This analysis shows that the concerns raised by ODAC, in particular the comparative safety data with Taxol, may not have a basis in fact.

2. Updated Safety Analysis: *3/9/95*

2.1 Introduction

Volume 1.1, submitted on March 9, 1995, contains Rhone-Poulenc Rorer's updated safety data that includes patients from eight ongoing phase II and phase III breast cancer studies and eight phase II studies in various solid tumors conducted by the NCI and NCI-Canada. An analysis of the impact of elevated hepatic enzymes at baseline on the safety profile of docetaxel was provided. Additional data, supplied by fax on May 5, 1995, and in 3 volumes on May 23, 1995, at the Agency's request are included in the appropriate sections of this review.

2.2 Overview of Studies Included in this Update

Results are presented for the 26 phase II studies with docetaxel as single agent chemotherapy (see Section 1.2), supplemented with 139 patients entered on phase II and phase III breast cancer studies (Section 2.21), 83 patients on the TAX265 trial (Section 2.22), and 175 on phase II studies in various solid tumors (Section 2.23). Thus, there are a total of 1327 patients at the initial planned dose of 100 mg/m² and 79 at the initial planned dose of 75 mg/m².

2.21 Ongoing Breast Cancer Trials Sponsored by RPR

Study	Phase	Country	Patient Population	Study Design	Accrual (2/17/95)
TAX029	II	France	2nd Line	Docetaxel 100 mg/m²	19
TAX235	II	Europe	Alkylating or Anthracycline Failure (2nd Line)	Docetaxel 100 mg/m²	48
TAX264	II	US	Anthracycline Failure (2nd Line)	Docetaxel 100 mg/m²	40
TAX296	II	US	Taxol Resistant	Docetaxel 100 mg/m²	11
TAX303	III	Europe, Canada, Australia, S Africa	Alkylating Failure (1st and 2nd Line)	Docetaxel 100 mg/m² vs Doxorubicin 75 mg/m²	Docetaxel: 7
TAX304	III	Europe, Canada, Australia, S Africa	Anthracycline Failure (2nd Line)	Docetaxel 100 mg/m² vs Mitomycin C + Velban	Docetaxel: 11
TAX311	III	US	Anthracycline Failure (1st and 2nd Line)	Docetaxel 100 mg/m² vs Taxol 175 mg/m²/3h	Docetaxel: 3

Baseline characteristics, course of treatment, and toxicity were summarized for 139 patients previously treated for metastatic disease who received docetaxel 100 mg/m² on the six studies tabulated above. The data cut-off date was 2/17/95.

- **Patient Characteristics**

The median age of the 139 patients was 53 years (range 26-78 years). The baseline WHO performance status was 0-1 in 83%. All patients had metastatic disease. Most (71%) had 2 or more organs involved. Specifically, 51% of patients had liver involvement, 45% had bone, 34% had lymph node disease, and 34% had lung disease. Most patients (123) had received prior chemotherapy for advanced disease; 15 patients had received adjuvant or neoadjuvant chemotherapy. Seventy-four patients had received 2 or more prior chemotherapy regimens.

- **Treatment Administration**

A total of 558 cycles were administered: 442 (79%) at the initial planned dose of 100 mg/m², 88 (16%) at 75 mg/m² and 27 (5%) at 55 mg/m². On the TAX264 trial, only 57% of treatment cycles were dosed at 100 mg/m², while 100% of docetaxel cycles were dosed at 100 mg/m² in the TAX304 trial (both trials enroll anthracycline-failures). Treatment delays of 3 days or more were required in 38 cycles. Dose reductions were required in 51 cycles (9%); in 30 of these cycles, dose reductions occurred after the first cycle.

- **Efficacy Results**

No information is provided on response rates, time to disease progression, response duration or survival.

- Safety Results

Of the 139 treated patients, the most frequent possibly or probably related AEs were: alopecia (98 patients), asthenia (90 patients, severe in 23), stomatitis (85 patients), fluid retention (80 patients, severe in 11), neuro-sensory (77 patients), skin (66 patients), diarrhea (56 patients), nausea (47 patients), nail disorder (46 patients), fever in the absence of infection (39 patients), myalgias (31 patients), vomiting (27 patients), infection (26 patients, grade 3-4 in 7), neuromotor (19 patients), arthralgias (10 patients), and pulmonary (excluding fluid retention, 9 patients).

- **Acute Hematologic Toxicity**

Leukopenia and neutropenia were observed in 128 of 130 evaluable patients. Grade 3 or 4 neutropenia was observed in 122 patients (93%). There were 322 evaluable cycles (with at least one blood count between days 2 and 19) with grade 4 neutropenia; in 16 cycles the grade 4 neutropenia lasted > 7 days. The median neutrophil nadir was 0.1 x 10^3/mm³ (range 0-3.0)

and the median day to nadir was 7 days (range 5-14).

Thrombocytopenia was observed in 22 patients, and was grade 3-4 in nine. The median nadir of platelets by patient was 175 x $10^3/mm^3$ (range 0-453). The median day to nadir was 7 days (range 3-43).

Anemia was observed in 131 of 138 patients, and was grade 3-4 in 16 patients. The median nadir of hemoglobin was 9.9 g/dl, with a median day to nadir of 12 (range 2-41).

- **Reasons for Treatment Withdrawal**

Of the 139 patients, 76 (55%) were still on treatment as of the cut-off date (2/17/95). Of the 63 patients off study, reasons for withdrawal were: 25 due to disease progression, 15 due to adverse event, 10 due to death, 5 withdrew consent, and 8 withdrew for other reasons.

The toxicities leading to withdrawal in the 15 patients are listed below. The median number of treatment cycles received was 5 (range 4-10). One patient experienced a severe chlostridial infection with diarrhea that was believed to be remotely related to docetaxel. Eleven of the remaining 14 patients (79%) withdrew due to fluid retention alone or in combination with other toxicities, as follows:

fluid retention, moderate to severe: 7
fluid retention, moderate to severe + neurotoxicity: 3
fluid retention, moderate to severe + neurotoxicity + asthenia/malaise: 1
neurotoxicity + asthenia/malaise: 1
insufficient information: 2

Of the ten patient deaths on study, 4 were treatment-related: two died of sepsis (both in TAX264) and two died of gastrointestinal hemorrhage (TAX264 and TAX235) with coagulopathy. One patient died of subarachnoid hemmorhage (TAX304) and five patients died of their disease. The median number of treatment cycles received was 2.5 (range 1-7).

Comments:

1. With regard to the specific safety issues enumerated above (Section 1.3), the toxic death rate in this group of breast cancer patients was 2.9% (4/139), and the septic death rate was 1.4% (2/139). Both of these rates are higher than the 1.6% toxic death rate and 0.9% septic death rate quoted for 316 breast cancer patients in the Updated ISS (see Section 1.31).

2. No information was provided on the incidence of febrile neutropenia. The overall infection rate by patient was 19%. Grade 3-4 infections occurred in 27% (7/26) of patients developing infections. The overall incidence of fluid retention was 58%. These rates are comparable to those reported previously (see Sections 1.32 and 1.33).

3. Of the 80 patients who developed fluid retention, there were 41 patients with moderate or severe events (i.e., symptomatic); of these, 11 patients withdrew treatment. No specific information on premedication use was provided, median cumulative dose to onset of symptomatic fluid retention, median cumulative dose to treatment discontinuation, performance status or other quality of life measures on study, response to treatment, or supportive measures required.

4. Of concern was the somewhat higher incidence of grade 3-4 thrombocytopenia (6%) and of grade 3-4 anemia (12%) in this patient group. These figures were 4% and 9%, respectively, for 927 evaluable patients reported in the Updated ISS. Note that there were two deaths reported from gastrointestinal hemorrhage and one of subarachnoid hemorrhage. There is however, insufficient information to draw any specific conclusions.

2.22 EORTC Trial TAX265: Docetaxel 50 mg/m² days 1 and 8

Baseline characteristics, course of treatment, and toxicity were summarized for 83 patients previously treated for advanced or metastatic disease who received docetaxel 50 mg/m² on a day 1, day 8 schedule, every 21 days; in the phase I program, this schedule was associated with the highest frequency of fluid retention. Patients were randomized to one of two premedication regimens: methylprednisolone (40 mg/day) + cetirizine (10 mg/day) on days -1, 1, and 2 of docetaxel treatment (Arm A, +Steroids) vs cetirizine alone (Arm B, -Steroids). Note that 12 of 41 patients on Arm A and 15 of 42 patients on Arm B also received daily corticosteroids while on study for other reasons (e.g., treatment of brain metastases, dyspnea, edema, skin toxicity, etc.).

- Patient Characteristics

The median age of the 83 patients was 51 years (range 28-72 years). Forty-three patients had single visceral involvement, 18 had multiple visceral involvement, and 22 had soft tissue or bone only disease. Specifically, 45% of patients had liver involvement, 48% had bone, 57% had lymph node disease, and 30% had lung disease. All patients had received prior chemotherapy for metastatic disease; 34 patients had also received adjuvant or neoadjuvant chemotherapy.

- Treatment Administration

A total of 415 cycles were administered: 206 (50%) at the initial planned dose of 50 mg/m² on d1 and d8, 136 (33%) at 32-40 mg/m² on d1 and d8, 63 (15%) at 40-50 mg/m² on d1 only, and 10 (2%) at various other combinations. More cycles were delivered at full dose to patients on Arm A than to patients on Arm B (125 vs 81 cycles). Treatment delays of 3 days or more were required in 59 cycles: 29 cycles in Arm A and 30 in Arm B. With regard to fluid retention, 2 patients on Arm A had delays of 7 and 15 days each due to edema and pleural effusion, and 1 patient required a delay of 7 days due to weight gain. On Arm B, 2 patients

were delayed for 7 and 56 days each due to edema and/or pleural effusion. Dose reductions were required in 57 cycles: 22 cycles in Arm A and 35 cycles in Arm B.

Patients on Arm A received a median of 6 cycles (range 1-12), while patients on Arm B received a median of 5 cycles (range 1-11). The median cumulative dose per patient was 461 mg/m^2 (range 98-1036 mg/m^2) for Arm A and 379 mg/m^2 (range 51-827 mg/m^2) for Arm B. **Comment:** ***In the original NDA, the median dose to onset of any fluid retention was reported to be 508 mg/m^2 for long-term corticosteroid premedication, but only 304 mg/m^2 for antihistamine premedication. Thus, one would predict from the cumulative doses delivered in this trial that patients on Arm A (+Steroids) will fare better than patients Arm B (- Steroids) with regard to complications of fluid retention.***

- **Efficacy Results**

The overall response rate was 34% (1 CR and 27 PRs) for patients on this trial. Responses were noted in 13 of 33 nodal sites, in 12 of 35 liver sites, and in 6 of 19 chest wall sites.

- **Safety Results**

Of the 82 evaluable patients, the most frequent possibly or probably related AEs were: alopecia (75 patients), asthenia (67 patients), fluid retention (23 with weight gain, 38 with pleural effusions, 4 with pericardial effusions, and 38 with edema), skin (53 patients), diarrhea (51 patients), stomatitis (44 patients), nausea (44 patients), neurosensory (39 patients), vomiting (35 patients), fever in the absence of infection (27 patients), myalgias (15 patients), infection (13 patients, grade 4 in 1), and neuromotor (7 patients).

- **Acute Hematologic Toxicity**

Neutropenia occurred in 77 of 82 evaluable patients; 44 patients had grade 4 neutropenia. No information was provided on the duration of or time to recovery from WBC nadirs. Eleven of 93 treatment cycles with grade 4 neutropenia were complicated by neutropenic fever (fever $\geq$ 2, no documented infection). There was no grade 3 or 4 thrombocytopenia, and only 2 patients with grade 4 anemia.

- **Fluid Retention**

In Arm B (-Steroids) the incidence of edema was 54% (severe in 5%); the incidence of pleural effusion was 49% (severe in 15%). The median docetaxel dose to onset of edema or pleural effusion was 296 mg/m^2, equivalent to 3 cycles of treatment at full dose. Treatment was discontinued in 32% of patients. **Comment:** *This experience is analogous to that of the 171 patients in the original NDA given antihistamine premedication. In this group, the overall incidence of fluid retention was 61% (severe in 15%), and the median cumulative dose to onset of fluid retention was 304 mg/m^2.*

In Arm A (+Steroids), the incidence of edema was 39% (severe in 5%); the incidence of pleural effusion was 44% (severe in 5%). The median docetaxel dose to onset of edema was 550 mg/m², and 571 mg/m² for pleural effusion. These doses are significantly higher than in Arm B (p=0.003 and p=0.006, respectively). Only 5% of patients discontinued treatment due to fluid retention. **Comments:** *1) This experience is analogous to that of the 82 patients in the original NDA given long-term corticosteroid premedication. In this group, the overall incidence of fluid retention was 33% (severe in 2%), and the median cumulative dose to onset of fluid retention was 508 mg/m². 2) In the ODAC Briefing Document of June 8, 1995, the cumulative dose to onset of fluid retention for patients on Arm A was given as 423 mg/m², which was significantly higher than that for Arm B, p=0.0017.*

- **Reasons for Treatment Withdrawal**

Reasons for withdrawal were: 44 due to disease progression, 22 due to adverse events, 3 due to death, 3 withdrew consent, 9 due to end of the protocol, and 1 due to clinical deterioration and dyspnea. One patient was never treated. Of the three patient deaths on study, two died of their disease and one of unknown causes.

The toxicities leading to withdrawal are listed below by premedication arm, as follows:
Arm A: (+Steroids): Median cumulative dose = 636 mg/m² (range 289-980 mg/m²)
edema/pleural effusion: 2
dyspnea: 2
neurotoxicity + asthenia: 1
asthenia + nail disorder: 1
asthenia + neurotoxicity + skin + nail disorder: 1
skin + mucositis: 1

Arm B (-Steroids): Median cumulative dose = 428 mg/m² (range 200-827 mg/m²)
edema/pleural effusion/pericardial effusion/weight gain: 9
asthenia + dyspnea + edema or pleural effusion: 2
neurotoxicity + edema and pleural effusion: 1
neurotoxicity: 1
dyspnea (pre-existent + drug-related?): 1

Comments:
1) With regard to the specific safety issues enumerated above (Section 1.3), there were no confirmed toxic deaths in this group of breast cancer patients (one unexplained death).

2) The overall infection rate by patient was 16%. Grade 3-4 infections occurred in only 1 of 13 patients (8%) developing infections. These figures are both lower than previously reported.

3) The randomized nature of this study lends scrutiny to two patient populations that are reasonably comparable except for premedication regimens. The study results are perhaps

the strongest evidence for a beneficial effect of steroid premedication.

2.23 Ongoing NCI and NCI-Canada Studies

Study	Indication	Group	No. of Sites	Accrual
TAX251	Gastric	NCI	9	30
TAX262	Cervix		1	15
TAX274	Head & Neck		1	28
TAX275	Sarcoma		3	18
TAX276	Melanoma		3	35
TAX277	Bladder		1	25
TAX263	Sarcoma	NCI-Canada	10	13
TAX278	Glioma		11	11

Appendix III (3/9/95 submission, attached) summarizes preliminary data on 175 patients in 6 NCI and 2 NCI-Canada phase II studies in various solid tumors. Information has not been provided for 3 NCI studies in non-Hodgkin's lymphoma, prostate cancer (docetaxel at 75 mg/m²) and SCLC. The cut-off dates for the NCI studies was 2/17/95, and 2/9/95 for the NCI-Canada studies. Note that on the TAX278 trial, 4 patients previously treated with chemotherapy received docetaxel at 75 mg/m².

- NCI Studies

Of the 151 patients, 87% had a baseline PS of 0-1. Patients received a median of 3 treatment cycles (range 1-16). Grade 4 neutropenia was noted in 15 of 54 (28%) evaluable patients. Febrile neutropenia was reported in 61 of 151 (40%) patients; 44 of these patients were hospitalized. Note that each study used a different definition of febrile neutropenia. There were seven documented infections and two septic deaths.

Fluid retention was noted in only 22 of 147 (15%) evaluable patients, but was moderate or severe in 19 (13%). Patients were premedicated with steroids for 1 day + antihistamines ± cimetidine. One patient discontinued treatment due to fluid retention. Fifteen patients were hospitalized for non-febrile complications including edema/pleural effusion, anemia, rash, nausea/vomiting/diarrhea/dehydration, deep venous thrombosis, transient ischemic attack, atypical chest pain, and small bowel obstruction.

As of 2/17/95, 138 patients were off study, 14 withdrawn for toxicity, 2 septic deaths (1.3%), and one death each to progressive disease, cardiac arrest, and sudden unexplained death.

- **NCI-Canada Studies**

Of the 24 patients, 63% had a baseline PS of 0-1. Patients received a median of 2 treatment cycles (range 1-7). Grade 4 neutropenia was noted in 14 of 24 (58%) evaluable patients. Febrile neutropenia was reported in 4 (17%) patients, all of whom were hospitalized. Febrile neutropenia was not strictly defined. There were four documented infections and no septic deaths. As of the cut-off date, 20 patients were off study, 2 withdrawn due to toxicity.

Fluid retention was noted in 8 (33%) evaluable patients, but was moderate or severe in 5 (21%). Patients were premedicated with steroids for 3 days. No patient discontinued treatment due to fluid retention. Ten patients were hospitalized for non-febrile complications including cerebral edema, congestive heart failure, seizures due to subtherapeutic phenytoin level, abdominal abscess, and urinary tract infection.

Comments:

1) The incidence of febrile neutropenia in the NCI studies is exceptionally high and may reflect the six different definitions used, some of which were very inclusive (e.g., "neutropenic fever as stated in the patient's medical record", or grade II neutropenia and fever > 38.5°C"). The septic death rate for this patient group with several different solid tumors was 1.3% (2/151) as compared to 0.9% for the 316 breast cancer patients in the Updated ISS.

2) Despite the low median number of treatment cycles given in the NCI and NCI-Canada trials, there were 30 patients who developed fluid retention, of which 24 (80%) were symptomatic. Only one patient discontinued treatment. Additional information on supportive care measures required, evolution of performance status and other quality of life measures while on study, and response rates in symptomatic patients would be extremely helpful.

2.3 Specific Safety Results - Docetaxel at 100 mg/m^2 Only

2.31 Toxic Deaths

In this update, there were 26 toxic deaths among 1327 patients treated at the initial planned dose of 100 mg/m^2, for a toxic death rate of 2%. Nineteen deaths were sepsis-related, for an overall septic death rate of 1.4%. Among breast cancer patients, the updated toxic death rate was 2% (9/455), and the septic death rate was 1.1% (5/455). Among 7 toxic deaths occurring in breast cancer patients during the first cycle, 4 deaths occurred in patients with elevated SGOT/SGPT levels at baseline (see Section 2.35). Among solid tumor patients on NCI-sponsored studies, the septic death rate was 1.3% (2/151). There were no treatment-related deaths among the 24 solid tumor patients on NCI-Canada-sponsored studies. **Comment:** *Note*

that in the previous analysis (Section 1.31), the sponsor used the total number of patients treated at docetaxel 100 and 75 mg/m² for the denominator when calculating overall death rates. However, use of 1327 instead of 1406 does not alter the death rates much. The twelve recent patient deaths, five in breast cancer patients, reported under IND are not included among the 26 toxic deaths reported here.

Reviewer Conclusions:

1) The septic death rate for docetaxel as a 1-hour infusion in the updated analysis of 1327 patients is not substantially different from that reported for the original group of 1010 patients (1.4 vs 1.5%).

2) There was a slight increase in septic death rate among the 139 recently treated breast cancer patients as compared to the original 316 patients (1.4% vs 0.9%).

3. The septic death rates for docetaxel remain several-fold higher than the 0.2% rate reported for paclitaxel as a 3-hour infusion by Bristol-Myers Squibb in its NDA submission (see additional discussion in Section 1.31).

2.32 Hematologic Toxicity - Docetaxel at 100 mg/m²

For this analysis, the definition of febrile neutropenia has been restricted to include only patients with fever ≥ 38°C and grade 4 neutropenia, requiring antibiotics and/or hospitalization. Using this definition, the overall incidence of febrile neutropenia was 15% among 1327 patients (vs 24% among 931 patients using the original definition of febrile neutropenia that included grade 3 or 4 neutropenia and did not stipulate hospitalizations and/or antibiotic usage). Among the 455 breast cancer patients, the incidence of febrile neutropenia was 18% (restrictive definition). Although the six NCI studies used several different definitions of febrile neutropenia, the sponsor combined them for a 40% incidence of febrile neutropenia among 151 patients. Similarly, the two NCI-Canada studies were combined giving a 17% incidence of febrile neutropenia among 24 patients. **Comment:** *Note that the frequency of hospitalizations for febrile neutropenia in NCI studies was 29%.*

The overall rate of "bacteriologically-documented" infections was 17% among 1327 patients treated at the initial planned dose of 100 mg/m². In particular, the overall infection rate was only 5% in NCI studies. **Comment:** *The overall incidence of "documented" infections was 20% in the initial 931 patients (Section 1.32), but the incidence of "bacteriologically-documented" infections in the subsequent 396 patients was only 10%. No explanation is provided for this diminution in infection rate, although the low rate observed in the NCI studies may have lowered the overall rate. It is also not clear whether the term "bacteriologically-documented" infection is more restrictive than "documented" infection.*

Among 455 breast cancer patients, the infection rate was 22%; among the 133 anthracycline-

resistant breast cancer patients it was 28% (Section 1.32).

Reviewer's Conclusions: *Again, in the absence of a randomized comparison between docetaxel and paclitaxel, it is problematic to directly compare treatment-related febrile neutropenia and infection rates for these two agents in analogous patient populations. The data quoted from the paclitaxel NDA and package insert suggest that the incidence of febrile neutropenia may be lower for paclitaxel (2%) when given as a 3-hour infusion than for docetaxel dosed at 100 mg/m² over 1 hour. The incidence of infections during treatment may be comparable for both agents.*

2.33 Fluid Retention - Docetaxel at 100 mg/m²

There are 1070 patients in 32 studies (excluding TAX265) evaluable for analysis of fluid retention. These patients received a median of 4 treatment cycles (range 1-25). The overall incidence of fluid retention, regardless of premedication, was 52% with moderate reactions in 24% and severe reactions in 9.4%. Treatment was discontinued due to fluid retention in 10%. **Comment:** *These figures are similar to those reported in the Updated ISS for 931 patients in 26 studies (Section 1.33).*

- **Effect of the 5-day Dexamethasone Premedication Regimen in Breast Cancer**

In the 3/9/95 document, an updated analysis was provided for 104 breast cancer patients in 7 studies who received premedication with dexamethasone on days -1, 1, 2, 3, and 4 of docetaxel treatment. Additional information, provided in RPR's Responses to FDA (5/23/95), and in the ODAC Briefing Document (6/8/95) have been incorporated in this section. This 104 patient group includes the 32 breast cancer patients from completed US studies that were reviewed in Section 1.33 (median of 5 treatment cycles, 3% rate of treatment discontinuation due to fluid retention). The additional patients are from ongoing phase II (TAX264 and TAX296) and phase III (TAX303, TAX304, and TAX311) trials.

The median age of the 104 patients was 53 (range 26-80 years) and 78% had a WHO performance status of 0-1. They had received a median of 3 treatment cycles (range 1-13); 63% of cycles had been dosed at 100 mg/m². The median cumulative dose given was 298 mg/m² (range 99-975 mg/m²). The overall incidence of fluid retention (49%), moderate (15%) and severe (5%) reactions, and treatment withdrawals (2%) confirm the initial findings for the 32 patients submitted previously (Section 1.33). The cumulative dose to treatment discontinuation was not calculable for the two patients withdrawn due to fluid retention (see Kaplan-Meier plot in the Appendix.) The overall response rate was 41% among 39 second line breast cancer patients evaluable for response in this group.

A comparator group of 60 breast cancer patients from the original NDA received no premedication. The median age of these patients was also 53 (range 29-73 years) and 83% had a WHO performance status of 0-1. They had received a median of 5 treatment cycles

(range 1-13); 74% of cycles had been dosed at 100 mg/m². The median cumulative dose given as 453 mg/m² (range 99-884 mg/m²). The overall incidence of fluid retention (77%), moderate (32%) and severe (20%) reactions, and treatment withdrawals (32%) were reported previously for this group in Section 1.33. The cumulative dose to treatment discontinuation was 621 mg/m² (19 patients withdrawn). The overall response rate was 58% among 60 first and second line breast cancer patients evaluable for response.

Information on evolution of performance status on and off study, supportive measures including drainage procedures and hospitalizations on and off study will be supplied when available.

Comments: *The table below is adapted from that previously shown in Section 1.33, updated to include the experience with the 5-day dexamethasone premedication regimen in 104 breast cancer patients. Symptomatic patients are defined as those with moderate or severe events.*

Severity of Fluid Retention in Breast Cancer

Fluid Retention	No Premedication (N=60)[a]	Dexamethasone 5 days (N=32)[b]	Dexamethasone 5 days (N=104)[a]
# Patients with Toxicity	46	14	51
Mild	33%	43%	59%
Moderate	41%	43%	31%
Severe	26%	14%	10%
Symptomatic	67%	57%	41%
# Pts Withdrawn	19	1	2

[a] *Table 8, Updated Specific Safety Analysis, 3/9/95*
[b] *Updated ISS, Table 16*

The overall incidence of fluid retention (49%) remains high, despite the use of 5-day corticosteroids. However, there is a suggestion that more patients are experiencing mild rather than moderate or severe events: only 41% of patients are symptomatic. This may be related to the lower median cumulative dose of docetaxel treatment given, to the use of corticosteroids, or to other as yet unknown reasons. No information is provided on supportive care measures required to treat fluid retention. Thus, it remains difficult to assess the net clinical benefit of corticosteroid premedication.

- **Reversibility of Fluid Retention**

TAX237 Trial: At FDA's request, RPR provided follow-up information for 25 of the patients developing fluid retention on the TAX237 trial (See Section 1.33) in their Response to FDA (5/23/95). A summary table is included in the Appendix.

As background, additional information from the TAX237 study report submitted in the original NDA (July 1994) has been summarized here. Thirty-four first line breast cancer patients were treated with docetaxel at 100 mg/m² without routine premedication. The median age was 52 (range 29-65 years). The median number of treatment cycles received was 5 (range 1-10), and the median cumulative dose was 489 mg/m² (range 100-907 mg/m²). There were 5 CRs and 17 PRs for an overall response rate of 65%. The median time to first response was 11 weeks and median response duration was 44 weeks (calculated from the first infusion).

Fluid retention developed in 26 (76%) patients, with 8 moderate (24%) and 6 severe cases (18%). The median cumulative dose to the onset of fluid retention for the 26 patients was 322 mg/m² (range: 100-779+mg/m²).

Seventeen patients in the original report discontinued treatment for fluid retention with a median dose to treatment discontinuation of 600 mg/m² (range: 348-907+ mg/m²). Five patients discontinued due to severe fluid retention (patients , 5 due to moderate symptoms (patients , and 7 due to mild symptoms (patients . See clinical summaries for the five withdrawn patients with severe fluid retention in the Appendix. RPR's summary table also indicates that patients discontinued treatment with mild fluid retention, and patient for cutaneous toxicity associated with mild fluid retention. **Comment:** *All but two of these patients had responded to docetaxel treatment. The difference between the median dose to treatment discontinuation and the median dose to onset of fluid retention suggests that symptomatic patients remained on treatment for several weeks prior to withdrawal.*

Recovery information was available for 20 of the 26 patients with fluid retention (8 had precise resolution dates and 12 were known to have recovered at a follow-up visit). For these patients, the median time to disappearance of fluid retention from onset of toxicity was 34 weeks, and the median time to disappearance of fluid retention from last infusion was 25 weeks (range 3-60 weeks). Kaplan-Meier plots from the TAX237 study report are included in the Appendix. For 13 of the 14 patients with moderate or severe fluid retention, the median "time to improvement of fluid retention symptoms" was 74 days (range 49-174 days).

The evolution of performance status for 25 of the patients with fluid retention after study discontinuation was: improvement in 3, stable in 9, deterioration in 8, unknown in 5. Of the eight patients who declined off study, disease progression was the cause in 7, while increase in fluid retention severity was the cause in 1.

Twenty-one patients received treatment for fluid retention, including diuretics alone in 9 patients, or diuretics plus flavonoids (vascular protectors) in 9 patients. Seven patients required drainage of pleural effusions or ascites; malignant involvement was confirmed in five patients. Four patients were hospitalized for drainage procedures.

At last follow-up, 15 patients had died of disease progression. Of the ten living patients, two were disease-free at 16+ (patient and 30+ months (patient , without additional treatment given after docetaxel.

Comments:

1) The duration of follow-up in this updated analysis was not given. In 7/94 when the original study report was submitted, the median follow-up was 17 months (range 15-20 months).

2) The TAX237 trial demonstrates the delicate balance between the risks and benefits of docetaxel treatment. Recall that the proposed indication for docetaxel in this NDA is in second line breast cancer patients (overall response rate 41%), rather than first line patients (overall response rate 59%). One wonders how these patients might have fared if premedication with corticosteroids had been given.

Regression Analysis: There were 90 patients treated on phase II studies who developed fluid retention and who had adequate recovery information. (Recovery dates were not available for an additional 237 patients with fluid retention.) RPR's Response to FDA (May 23, 1995) included the following background information. The median age was 53 years (range 29-77 years). There were 26 males and 64 females. WHO performance scores of 0-1 were present in 80%. No prior therapy had been given in 52%, whereas 39% had prior chemotherapy ± radiotherapy ± hormones. The median number of treatment cycles received was 6 (range 1-13), and the median cumulative dose was 502 mg/m² (range 100-1315 mg/m²). The median cumulative dose to the onset of moderate to severe fluid retention was 397 mg/m². Nineteen (21%) patients discontinued treatment due to fluid retention and 7 (8%) due to other toxicities.

The regression analysis (see Appendix) showed that the cumulative dose of docetaxel had no impact on time to recovery of fluid retention ($p=0.3143$). The median time to disappearance of fluid retention from last infusion was 16 weeks. RPR indicates that if regression analysis had been applied to the TAX237 data above, a shorter median time to disappearance of fluid retention would have been obtained (18-21 weeks instead of 25 weeks). RPR concludes that there is no discrepancy between the estimates in the two analyses, and that the duration of symptomatic fluid retention is likely to be shorter.

- **Pathophysiology**

For a detailed discussion, see Section 1.33. RPR now reports that symptomatic treatment with flavonoids (diosmine 2 g/day) and benzopyrones (Lysedem 135 mg/day) is currently being

evaluated in Europe.

Comments: *Preclinical studies have not as yet elucidated the mechanism of fluid retention in humans. A study conducted in cynomologous monkeys (Report No. RPR/RD/CRVA/SM 92-0292) evaluated two doses of docetaxel (25 and 50 mg/m²) given IV every 3 weeks over a 9-month period. Macroscopically, no edema was observed. However, due to severe toxicity, monkeys administered a single dose at 50 mg/m² were removed from the study. Four of six monkeys (3 males, 1 female) were sacrificed moribund on study days 8, 9, 15, and 16. Histopathologic examinations were not performed in any of the animals.*

Dr. Eugene Herman, of the DRT Pharmacology/Toxicology Branch of CDER, has initiated a preclinical study of docetaxel evaluating whether fluid retention is related to microvascular damage induced by activation of endothelial or other immune effector cells. Docetaxel, provided by RPR, will be administered to spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats with normal arterial pressure. The SHR rat has been found to be sensitive to the cardiotoxic effects of other anticancer agents, such as doxorubicin. Doses of 2.5, 5.0, 7.5 and 10.0 mg/kg will be evaluated, given IV every 3 weeks for ten weeks. Tissues obtained at necropsy will be evaluated for the presence of specific immune effector cells (NK cells, T cytotoxic/suppressor cells, T helper cells, macrophages) and by electron microscopy (see protocol attached).

- **Protocol Amendments**

Protocols for ongoing trials have been amended to include premedication with dexamethasone 8 mg po BID for 5 consecutive days, starting 1 day prior to each treatment cycle. Taxotere is delayed in patients who do not begin taking oral dexamethasone the day before.

Patients developing new onset symptomatic edema, or other signs of increasing fluid retention, are recommended to initiate treatment with oral diuretics including: dyazide one capsule po qd up to tid, furosemide 40 mg po qd, and metolazone 2.5 mg po qd. No dose reduction is recommended.

Some protocols also include the following guidelines regarding effusions or ascites: "If SD, PR, or CR with new or increased effusion but without edema, perform a diagnostic tap to rule out PD. If SD, PR, or CR with new or increased effusion but with edema, do not perform a diagnostic tap unless patient has significant symptoms, since the cause is probably toxicity".

Comment: *The proposed labeling does not offer any recommendations regarding the management of fluid retention.*

2.34 Performance Status

- **At Baseline**

At baseline, the ECOG or WHO PS for the original 931 patients in the phase II program reported previously was: PS0, 29%, PS1, 56%, ≥PS2, 15%. Among the 455 breast cancer patients it was: PS0, 33%, PS1, 51%, ≥PS2, 15%. The breakdown was very similar among the 151 patients on NCI studies. However, the 24 patients on NCI-Canada studies had PS0, 30%, PS1, 33%, and ≥PS2, 37%. Comment: ***With the exception of the NCI-Canada patients, all other cohorts treated with docetaxel in this report included les. n 20% of patients with a PS of 2 or higher. This is comparable to the patient base' aracteristics in the Bristol-Myers Squibb paclitaxel pivotal study. See Section 1.34 for ac onal details.***

- **Quality of Life: Evolution of Performance Scores**

Table 4.01 (see Appendix) lists the evolution of patient WHO performance status and reasons for treatment withdrawal by best overall response for the 316 first and second line breast cancer patients treated at the initial planned dose of 100 mg/m².

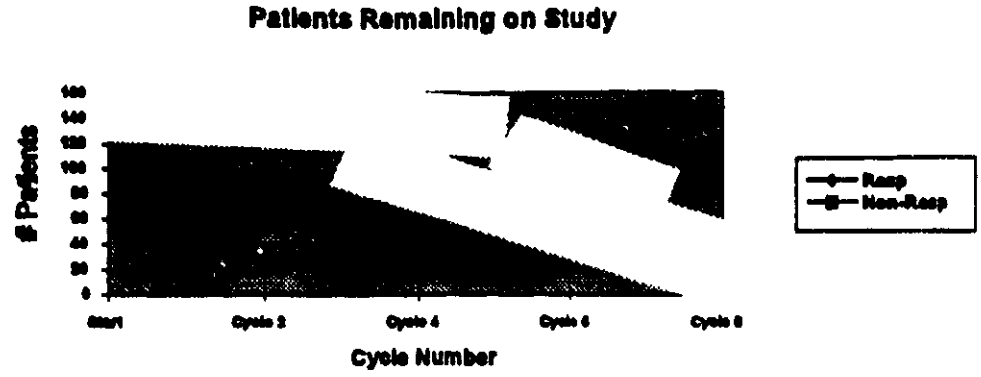
Overall, the response rate was 51% (17 CRs and 143 PRs). The table below summarizes the performance status of patients on study and reasons for treatment withdrawal among the 160 responders. Note the marked increase in the number of patients withdrawn due to toxicity after cycle 4. There were 53 patients that went off study between cycles 4 and 6: 41 withdrew for toxicity and other reasons, and 12 for disease progression. Despite patient dropouts, the proportion of patients remaining on study with an improved or stable performance status was constant, with 68% of patients at cycle 6 (64/94) and at cycle 8 (30/44) improved or stable.

QOL Measure	Cycle 2	Cycle 4	Cycle 6	Cycle 8
PS Improved	14	24	14	7
PS Stable	119	90	50	23
PS Worsened	15	27	27	12
PS Missing	11	6	3	2
WD: Toxicity	1	5	37	57
WD: Other	0	6	15	28
Progression	0	2	14	31
Total # Patients	160	160	160	160

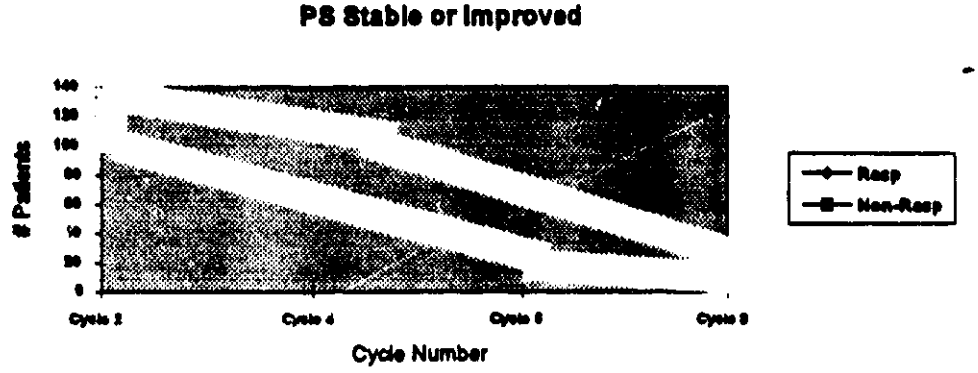
The table below summarizes the performance status of patients on study and reasons for treatment withdrawal among the 156 **non-responders** (patients with stable disease or no response). As expected, early withdrawals due to disease progression beginning in cycle 4 correlates with declines in performance status.

QOL Measure	Cycle 2	Cycle 4	Cycle 6	Cycle 8
PS Improved	13	5	3	1
PS Stable	94	59	23	9
PS Worsened	19	19	12	1
PS Missing	11	11	4	1
WD: Toxicity	6	16	28	35
WD: Other	3	8	11	18
Progression	10	38	75	91
Total # Patients	156	156	156	156

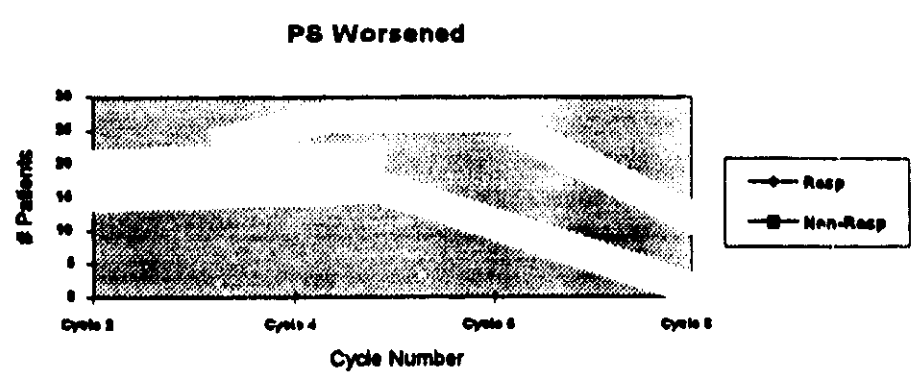
Comments: *These data are represented graphically on the next two pages. As expected, the number of patients with stable or improved performance status decreased over time, and the number of patients withdrawn for disease progression increased over time for both responders and non-responders. However, the number of patients with worsened performance status is higher for responders beginning with cycle 4 and the number of patients withdrawn for toxicity is higher at cycles 6 and 8. These events may be explained by the onset of fluid retention around cycle 4.*



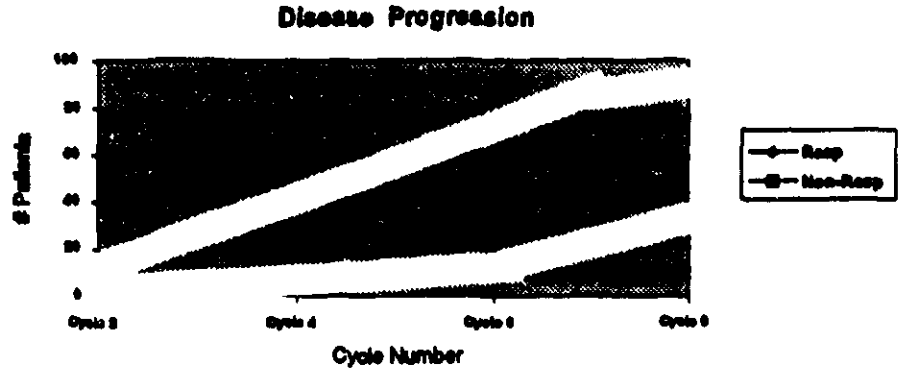
The drop-out rate for responders and non-responders appears fairly uniform after cycle 4.



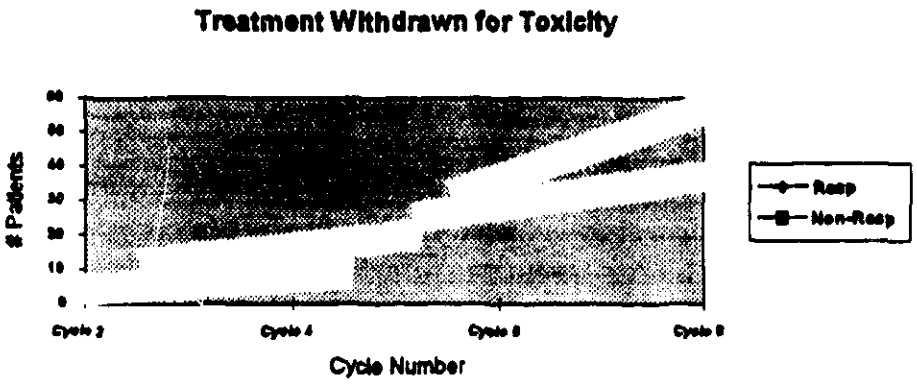
The number of patients with a performance status that was improved or remained stable compared to baseline declined at a similar rate for responders and non-responders.



The number of responding patients with a worsened performance status appeared to increase at cycles 4 and 6.



As expected, more non-responders withdrew for disease progression over time.



However, more responders withdrew for reasons of toxicity after cycle 4.

2.35 Tolerance in Patients with Elevated Hepatic Enzymes

- **Elevated Transaminases**

This is the first RPR submission regarding tolerance of docetaxel therapy in patients with elevated hepatic enzymes at baseline. In this retrospective clinical safety analysis, abnormal hepatic enzymes was defined as an SGOT or SGPT > 1.5 x N. Note that subsequent analyses submitted in the Response to FDA (May 23, 1995) and in the ODAC Briefing Document (June 8, 1995) use a different definition that includes alkaline phosphatase.

There were 895 patients evaluable for safety and baseline liver function tests treated on 25 phase II studies at the initial planned dose of docetaxel of 100 mg/m². Of these, 95 had an SGOT or SGPT > 1.5 x N, and 800 had levels ≤ 1.5 x N. Appendix V (3/9/95 submission, attached) summarizes the tolerance of docetaxel treatment in patients with normal and elevated baseline hepatic function. **Comment:** *At the Agency's request, RPR supplied the distribution of SGOT/SGPT elevations among patients at baseline in a fax dated May 5, 1995. There were 92 patients with baseline elevations of SGOT: grade 1 elevations in 62; grade 2 in 27, and grade 3 elevations in 3 patients. There were 68 patients with baseline elevations of SGPT: grade 1 elevations in 50 patients, and grade 2 in 18 patients. The sponsor's analysis, however, is based on 95 evaluable patients.*

For patients with normal baseline hepatic function: 58% were female, 30% had breast cancer and 29% had NSCLC, the median age was 57 years, 86% had a WHO PS of 0-1, and 29% had liver metastases. For patients with elevated baseline hepatic function: 68% were female, 56% had breast cancer and 8% had NSCLC, the median age was 51 years, 79% had a WHO PS of 0-1, and 83% had liver metastases.

Compared to patients with normal baseline transaminases, the patients with elevated transaminases had a significantly higher incidence of grade 3-4 leukopenia (88 vs 75%), grade 3-4 thrombocytopenia (8 vs 2%), and grade 3-4 anemia (20 vs 8%). Febrile neutropenia with or without infection (all grades) was more frequent (35 vs 17%), as was grade 3/4 stomatitis (13 vs 4%). These patients also had significantly higher rates of dose reduction (35% of cycles vs 25%), treatment withdrawals due to toxicity (26% vs 17%), and toxic deaths (5% vs 1%). However, the incidence of grade 3/4 neutropenia was high in both groups (95 vs 92%).

In the population PK analysis submitted in the original NDA, patients with elevated transaminases at baseline had a docetaxel clearance that was decreased by 20%. Based on PK/PD considerations, and on the analysis above, the sponsor has proposed that:

1. use of docetaxel at 100 mg/m² be limited to patients with hepatic transaminases ≤ 1.5 times normal, and

2. the starting dose of docetaxel be reduced by 25% (to 75 mg/m²) in patients with elevated

baseline transaminases. The presence of liver metastases, without abnormal transaminases, is not in itself a reason to reduce the starting dose of docetaxel.

Comments: ***The following analysis has been undertaken to determine what contribution was made by the subset of patients with elevated LFTs at baseline to the overall toxicity profile.***

Hematologic Toxicity: Overall, the 95 patients with elevated LFTs at baseline comprised 11% of the total study population and accounted for roughly 15% of patients with grade 3/4 neutropenia or severe infection, no septic deaths, but 38% of toxic deaths.

Patient Group	Patients w/ Febrile Neutropenia gr 3/4	Patients with Severe Infection	Deaths	
			Septic	Toxic
All (N=895)	205	51	5	13
Elevated LFTs at Baseline (N=95)	31 (15%)	8 (16%)	0	5 (38%)
Normal LFTs at Baseline (N=800)	174 (85%)	43 (84%)	5 (100%)	8 (62%)

Patients with elevated LFTs at baseline received only 10% of all cycles delivered, but 15% of the cycles that were complicated by either grade 3/4 febrile neutropenia or grade 3/4 infection.

Patient Group	Total Cycles (%)	Cycles w/ Febrile Neutropenia gr 3/4	Cycles with Infection grade 3/4
All	4239	274	55
Elevated LFTs at Baseline	414 (10%)	40 (15%)	8 (15%)
Normal LFTs at Baseline	3825 (90%)	234 (85%)	47 (85%)

Perhaps the most striking findings, however, occurred during the first cycle of treatment: patients with elevated LFTs accounted for one-quarter of patients developing grade 3/4 febrile neutropenia and infections, and one-half of toxic deaths (see table below). All four patients with elevated LFTs who died during the first cycle were breast cancer patients.

Patient Group	Patients w/ Febrile Neutropenia gr 3/4	Patients w/ Infection grade 3/4	Toxic Deaths
All (N=895)	74	19	8
Elevated LFTs at Baseline (N=95)	19 (26%)	5 (26%)	4 (50%)
Normal LFTs at Baseline (N=800)	55 (74%)	(74%)	4 (50%)

Severe Non-Hematologic Toxicity:

Patient Group	Stomatitis grade 3/4	Skin Toxicity grade 3/4	Fluid Retention severe	Neurosensory grade 3/4
All (N=895)	47	65	88	32
Elevated LFTs at Baseline (N=95)	12 (26%)	9 (14%)	11 (12%)	5 (16%)
Normal LFTs at Baseline (N=800)	35 (74%)	56 (86%)	77 (88%)	27 (84%)

Patients with elevated LFTs at baseline accounted for one-quarter of the cases of grade 3 or 4 stomatitis but did not appear to be at much greater risk for other non-hematologic toxicities, such as severe skin reactions, fluid retention or neurosensory toxicity. During the first cycle of treatment, severe stomatitis was more frequent among patients with elevated LFTs than expected (see below). Severe fluid retention and neurosensory toxicity occurred infrequently in both groups during the first cycle.

Patient Group	Stomatitis grade 3/4	Skin Toxicity grade 3/4	Fluid Retention severe	Neurosensory grade 3/4
All (N=895)	31	21	7	1
Elevated LFTs at Baseline (N=95)	8 (26%)	4 (19%)	1 (14%)	0
Normal LFTs at Baseline (N=800)	23 (74%)	17 (81%)	6 (86%)	1 (100%)

- **Elevated Alkaline Phosphatase**

At the Agency's request, an analysis was provided for patients with elevated baseline alkaline phosphatase and normal transaminases (5/5/95 fax and Response to FDA, 5/23/95). A total of 21 patients had an alkaline phosphatase level > 2.5 x normal in the setting of normal hepatic transaminases. Of these, 17 (81%) had liver metastases. One patient had grade 4 febrile neutropenia at first cycle and one discontinued treatment after the first cycle (same patient??); three patients had their dose reduced at the second cycle. The severity of myelosuppression experienced by this small subset of patients was not different from that of 775 patients with normal hepatic enzymes and normal alkaline phosphatase levels at baseline.

- **Elevated Total Bilirubin**

Patients with elevated total bilirubin levels were excluded in the phase II trials, however, 7 patients were entered: four with NCI grade 2 elevations, two with NCI grade 3 elevations, and one with an NCI grade 4 elevation.

This reviewer has identified four patient deaths associated with bilirubinemia and/or jaundice to date. Liver metastases were present in two cases, absent in one and status was unknown in the fourth. These are summarized below:

TAX266 (Original NDA, 7/27/94): 50 year old female with breast cancer, liver metastases, and bilirubin of 1.8 at study entry (protocol violation). Following the first infusion, she was hospitalized with febrile neutropenia, grade 3 thrombocytopenia, elevated PT and PTT, grade 3 mucositis, diarrhea, and rash. On day 10 of the cycle, she was noted to have improvement of mucositis and marrow recovery, however, on day 12 she developed hematemesis, respiratory failure requiring intubation and died the next day (10/18/92). Autopsy revealed that 80% of the liver had been replaced by tumor, PK studies showed a 60% decrease in docetaxel clearance, and an AUC of 11.6 which was two-fold higher than that for an average patient (5.5 mg x h/mL).

TAX286 (Updated ISS, 11/7/94): 42 year old female with breast cancer, liver metastases, bilirubin > 1.25 and elevated SGOT at study entry (protocol violation). Following the first infusion, she was hospitalized with febrile neutropenia, grade 2 anemia, grade 4 thrombocytopenia, grade 4 mucositis, prolonged PT, elevated creatinine, and hypotension. The patient expired on day 8 due to acute orogenital hemorrhage (8/12/93). No autopsy or PK studies were performed.

TAX301 (Telephone report 2/13/95, filed under IND Report of death "probably related" to docetaxel in a 56 year old female with breast cancer treated in France . The patient received her third course of docetaxel on 12/14/94. She developed edema and jaundice and was hospitalized. She died on 2/2/95. No written report has been submitted.

CALGB-9256 (Safety report to IND Report of death in a 70 year old female with non-Hodgkin's lymphoma treated at Memorial Hospital, Chattanooga, TN After the fifth cycle of treatment (9/15/94) the patient was admitted (10/9/94) with elevated amylase (214), lipase, AST, ALT, and alkaline phosphatase, and a diagnosis of pancreatitis. CT scan (10/10/94) showed an enlarged pancreas, ascites, but no evidence of liver metastases or bile duct dilatation (patient was s/p cholecystectomy). Percutaneous liver biopsy, performed on 10/19/94, and reviewed at AFIP, revealed combined hepatocellular and cholestatic injury consistent with drug effect. The patient continued to develop progressive hepatic failure, jaundice (bilirubin 18), pleural effusions and ascites, and expired on 10/28/94.

The sponsor has submitted a new phase I protocol (TAX008, 1/26/95) that will address dosing and pharmacokinetics in advanced cancer patients with elevated serum bilirubin levels at study entry. The proposed starting dose of docetaxel in this trial is 40 mg/m².

- **Correlation with PK Data**

The TAX008 protocol referenced the following abstract: P. Francis et al., Proc ASCO, 13:138, 1994 (attached). Evaluation of 108 patients with breast, ovarian, lung and colon cancer treated on four phase II studies with docetaxel 100 mg/m² revealed that the subset of 19 patients with liver metastases, SGOT > 37 U/L and alkaline phosphatase > 115 U/L had significantly higher rates of admission for nadir fever, leukopenia grade 4, thrombocytopenia grades 2-3, mucositis grades 3-4, and skin rash grades 3-4, as compared to 17 patients with liver metastases and normal hepatic enzymes or to 71 patients without liver metastases ($p < 0.04$). Reduced docetaxel clearance was observed only in the group of 19 patients with both liver metastases and abnormal hepatic enzymes.

Reviewer's Conclusions:

1) Minimal elevations in transaminases or total bilirubin appear to predict for a worse treatment outcome. Baseline elevations of alkaline phosphatase alone was not predictive in a small subset of patients. The Francis et al. abstract suggests that the combination of elevated alkaline phosphatase and SGOT in patients with liver metastases is associated with reduced docetaxel clearance and increased myelosuppression and mucositis.

2) The sponsor's proposal to reduce the starting dose of docetaxel in patients with baseline LFT abnormalities may be reasonable. However, there is no clinical experience demonstrating that 75 mg/m² is a safe dose in second line breast cancer patients with LFT abnormalities.

3) It follows that patients developing elevation of LFTs during docetaxel treatment may be at risk for the development of severe myelosuppression and stomatitis. At present it is not known whether a 25% dose reduction should be recommended for such patients.

2.36 Multicenter Nature of Taxotere Clinical Trials

The sponsor presents the following data for the 316 breast cancer patients treated on eight first and second line phase II trials: number of patients treated, number of sites, response rate, per cent of patients withdrawn due to toxicity, per cent of patients withdrawn due to fluid retention, use of 5-day corticosteroid premedication, and number of toxic deaths. There was no clear correlation between number of sites/study and response rate (ranging from 29-68%), per cent of patients withdrawn for toxicity (ranging from 7-53%), per cent of patients withdrawn for fluid retention (ranging from 5-50%), and number of toxic deaths (ranging from 0-2). The sponsor points out that the two trials utilizing the 5-day dexamethasone premedication (TAX233 and TAX267) had low rates of treatment discontinuation due to any toxicity (7 and 24%), and the lowest rates of treatment discontinuation due to fluid retention (5 and 7%).

Comment: *Only 20 of 41 patients entered on TAX233, and only 12 of 42 patients on TAX267 received the 5-day dexamethasone premedication (Table 16, ISS, 9-1-36). The overall incidence of fluid retention was 42% in the TAX233 trial, and 60% in the TAX267 trial. The median cumulative dose to onset of fluid retention was 540 mg/m² in the TAX233 trial, and 400 mg/m² in the TAX267 trial. Thus, while the association of corticosteroid use with the lowest withdrawal rates due to fluid retention among breast cancer trials is encouraging, the TAX233 and TAX267 trials do not adequately address the usefulness of corticosteroids in ameliorating fluid retention. Again, the major concern of ODAC members was the fact that patients on the TAX233 and TAX267 trials (2 of the 4 pivotal trials for the proposed indication for second line therapy of metastatic breast cancer) were treated primarily at a single institution.*

2.4 Sponsor's Conclusions

A large representative patient population has been treated with docetaxel in multicenter trials.

Rates of toxic death, febrile neutropenia and infection are comparable to other recently approved cytotoxic agents.

Fluid retention has been ameliorated by the 5-day corticosteroid premedication and is no longer a major impediment to docetaxel treatment.

A dose of 75 mg/m² might be considered in patients with abnormal baseline hepatic enzymes.

Docetaxel 100 mg/m² as a 1-hour infusion every 3 weeks has an acceptable therapeutic index for the treatment of patients with locally advanced or metastatic breast cancer.

3. Response to FDA: May 23, 1995

Responses to the Agency's questions (attached) regarding fluid retention were included in Section 2.33. The following represents RPR's responses to questions regarding the tolerance of docetaxel in 1) patients with elevated hepatic enzymes at baseline who received a dose reduction in later cycles, and 2) patients who develop elevations of hepatic enzymes on study.

3.1 Patients with Elevated Hepatic Enzymes Who Were Dose-Reduced

"Elevated" LFTs in this analysis has been redefined as any elevation of alkaline phosphatase > 2.5 x ULN associated with SGOT and/or SGPT > 1.5 x ULN. "Normal" function includes patients with both SGOT and/or SGPT $\leq$ 1.5 x ULN and AP $\leq$ 2.5 x ULN, as well as individuals with isolated SGOT and/or SGPT > 1.5 x ULN, or AP > 2.5 x ULN.

- **Background**

These definitions were based on a population PK model that showed that patients with the combination of abnormalities above had a 27% decrease in docetaxel clearance that resulted in a 38% increase in systemic exposure (AUC). On the other hand, isolated elevations of transaminases alone or alkaline phosphatase were not associated with a significantly lower clearance. Logistic regression models showed that the odds of grade 4 neutropenia and of febrile neutropenia approximately doubled for a 38% increase in AUC.

Recall that there were 95 patients with a baseline SGOT/SGPT > 1.5 x N in the overall database presented in Section 2.35. The sponsor has broken this group down to a subset of 37 patients with AP > 2.5 x N, and a group of 58 patients with AP $\leq$ 2.5 x N (see Appendix for more details; this data was presented by Dr. Robert Bellet of RPR at an NCI-sponsored meeting held in Bethesda on 7/27/95).

Event	T > 1.5 x N + AP > 2.5 x N	T > 1.5 x N + AP $\leq$ 2.5 x N	T $\leq$ 1.5 x N + AP $\leq$ 2.5 x N
# of Patients	37 (4%)	58 (7%)	775 (89%)
Feb Neutro grade 4 at first cycle	7 (19%)[1]	14 (24%)[2]	61 (8%)
Infection gr 3+4 at first cycle	5 (14%)[3]	0	18 (2%)
Toxic Deaths after first cycle	4 (11%)[4]	0	4 (0.5%)

[1] Compared to the 775 patients, p= 0.03
[2] Compared to the 775 patients, p= 0.0003
[3] Compared to the 775 patients, p= 0.003
[4] Compared to the 775 patients, p= 0.001

Note that the number of patients with normal transaminases and alkaline phosphatase has declined from 800 (Section 2.35) to 775. This is presumably because 21 patients with isolated AP elevations have been excluded.

Patients with isolated transaminase elevations at baseline are at a much higher risk of developing febrile neutropenia grade 4 at first cycle compared to patients with totally normal LFTs. However, these patients did not show significant differences in other safety parameters. For this reason (coupled with PK data?), they were included in the sponsor's "normal" LFT group in this and subsequent analyses.

Patients with both transaminase and AP elevations are at increased risk for serious infection at first cycle and for toxic deaths after the first cycle, as shown above. All 37 patients had liver metastases. In addition, these patients experienced more skin toxicity, stomatitis, acute hypersensitivity reactions, and asthenia at first cycle, more treatment discontinuations after first cycle, and more dose reductions at second cycle (see sponsor's table). Hence, the sponsor has designated these patients as "elevated" LFT patients in this and subsequent analyses. Furthermore, all seven patients who were protocol violators due to elevated bilirubin level fell in this group and had liver metastases (Dr. R. Bellet, 7/27/95).

Comment: *There now appears to be a discrepancy in the number of toxic deaths that occurred among the 95 patients with abnormal transaminases at baseline. In Section 2.35 (sponsor's Appendix V), there were a total of 5 toxic deaths, and 4 occurred at the first cycle. In this analysis, there are 4 toxic deaths occurring after the first cycle in this group. If there were only 5 deaths total, then one of these statements is incorrect.*

Finally, among the 775 patients without LFT abnormalities, the presence of liver metastases was not predictive of increased adverse events. These data are included in the Appendix for reference. Note that of the "best case" patients (559 with normal transaminases, normal AP, no liver metastases), 45 (8%) experienced febrile neutropenia grade 4 at first cycle, 87 (17%) required a dose reduction at the second cycle, 36 (6%) discontinued treatment and 4 (0.7%) patients had toxic deaths after the first cycle. (Recall that there also were 4 toxic deaths at the first cycle among patients without LFT abnormalities (Section 2.35); it is not known how many of these occurred in patients without liver metastases.)

Sponsor's Conclusions:

1) "A starting dose of 70 mg/m² (30% dose reduction) should be given to patients with baseline hepatic impairment as defined above; because of the clearance reduction, these patients should have a systemic drug exposure (AUC) similar to that of the normal population treated at 100 mg/m²."

2) "Patients with abnormal serum bilirubin, SGOT or SGPT > 3.5 x N or alkaline phosphatase > 6 x N should not be treated with docetaxel til specific data are available."

3) These "results are valid up to the upper range (90th percentile) of data available in the current database, i.e., 3.5 x N for SGOT and SGPT and 6 x N for alkaline phosphatase."

Reviewer's Comments:

1) The incidence of a particular toxicity at first cycle should not be confused with overall incidence rates among patients, which may be higher.

2) PK data aside, given the poor tolerance of docetaxel in patients with liver impairment as defined as isolated SGOT and/or SGPT > 1.5 x N and presented in Section 2.35, and the 24% febrile neutropenia rate at first cycle presented above, the reviewer questions the validity of including such patients in the "normal" group.

3) Specific clinical safety data to support the proposed treatment cut-offs (SGOT/SGPT levels > 3.5 x N and alkaline phosphatase levels > 6 x N) have not been submitted.

4) Inclusion of all the bilirubin protocol violators among the 37 patients places the group with abnormal transaminases and AP at very high risk for myelosuppression (see the outcome in patients with elevated bilirubin below). One wonders what the safety profile would look like if the patients with elevated bilirubin levels were left out.

5) All 37 patients with abnormal transaminases and AP also had liver metastases. Are liver metastases predictive for a worse outcome in the setting of minimal LFT elevations?

6) The sponsor's new definitions cause the "elevated" LFT group to shrink and could potentially obscure differences between the "normal" and the "elevated" groups with respect to febrile neutropenia or other parameters.

- **Effect of Dose Reduction**

There were a total of 367 patients treated with docetaxel at an initial planned dose of 100 mg/m² who were subsequently dose-reduced by 25% or more (1025 or 79% of treatment cycles were given at 75 mg/m², while 269 or 21% of cycles were at $\leq$ 55 mg/m²). The median age of patients in this group was 57 (range 26-80 years), and there were 103 males and 264 females. A WHO performance status of 0-1 was noted in 87% at study entry. There were 181 breast cancer patients, 88 lung cancer patients, and 98 patients with other tumor types. Prior chemotherapy $\pm$ radiotherapy $\pm$ hormones had been given to 61%. No prior therapy had been given to 30%. A median of 5 cycles had been administered (range 1-25). The median cumulative dose was 450 mg/m² (range 102-1564 mg/m²). An overall objective response rate of 67% in breast cancer and 43% in lung cancer was reported for this group.

Abnormal liver function was noted in 15 patients, and "normal" liver function in 330 (LFTs

unknown for 22 patients?). Tabulation of treatment-related toxicities for the two groups following dose reduction is attached. Compared to "normal" patients, patients with "elevated" LFTs had a higher incidence of: grade 4 neutropenia (80% vs 64%), thrombocytopenia (27% vs 8%), infection (27% vs 18%), vomiting (27% vs 15%), stomatitis (40% vs 32%), and skin toxicity (73% vs 57%).

The subset of second line breast cancer patients (104 with "normal" and 8 with "elevated" LFTs) is also shown. Compared to "normal" patients, those with "elevated" LFTs had a higher incidence of thrombocytopenia (38% vs 9%), febrile neutropenia and hospitalization (13% vs 5%), infection (25% vs 15%), nausea (50% vs 32%), vomiting (50% vs 15%), stomatitis (50% vs 39%), asthenia (75% vs 67%), myalgia (38% vs 28%), skin toxicity (88% vs 52%), and fluid retention (88% vs 57%).

Comments:
1) Since a dose reduction from 100 mg/m² had been prescribed, all 367 patients had experienced one or more adverse events prior to those described in this analysis.

2) The numbers of patients in the "elevated" LFT groups, especially for the second line breast cancer subset, are quite small. Despite this, it appears that patients with "elevated" LFTs experience more hematologic and non-hematologic toxicity than "normal" patients, even after a dose reduction of 25% or more.

3) Since there is no clinical experience with initial treatment of second line breast cancer patients at the 75 mg/m² dose (see below), the findings above in 8 second line patients with "elevated" LFTs will serve as the clinical basis for recommending treatment with docetaxel 75 mg/m² in these patients in the product labeling.

- **Efficacy in the Presence/Absence of Baseline LFT Abnormalities**

The sponsor has compared the efficacy of docetaxel in breast cancer patients treated initially with docetaxel 100 mg/m², according to baseline LFTs. Abnormal LFTs here were defined as SGOT/SGPT > 1.5 x ULN and/or AP > 2.5 x ULN. Response rates in patients with "normal" baseline LFTs treated with docetaxel 100 mg/m², with or without dose reductions after the first cycle, were approximately 60% for first line and 44% for second line patients. Efficacy in the subset of "normal" patients who had dose reductions was not provided.

Response rates in the subset of patients with "elevated" LFTs who had dose reductions were approximately 40% for both first and second line patients, however, the numbers of patients in these groups was very small (5 patients for first line and 8 for second line).

3.2 Patients Treated at the Initial Planned Dose of 75 mg/m²

There were a total of 75 patients treated with docetaxel at an initial planned dose of 75 mg/m²

(360 or 83% of treatment cycles were given at 75 mg/m², while 73 or 17% of cycles were at ≤ 55 mg/m²). The median age was 54 (range 36-71 years), and there were 10 males and 65 females. A WHO performance status of 0-1 was noted in 80% at study entry. There were 55 first line breast cancer patients, and 20 lung cancer patients. Prior chemotherapy ± radiotherapy ± hormones had been given to 37%. No prior therapy had been given to 48%. A median of 5 treatment cycles had been administered (range 1-20). The median cumulative dose was 360 mg/m² (range 1-1479 mg/m²). An overall objective response rate of 47% in breast cancer and 10% in lung cancer is reported for this group.

There were baseline LFTs available for 72 of the patients. Using the new definition above, all would be classified as "normal" (see attached). The incidence of grade 4 neutropenia was 90%, thrombocytopenia 7%, febrile neutropenia and hospitalization 6%, infection 22%, nausea 44%, vomiting 19%, diarrhea 29%, stomatitis 33%, asthenia 57%, myalgias 10%, neurotoxicity 42%, skin toxicity 46%, allergy 41%, and fluid retention 64% (10% severe).

Compared to the 330 "normal" patients described above (treated with docetaxel at an initial planned dose of 100 mg/m², then dose-reduced by 25% or more), "normal" patients beginning at 75 mg/m² had a greater incidence of grade 4 neutropenia (90% vs 64%), nausea (44% vs 34%), and allergy (41% vs 17%). On the other hand, these patients had a lesser incidence of asthenia (57% vs 69%), myalgias (10% vs 19%), neurotoxicity (42% vs 59%), and skin toxicity (46% vs 57%). Other toxicities occurred with similar frequency in both "normal" groups. Comment: *Docetaxel administered at an initial dose 75 mg/m² is associated with considerable myelotoxicity (grade 4 neutropenia and infection), but with an improved febrile neutropenia rate and a somewhat ameliorated non-hematologic toxicity profile, compared to administration of docetaxel at an initial dose of 100 mg/m² with subsequent dose reductions. However, note that all breast cancer patients in this group are first, not second, line.*

The sponsor has also provided a tabulation of safety concerns for the 72 "normal" patients, broken down by all normal LFTs (57 patients), isolated transaminase elevations (9 patients) and isolated alkaline phosphatase (6 patients, see attached). The most notable finding is that of treatment discontinuations due to adverse events in 4/9 patients with isolated transaminase elevations.

3.3 Tolerance in Patients Who Develop LFT Abnormalities on Docetaxel

The sponsor has submitted three tables (see attached) summarizing the toxicities in the overall patient population and in second line breast cancer patients, according to whether levels of SGOT/SGPT, AP, or bilirubin were normal during the study or elevated at any time during the study. The reviewer assumes that normal here refers to the normal range for these tests and elevated to any abnormality outside the normal range. (Note, however, that baseline LFTs in all patients included in these tables were "normal"; the quotation marks here suggest that patients with isolated transaminase or AP elevations were included.)

Focusing on the second line breast cancer patients, there were 71/282 (25%) patients with an elevation of SGOT/SGPT, 23/282 (8%) patients with an elevation of alkaline phosphatase, and 25/282 (9%) with an elevation of bilirubin at any time. These abnormalities were seen with similar frequencies in the overall patient population (988 patients).

Elevations of any one of these LFTs, particularly of bilirubin, was associated with increased myelosuppression. The incidence of grade 4 neutropenia was 92%, 96%, and 100%, respectively, in patients with elevation of SGOT/SGPT, AP, or bilirubin. The incidence of thrombocytopenia was 23%, 26%, and 48%, respectively, in patients with elevation of SGOT/SGPT, AP, or bilirubin. The incidence of febrile neutropenia was 20% and 28%, respectively, in patients with elevation of SGOT/SGPT or bilirubin. The incidence of infection was 31% and 24%, respectively, in patients with elevation of SGOT/SGPT or bilirubin. Similar trends were noted in the overall patient population.

Reviewer's Conclusions:

1) It is difficult to ascertain what combination of LFT abnormalities confers an increased risk of myelosuppression in patients treated with docetaxel. If one accepts the sponsor's original safety review of isolated transaminase elevations as valid, then the new definition of "elevated" LFTs as derived from the population PK model seems too narrow.

2) The "at risk" population among second line breast cancer patients at any time during docetaxel treatment is difficult to estimate from these data, but could be as high as 25% (isolated elevation of transaminases), or as low as 8-9% (isolated elevation of AP or bilirubin), depending on how conservatively it is defined. There is insufficient information here to estimate the size of an "at risk" population described by a combination of LFT abnormalities developing on treatment.

3) It is not clear that dose reduction to 75 mg/m² (from 100 mg/m²) will sufficiently ameliorate the toxicities associated with abnormal LFTs in second line patients (total of 8 such patients, or 15 in the overall database). Initial treatment with 75 mg/m² in the target population, second line breast cancer patients, has not been studied. While the Japanese clinical experience includes second line patients treated with 60 mg/m², all but three had "normal" LFTs (see below).

4) It is not known whether interruption of treatment until LFTs resolve will be a realistic approach (i.e, will resolution occur quickly enough so that subsequent treatment cycles are not delayed too long and efficacy compromised).

4. ODAC Briefing Document: June 8, 1995

4.1 Update on Second Line Breast Cancer Patients

As reported in Section 2.2, there were a total of 1327 patients treated at the initial planned docetaxel dose of 100 mg/m². Of these, 1070 patients were enrolled in RPR-sponsored trials at the dose and schedule for which approval is sought (100 mg/m² IV over 1 hour every 3 weeks). A subset of 301 second line breast cancer patients will be reviewed here (see RPR's tables attached). Docetaxel efficacy in 162 of these patients was discussed at the December 1994 ODAC Meeting. Efficacy data in the remaining 139 patients is incomplete or not available (trials ongoing).

The median age of the 301 second line breast cancer patients was 51 (range 26-80 years), and a WHO performance status of 0-1 was noted in 83% at study entry. All patients had received prior chemotherapy, 58% had been given 2 or more regimens. These patients received a median of 4 treatment cycles of docetaxel (range 1-18). There were 1067 (72%) cycles given at 100 mg/m², 346 (23%) cycles given at 75 mg/m², while 75 or 5% of cycles were at $\leq$ 55 mg/m². The median cumulative dose was 404 mg/m² (range 99-1608 mg/m²).

A complete biochemical profile was available for 297 of these patients: 282 with "normal" LFTs and 15 with "elevated" LFTs (using the PK-derived definition in Section 3.1). Patients in the "normal" LFT group received a median of 5 cycles (range 1-18). Patients in the "elevated" LFT group received a median of 3 (range 1-8) cycles, with discontinuations due to toxicity or disease progression.

Toxic deaths occurred with greater frequency in the "elevated" group (3/15 or 20%) as compared to the "normal" group (4/282 or 1.4%, p= 0.003). Deaths in the "elevated" group were due to sepsis in 1 patient, and to gastrointestinal hemorrhage/thrombocytopenia/liver impairment in 2 patients. All four deaths in the "normal" group were sepsis-related.

Treatment discontinuations occurred in the "elevated" group in 3/15 (20%) patients (all due to fluid retention), and in 39/282 (8%) "normal" patients (due to fluid retention, neurotoxicity, allergy/skin reactions, asthenia, and other reasons).

The incidence of grade 4 neutropenia was similar in both "normal" and "elevated" groups (92% vs 87%). However, patients in the "elevated" group, had a 53% incidence of thrombocytopenia (grade 4 in 20%), a 40% incidence of febrile neutropenia (defined as at least one day of fever > 38.5°C, with grade 4 neutropenia requiring antibiotics and/or hospitalization), and a 40% incidence of infection.

In the "elevated" group, the incidence of severe non-hematologic toxicity was remarkable for stomatitis (40%), skin toxicity (20%), nausea and vomiting (13% each).

4.2 Sponsor's Conclusions/Actions

The sponsor has concluded that:

"since the safety profile of the compound is substantially better in patients with 'normal' hepatic enzymes at baseline, the restriction of use of Taxotere at 100 mg/m² only in patients with 'normal' hepatic tests at baseline should further enhance this [risk/benefit] ratio", and

"based on population PK/PD and clinical observations, and in order to reduce the morbidity associated with Taxotere, it should not be administered at usual doses to patients with hepatic impairment".

- **Protocol Amendments**

Protocols for ongoing phase II and III trials have recently been amended to: 1) tighten patient inclusion criteria, and 2) provide guidelines for dose reduction when abnormal LFTs develop. For example, the patient inclusion criteria for TAX317, a phase III trial in NSCLC, require: "total bilirubin $\leq$ ULN, SGOT and/or SGPT $\leq$ 1.5 x ULN, and alkaline phosphatase $\leq$ 5 x ULN". Dose reductions on most studies now follow the schema below:

Bilirubin		Alkaline Phosphatase		SGOT/SGPT	Action
> ULN	or	> 5 x ULN	or	> 5 x ULN	Wait $\leq$ 3 weeks. If recovered*, dose reduce by 25%. If not, off study.
$\leq$ ULN	and	$\leq$ 5 x ULN	and	1.6 - 5 x ULN	Dose reduce by 25%

*Bilirubin $\leq$ ULN and alkaline phosphatase $\leq$ 5 x ULN and SGOT/SGPT $\leq$ 5 x ULN

- **Ongoing/Planned Trials**

As noted above, the TAX008 trial was initiated to evaluate docetaxel dosing (beginning at 40 mg/m²) in advanced cancer patients with elevated serum bilirubin. The sponsor has also committed to perform a study in 40 hepatically-impaired patients with metastatic breast cancer to assess response rate, duration of response, and safety of docetaxel at 75 mg/m². The study report is expected in 1997. Details of this trial have not been discussed with FDA.

- **Proposed Labeling**

The updated proposed product labeling states the following under WARNINGS: "liver function tests should be measured at baseline and before each cycle. Patients who have

elevated liver function tests may require an adjustment in dosage".

Regarding dose adjustments during treatment in patients with hepatic impairment it states: "In patients who have concurrent increases in alkaline phosphatase values > 2.5 times the upper limit of normal and elevations of transaminase values (ALT and/or AST) > 1.5 x ULN, the recommended dose of Taxotere is 75 mg/m². For those patients with increased serum bilirubin, and/or > 6 times the ULN for alkaline phosphatase, and values > 3.5 x ULN for ALT and/or AST, no adjustment can be recommended and Taxotere should not be used unless the potential benefit outweighs the risk".

Reviewer's Comments:

1) Clinical data has not been provided specifically addressing how the choice of treatment cut-offs (i.e., AP levels >6 x ULN, or SGOT/SGPT levels >5 x ULN, alone or in combination) was made. Hence, it is not possible to know if the sponsor's guidelines are reasonable.

2) Given the retrospective clinical data presented thus far, one would have expected a recommendation to treat only those patients (on or off protocol) with total bilirubin ≤ ULN, SGOT and/or SGPT ≤ 1.5 x ULN, and alkaline phosphatase ≤ 2.5 x ULN, rather than ≤ 5 x ULN, with docetaxel 100 mg/m². A recommendation could be made to interrupt treatment, for either bilirubin > ULN, or SGOT/SGPT > 1.5 x ULN, or AP > 2.5 x ULN. Recovery would be defined as bilirubin ≤ ULN and SGOT/SGPT ≤ 1.5 x ULN and alkaline phosphatase ≤ 2.5 x ULN.

3) The benefit of a 25% dose reduction alone in patients with hepatic impairment in retrospective analyses has not been demonstrated. Prospective studies should explore this issue further.

4) Note the following approach taken by investigators involved with the TAX202 protocol (phase II neoadjuvant trial in Stage III breast cancer): patients must have a bilirubin ≤ ULN and SGOT ≤ 2.5 x ULN to enter. If either rises above admission criteria, treatment is interrupted until levels fall. If elevations persist after withholding therapy for two weeks, the patient is taken off study. This approach is far more conservative than the guidelines discussed above, and is being recommended for a patient population (Stage III breast cancer) that is far less likely to develop hepatic abnormalities during treatment than the target population of interest (Stage IV, second line).

5. Japanese Clinical Experience

The Japanese studies in metastatic breast cancer were previously summarized in the Integrated Summary of Efficacy and the Integrated Summary of Safety (submitted July 1994) and described in Sections 7 and 9 (review sent to ODAC in December 1994). No primary data from Japanese trials was submitted. The following includes additional data provided on July 21, 1995 (see Appendix).

The TAX242, TAX279, and TAX289 studies enrolled 206 breast cancer patients, of which 190 were eligible. The median age was 53 (range 20-79 years), and 83% had a WHO performance status of 0-1. Prior chemotherapy had been given to 174 patients. The most common histologies seen were solid tubular and scirrhous carcinoma, and the most frequent sites of metastasis were in lymph nodes, followed by "recurrence", lung, and bone. Docetaxel was administered at 60 mg/m² as a one hour continuous infusion every 3-4 weeks without corticosteroid premedication. A median of 4 treatment cycles (range 1-10) was given to second line patients with a median cumulative dose of 240 mg/m² (range 60-600 mg/m²).

The overall response rate (intent to treat analysis, N=206) was 43%, including 10 CRs and 78 PRs. Response rates at individual sites ranged from 61% in liver, 56% in lymph nodes, 54% in "recurrence", 52% in breast, to 40% in lung. The overall response rate among the 174 patients previously treated with chemotherapy was 46%, and 47% among 127 anthracycline-pretreated patients.

Adverse reactions were graded according to Japanese Society for Cancer Therapy Guidelines. All but three patients had "normal" LFTs. There were two toxic deaths among second line patients (1.1%) and 3 patients discontinued due to toxicity (1.7%). Neutropenia occurred in 96% of patients, and was grade 4 in 76%. Thrombocytopenia was noted in 14% of patients, and was grade 4 in 2 patients. Febrile neutropenia was reported in 18 patients (10%). **Comment:** *For reference, the incidence of hematologic toxicities among the 282 second line breast cancer patients with "normal" LFTs treated initially with 100 mg/m² (Table 6, ODAC Briefing Document) were: neutropenia, 99%; neutropenia grade 4, 92%; thrombocytopenia, 14%; and febrile neutropenia, 16%.*

The most common non-hematologic toxicities were alopecia (87%), asthenia (66%), nausea and vomiting (62%), fever (43%), skin toxicity (31%), diarrhea (27%), stomatitis (19%), arthralgias/myalgias/pain (14%), peripheral neuropathy (13%), fluid retention (13%), and allergy/shock (4%). **Comment:** *With the exception of alopecia, asthenia, nausea and vomiting, the incidence of non-hematologic toxicities, is much lower in the Japan experience (compare to Table 9 of the ODAC Briefing Document). The spectrum of toxicities is similar, however, to that observed in the high dose studies conducted in North America and Europe.*

Fluid retention developed in 22 patients, with 12 moderate and no severe cases. There were no treatment discontinuations due to fluid retention. The median cumulative dose to the

onset of fluid retention was 240 mg/m². **Comment:** *Compared to the second line breast cancer patients in North American/European studies, patients entered on Japanese trials had a lower incidence of fluid retention at baseline (2% vs 17%) and no patient had severe fluid retention at baseline. Thus, patient selection may have contributed to the favorable outcome with respect to fluid retention in the Japanese trials.*

- **Sponsor's Conclusions**

The objective response rates in second line breast cancer patients in Japan were comparable to those observed in North American and European studies. However, the median duration of response in Japan (4 months) was less favorable than the 6.2 month duration of response noted in other trials.

The incidence of grade 4 neutropenia, febrile neutropenia, and toxic death reported with docetaxel 60 mg/m² was lower than that observed at 100 mg/m².

The major non-hematologic toxicities, especially, fluid retention, occurred with lower incidence and severity at 60 mg/m².

6. RPR's Clinical Development Plan for Docetaxel

RPR has provided a timetable for the completion of ongoing/planned phase III studies, phase II combination studies with other antineoplastic agents, as well as studies designed to address specific safety concerns (e.g., use of corticosteroid premedication regimens to reduce fluid retention, use of G-CSF to ameliorate myelosuppression, dose reduction in patients with liver impairment at baseline). Submission of study reports is expected in 1996 and 1997 (see Appendix).

7. Reviewer's Conclusions

This amendment to NDA # 20,449 has focused on several safety issues related to docetaxel therapy in advanced breast cancer and other solid tumors. Comparisons have been made between docetaxel and paclitaxel, regarding treatment-related deaths, hematologic toxicity and fluid retention. New data on the duration of fluid retention, evolution of performance status, and tolerance of docetaxel in patients with liver impairment have been submitted.

- **Myelosuppression**

1. The septic death rate for the entire phase II program was 1.4% (1327 patients) and 0.6% for the 800 patients with baseline SGOT/SGPT $\leq$ 1.5 x N (3/9/95 submission, Section 2.35). Among breast cancer patients the septic death rate was 1.1% for the overall group of 455 patients treated at the initial planned dose of 100 mg/m^2 over 1 hour, and 1.4% for the 282 second line patients with "normal" LFTs (ODAC Briefing Document, Section 4.1).

The septic death rate of paclitaxel was 1% for 812 breast and ovarian cancer patients treated with doses ranging from 135 to 300 mg/m^2 given as 3- or 24-hour infusions, with or without G-CSF. The septic death rate of paclitaxel was 0.2% among 471 breast cancer patients treated at either 135 or 175 mg/m^2 over 3 hours.

Direct comparison of paclitaxel results to that of the docetaxel experience is fraught with difficulty. It has been shown that the same dose of paclitaxel administered as a 24-hour infusion is more myelotoxic than as a 3-hour infusion. In the absence of a randomized comparative trial of the two agents, it is not certain what dose/schedule of paclitaxel is most equivalent to the proposed dose/schedule of docetaxel.

If one compares the 455 breast cancer patients treated with docetaxel to the 471 patients treated with paclitaxel, baseline characteristics appear similar. Performance status at entry was 0-1 in roughly 80%; 29% (133/455) of docetaxel patients had anthracycline-resistant disease vs 23% of paclitaxel patients). However, the septic death rate was 5- to 7-fold higher for docetaxel than paclitaxel.

The overall toxic death rate for paclitaxel is not reported in the package insert. Thus, a formal comparison of this parameter for the two agents is not possible.

2. The incidence of grade 4 neutropenia with docetaxel treatment was markedly higher than that reported for paclitaxel. The incidence of grade 4 neutropenia for the entire phase II program was 76% (1327 patients) and 83% for the 800 patients with baseline SGOT/SGPT $\leq$ 1.5 x N (grade 3 and 4). Among breast cancer patients the incidence of grade 4 neutropenia was 92% for the overall group of 455 patients treated at the initial planned dose of 100 mg/m^2 over 1 hour, and 92% for the 282 second line patients with "normal" LFTs. For paclitaxel, the incidence of grade 4 neutropenia was 28% for the 175 mg/m^2/3 hour arm vs. 19% for the

135 mg/m²/3 hour arm.

3. The definition of febrile neutropenia in docetaxel trials has evolved over time. Using the most restrictive definition (fever > 38°C with grade 4 neutropenia requiring antibiotics and/or hospitalization), the incidence of febrile neutropenia was 15% among 1327 patients overall and 17% among 800 patients with normal transaminases. For breast cancer, febrile neutropenia rate was 18% for the 455 patients overall, and 16% for the 282 second line patients with "normal" LFTs. In previous reports, febrile neutropenia included grade 3 or 4 neutropenic fever, with no stipulation of hospitalization or antibiotic use. Using this more inclusive definition, the incidence was 24% among 931 patients overall, and 33% for the 133 anthracycline-resistant breast cancer patients. In the NCI experience (six studies in solid tumors using various definitions, some inclusive and some not) the incidence of febrile neutropenia was 40% in 151 patients.

The docetaxel results contrast with those of paclitaxel therapy which was associated with a several-fold lower incidence of febrile neutropenia. For advanced breast cancer patients treated at 175 or 135 mg/m², the incidence of febrile neutropenia was only 2%.

4. Infection rates for the two agents appear comparable. For docetaxel, infection rates were 17% among 1327 patients overall, 22% among the 455 breast cancer patients, and 28% among the 133 anthracycline-resistant breast cancer patients. Infection rates were 20% for the 800 patients with normal transaminases, and 23% for the 282 breast cancer patients with "normal" LFTs. In the NCI experience, the infection rate was only 5%, however. For paclitaxel, infection rates among breast cancer patients were 23% for the 175 mg/m² dose and 18% for the 135 mg/m² dose.

With regard to the severity of infections, recall that for the 133 anthracycline-resistant breast cancer patients in pivotal trials, 80% of the infections observed were associated with grade 3 or 4 neutropenia. These findings may be relevant to the septic death rate associated with use of this agent.

Thus, the sponsor's contention that the degree of myelosuppression associated with docetaxel treatment is comparable to that observed for paclitaxel cannot be validated by available data. A similar conclusion was also reached by Dr. Paul Bunn and other ODAC members at the December 1994 meeting. Additional clinical experience with docetaxel is warranted to explore the following possible alternatives to ameliorate docetaxel-induced myelosuppression:

1. In the event of febrile neutropenia and/or prolonged neutropenia, initiation of G-CSF therapy in the next cycle while maintaining docetaxel at full dose might be considered. If neutropenia-associated events still occur with G-CSF support, then dose reduction in future cycles will be required.

The sponsor has indicated a commitment to perform a phase II study in 30 patients to evaluate

the benefit of G-CSF, with a study report expected at the end of 1996. The study protocol has not yet been submitted, nor have the details of this trial been discussed with the Agency.

2. Treatment with lower doses of docetaxel should be further investigated. Recall that in Japan, docetaxel administered at 60 mg/m² every 3 weeks was fairly myelosuppressive, producing an 76% incidence of grade 4 neutropenia and a 10% incidence of febrile neutropenia in 174 evaluable second line breast cancer patients. This regimen was remarkably active, producing an overall response rate of 43% (5% CRs) among 206 patients with metastatic breast cancer. Direct comparison of a low and high dose of docetaxel in a randomized controlled setting would be preferable to individual studies evaluating different doses.

The sponsor has indicated a commitment to perform a randomized study in 200 second line breast cancer patients evaluating two different docetaxel doses (100 vs 75 mg/m²); response rate, time to progression, quality of life, and safety will be the primary endpoints. The study report would be available at the end of 1997. The study protocol has not yet been submitted, nor have the details of this trial been discussed.

- **Fluid Retention**

In the most recent analysis, the overall incidence of fluid retention was 52% (severe reactions in 9.4%) among 1070 patients, regardless of premedication. Previously, the overall incidence was reported to be 47% among 833 patients (Updated ISS). Of 389 patients with fluid retention, 66% were symptomatic (i.e., moderate or severe cases).

There are two cohorts of patients that did not receive premedication for fluid retention. In the original NDA, 315 patients on phase II trials were found to have a 40% incidence of fluid retention; of 126 patients with toxicity, 63% were symptomatic. In a subset of 118 breast and NSCLC patients, there was a 61% incidence of fluid retention; of 72 patients with toxicity, 67% were symptomatic (Updated ISS). Twenty-five patients withdrew treatment. Reasons for the relatively poor outcomes in this subset of patients were not adequately explored. Recall that this group has served as the comparator group to patients receiving corticosteroids.

Use of corticosteroids has not lowered the overall incidence of fluid retention. For example, the analysis of 104 breast cancer patients premedicated with dexamethasone noted a 49% incidence of fluid retention; however, of 51 patients with toxicity, only 41% were symptomatic. Thus, there is a suggestion that a favorable shift may have occurred, with a modest increase in the proportion of patients who are asymptomatic. The reasons for this shift are unknown, but may be explained by the low median cumulative dose that was given to this group of patients. Although only two patients discontinued treatment due to fluid retention, no clinical information is provided on the outcomes of the remaining 19 symptomatic patients who did not discontinue treatment. How did supportive measures for these patients differ from that given to the comparator group of 118 patients who did not receive premedication? In addition,

no information is provided on the risks of, or compliance with the dexamethasone regimen (16 mg/day for 5 days, every 3 weeks).

Perhaps the strongest evidence presented in support of a beneficial steroid effect is found in the EORTC TAX265 trial. This was a randomized trial in 83 breast cancer patients who received either 3 days of steroids + antihistamines or 3 days of antihistamines only. Recall that the dose and schedule used differs from that which is proposed, and the d1, d8 schedule was associated with the highest frequency of fluid retention in phase I trials. Patients on the antihistamine arm fared worse as would have been predicted from data presented in the original NDA. However, for patients who received steroids in addition to antihistamines the median dose to onset of edema and pleural effusion was significantly higher, and the rate of treatment discontinuation far lower. There is no reason to believe that patients on the two arms were supported differently. Again, no detailed information is provided in this regard.

Taking the findings of the TAX265 trial together with those reported in the original NDA, it is apparent that antihistamines may be harmful and steroids may be beneficial with respect to fluid retention. Yet the question still remains: should steroids be recommended for all patients receiving docetaxel? The answer to this question may be forthcoming in two years' time. The sponsor has committed to perform a phase III trial comparing 5 days of corticosteroids to other regimens in 240 patients. Rate of treatment discontinuation, cumulative dose to onset, incidence and severity of fluid retention will be primary endpoints. The study protocol has not yet been submitted, nor have the details of this trial been discussed.

Another potential benefit of corticosteroid premedication has been the postponement of the onset of symptomatic fluid retention. For example, the median cumulative docetaxel dose to onset of moderate or severe fluid retention in breast cancer patients was 490 mg/m² without premedication (60 patients), but 746 mg/m² with the 5-day dexamethasone regimen (32 patients). Again, since the 104 breast cancer patients given the 5-day regimen have received a low median cumulative dose of docetaxel (298 mg/m²), the number of patients actually dosed over 600-700 mg/m² was probably very small.

This updated analysis provided new data regarding the duration of fluid retention after docetaxel withdrawal, not available at the time of the ODAC Meeting. In this regard, there were two extremely disturbing findings. First, fluid retention lasted several weeks to months even after docetaxel was discontinued, regardless of symptomatic treatment. Given the expected longevity of patients with metastatic breast cancer receiving docetaxel as second line therapy, the complications of fluid retention, for some, would persist for the remainder of their lives (compare an overall median survival of 10.6 months, with an 8.5-month duration of fluid retention in the TAX237 experience). We do not know as yet, what positive contribution corticosteroids will make on the duration of symptomatic fluid retention. Second, the time to recovery from fluid retention was the same regardless of the cumulative dose received. Thus, a patient who must discontinue treatment for fluid retention after 2 cycles can expect to face the same consequences in terms of duration of fluid retention as a patient who discontinues

after 12 cycles, without having had the benefit of an antitumor response.

Finally, it should be pointed out that paclitaxel therapy has not been associated with fluid retention of a magnitude approaching that of docetaxel.

In conclusion, given the overall incidence, severity, and protracted nature of the fluid retention observed with docetaxel dosed at 100 mg/m^2 over 1 hour, it is imperative:

a) that a well-tolerated premedication regimen demonstrate a consistent reduction in the incidence of symptomatic (moderate or severe) fluid retention, and

b) that safe and effective supportive treatment be devised for patients who develop fluid retention, and

c) that approaches taken in (a) and (b) reduce the rate of treatment discontinuation due to docetaxel-related fluid retention, and

d) that approaches taken in (a) and (b) reduce the duration of symptomatic fluid retention,

so that patients responding to docetaxel treatment may continue to derive net clinical benefit.

Additional concerns also bear consideration. These are:

1. With regard to eligibility criteria of patients entered on ongoing and proposed trials, exclusion of patients with baseline signs and symptoms of fluid retention, namely peripheral or generalized edema, pleural or pericardial effusions, or ascites is warranted.

2. Use of antihistamines as premedication for fluid retention should be avoided.

3. If future trials of docetaxel are carried out with lower doses, the issues of fluid retention and appropriate premedication may become far less relevant. Recalling the Japanese clinical experience in 174 second line breast cancer patients treated at 60 mg/m^2, the overall incidence of fluid retention was only 13%, with no severe cases and no treatment discontinuations.

4. The discussion over the risks of fluid retention has evolved over time, with the primary focus now being the number of patients withdrawing treatment for this toxicity. This has apparently become a surrogate marker for the safety of docetaxel treatment. This being the case, the sponsor must demonstrate convincingly that undue harm does not befall those symptomatic patients who remain on treatment.

- **Docetaxel Tolerance in Patients with Elevated Hepatic Enzymes**

In January 1995, the sponsor submitted a new protocol (TAX008) evaluating docetaxel dosing and pharmacokinetics in advanced cancer patients with elevated serum bilirubin levels at entry. This protocol referenced an abstract (P. Francis.et al., Proc ASCO, 1994) which reported reduced docetaxel clearance and significantly higher rates of admission for nadir fever, leukopenia grade 4, thrombocytopenia, mucositis, and skin rash for 19 patients treated with docetaxel 100 mg/m² who had elevated SGOT and AP and had liver metastases, as compared to patients with liver metastases and normal LFTs or to patients without liver metastases. These findings and the submitted protocol served to draw attention to the potential hazards of docetaxel dosing in patients with hepatic impairment.

In March 1995, the sponsor provided retrospective clinical data addressing the risks of treatment with docetaxel at 100 mg/m² in patients with baseline SGOT or SGPT > 1.5 times normal. Compared to patients with normal baseline hepatic enzymes, this group had an increased incidence of grade 3-4 leukopenia, grade 3-4 thrombocytopenia, and grade 3-4 anemia, febrile neutropenia with or without infection, stomatitis, dose reductions, treatment withdrawals and toxic deaths.

Overall, the patients with elevated enzymes accounted for 11% of the population analyzed, but 38% of the toxic deaths. Focusing on the first treatment cycle only, these patients accounted for one-quarter of patients with grade 3 or 4 febrile neutropenia and grade 3 or 4 infection, and one-half of toxic deaths. Analysis of other cycles individually was not provided. With regard to non-hematologic toxicities, patients with elevated baseline hepatic enzymes accounted for one-quarter of patients developing grade 3 or 4 stomatitis during the first cycle and overall. Elevation of hepatic enzymes had no impact on the overall incidence of fluid retention. Consistent with these clinical findings, PK data have demonstrated that liver dysfunction can affect the clearance of both docetaxel and paclitaxel.

At that time, the sponsor proposed that use of docetaxel at 100 mg/m² be limited to patients with hepatic transaminases $\leq$ 1.5 times normal, and that the starting dose of docetaxel be reduced by 25% (to 75 mg/m²) in patients with elevated baseline transaminases.

In May and June, several additional retrospective analyses have been submitted by RPR, some at the request of FDA. Notable findings were:

The subset of patients with elevation of transaminases and alkaline phosphatase at baseline (37 patients, or roughly 4% of the overall database) experienced a significantly higher incidence of febrile neutropenia grade 4, infection, skin rash, stomatitis, and acute hypersensitivity reaction at first cycle, dose reductions at second cycle, and adverse events and toxic deaths after the first cycle. All of these patients had liver metastases, and seven patients were included who also had bilirubin elevations. Eight of these patients were second line breast cancer patients

who were evaluable for toxicity after a dose reduction of 25% or more in subsequent cycles. These patients continued to experience substantial hematologic and non-hematologic toxicity (incidence of neutropenia, 100%; neutropenia grade 4, 75%; thrombocytopenia, 38%; febrile neutropenia and hospitalization, 13%; infection, 25%; nausea and vomiting, 50%; stomatitis, 50%; asthenia, 75%; skin toxicity, 88%; and fluid retention, 88%).

Isolated alkaline phosphatase elevations at any time during docetaxel therapy predict for an increased incidence of grade 4 neutropenia (96%) and thrombocytopenia (26%).

Isolated bilirubin elevations at any time predict for an increased incidence of grade 4 neutropenia (100%), thrombocytopenia (48%), and febrile neutropenia (28%).

Isolated SGOT/SGPT elevations at any time predict for an increased incidence of thrombocytopenia (23%), febrile neutropenia (20%), and infection (31%).

The presence of liver metastases, without abnormal transaminases, was not predictive of increased adverse events.

There is no clinical experience treating second line breast cancer patients with docetaxel at an initial dose of 75 mg/m^2; only 3 second line patients with "elevated" LFTs were treated with 60 mg/m^2 in the Japanese experience.

The sponsor has proposed treatment guidelines in patients with hepatic impairment in ongoing trials and in the proposed product labeling (see Section 4.2) that utilize treatment cut-offs that are fairly high (e.g., values > 6 times the ULN for alkaline phosphatase and > 3.5 x ULN for SGOT and/or SGPT). No clinical data to support the choice of cut-offs has been provided.

These retrospective data raise the following, as yet unanswered, questions:

1) Why are seemingly minimal LFT abnormalities associated with such poor treatment outcomes?

2) Does the presence of liver metastases correlate with worse outcomes for patients with LFT abnormalities?

3) What combination of LFT abnormalities defines the "at risk" population?

Patients with "elevated" LFTs defined as the combination of SGOT/SGPT and alkaline phosphatase abnormalities at baseline are not at substantially greater risk for adverse events compared to patients with SGOT/SGPT > 1.5 x ULN as originally defined in the sponsor's March 9, 1995 document (see Section 2.35). Notable exceptions in this regard are the incidences for thrombocytopenia, infections, vomiting, and acute HSRs (see tables below). Thus, it would appear that the sponsor's new definition of hepatic impairment is too narrow.

conservative approach regarding the definition of patients with hepatic impairment seems warranted. Thus, a more inclusive definition, as was originally proposed, seems prudent. As new data from ongoing trials involving patients with liver dysfunction becomes available, perhaps a more liberal definition may be applicable.

Hematologic Abnormalities in Patients with Hepatic Impairment

Adverse Event	"Elevated" LFTs (N=42)[1]	Elevated LFTs (N=95)[2]
Neutropenia	86%	97%
-grade 3/4	-	95%
-grade 4	79%	-
Thrombocytopenia	29%	16%
Febrile Neutropenia, grade 4	24%	32%
Infections	33%	26%
-severe	17%	8%

[1] ODAC Briefing Document, Tables 6 and 8 [2] March 9, 1995 Document, Appendix V

Non-Hematologic Abnormalities in Patients with Hepatic Impairment

Adverse Event	"Elevated" LFTs (N=42)[1]	Elevated LFTs (N=95)[2]
Stomatitis	43%	52%
Skin Toxicity	62%	68%
Asthenia	52%	67%
Fluid Retention	38%	53%
Neurosensory Toxicity	31%	52%
Nausea	41%	38%
Vomiting	29%	25%
Diarrhea	36%	43%
Myalgia	21%	23%
Arthralgia	10%	11%
Acute HSRs	38%	25%

[1] ODAC Briefing Document, Table 9 [2] March 9, 1995 Document, Appendix V

4) How large is the "at risk" population? at baseline? during treatment?

For second line breast cancer patients, the proportion with the following isolated LFT abnormalities is estimated in the table below. The proportion of breast cancer patients with baseline elevations is taken to be the same as that described in the overall database of 895 patients (sponsor's original analysis, 3/9/95). Note that among anthracycline-resistant patients, the incidence of baseline SGOT/SGPT abnormalities was 35%. The proportion of patients with specific combinations of abnormalities cannot be estimated from available data.

Isolated Abnormality	Elevated at Baseline	Elevated at Any Time on Tx
SGOT/SGPT	11%	25%
Alkaline Phosphatase	2.5%	8%
Bilirubin	0.8%	9%

Thus, dosing decisions will be required for patients with baseline abnormalities, and for those developing abnormalities on docetaxel treatment. For some patients, decisions may be required at several timepoints.

5) Is a docetaxel dose of 75 or 60 mg/m² reasonable for patients with baseline hepatic impairment? for patients who develop hepatic impairment on treatment?

The following analysis was undertaken to determine the impact of elevated baseline hepatic enzymes and of dose reductions (25% or more) on anthracycline-resistant breast cancer patients receiving docetaxel at the initial dose of 100 mg/m². Data was derived from tables 14, 15, and 21 of the Data Listings for 78 patients on the TAX233 and TAX267 trials, two of the pivotal trials in the original NDA.

The tables reviewed did not specify reasons for dose reduction, but the individual study reports indicated that these were due to a combination of hematologic and non-hematologic toxicities. Dose reductions occurred in just over half the patients on these two trials. Of 44 patients that were dose-reduced, 29 patients had a 25% reduction, and 15 patients had >25% reduction. Dose-reduced patients received more treatment cycles compared to the total patient group. Despite the dose reductions, response rates did not appear to be compromised.

The incidence of grade 4 neutropenia was nearly universal among patients in these trials, and occurred in 73% and 87% of evaluable cycles in patients with normal and elevated LFTs, respectively (defined as cycles with at least one WBC report on days 6-10 of each cycle). It was not possible to determine the incidence of febrile neutropenia grade 4 from the data listings. The incidence of infections and stomatitis was substantially higher for all patients on these trials and for dose-reduced patients. In order to fully interpret this finding, it would be

necessary to know when the dose reductions were carried out in relation to the onset of infections and stomatitis in these patients.

Outcomes in Anthracycline-Resistant Breast Cancer Patients
Effect of Abnormal SGOT/SGPT at Baseline

Feature/Endpoint	Patient Subset w/ Elevated LFTs[a] N=95	Patient Subset w/ Normal LFTs[a] N=800	TAX233 + TAX267[b] Baseline LFTs Elevated N=27	Normal N=51
Pts w/ Liver Mets	83%	29%	56%	33%
Pts w/ Dose Reductions	-	-	56%	37%
Response Rate				
-all patients	-	-	41%	55%
-dose-reduced pts	-	-	47%	72%
Median #Cycles				
-all patients	4 (1-19)	4 (1-25)	5 (1-12)	5 (1-15)
-dose-reduced pts	-	-	9 (4-12)	7 (3-15)
Pts w/ Neutropenia				
-grade 3+4, all pts	95%	92%	-	-
-grade 4, all patients	-	-	96%	96%
-dose-reduced pts	-	-	100%	97%
Pts w/ Infections	26%	20%	56%	47%
-dose-reduced pts	-	-	67%	48%
Pts w/ Stomatitis	16%	7%	81%	65%
-dose-reduced pts	-	-	93%	76%
Deaths				
-Toxic	5 (5.3%)	8 (1.0%)	0	0
-Septic	0	5 (0.6%)	1 (3.7%)	0

[a] From Updated Safety Analysis, Appendix V, 3/9/95
[b] Compiled from Tables 14, 15, 21 of Data Listings in TAX233 and TAX267 Study Reports, 7/27/94

6) Should treatment be temporarily withheld when laboratory values have reached a certain level, then resumed when they have declined?

7) Which patients with hepatic impairment should not receive docetaxel at all?

- **Evolution of Performance Status on Docetaxel Treatment**

The sponsor provided information on the evolution of performance status for the original 316 advanced breast cancer patients treated with docetaxel as first or second line therapy (Table 4.01, Appendix I). In addition, information on treatment response and reasons for withdrawal from treatment was provided. This presentation (see Section 2.34 for details) gets to the heart of the issue of net clinical benefit by allowing risks and benefits to be compared at selected points in time. Note that this kind of presentation has not been provided for the group of second-line breast cancer patients on which the proposed indication for docetaxel rests.

Of great concern are the findings among 160 responders between cycles 4 and 6 of docetaxel treatment: there is a dramatic rise in the number of patients who were withdrawn for toxicity, and the number of patients with improved performance status at cycle 6 is balanced by an equal number of patients who have progressed. Recall that the time to first response to docetaxel in pivotal trials for advanced breast cancer was 13-15 weeks, or roughly between cycles 4-5, assuming no treatment delays. Thus, if patient withdrawals due to symptomatic fluid retention could be postponed until cycle 7-8 or even eliminated with the use of steroid premedication, then the period of time during which responders experience tumor regression, freedom from fluid retention, and stabilization or improvement of performance status would be greatly lengthened.

- **Comparison of Docetaxel to Paclitaxel**

Hematologic Toxicity:

The table below summarizes the major hematologic toxicities observed with docetaxel and paclitaxel. The most recent available data were included for the total evaluable patient population (1327 patients) and for the evaluable breast cancer patient population (455 patients) treated at the initial planned docetaxel dose of 100 mg/m^2. The information on paclitaxel is derived from the package insert. The following should be noted:

1. Breast cancer patients treated with docetaxel had higher rates of grade 4 neutropenia and infections, but similar rates of febrile neutropenia grade 4 and septic death, as compared to the total patient population treated.

2. Exclusion of patients with abnormal transaminases at baseline does not lower the incidence of neutropenia grade 3 or 4 neutropenia, febrile neutropenia grade 4, infections, thrombocytopenia, or anemia.

3. The incidence of toxic deaths for the 800 patients with normal baseline hepatic enzymes is half that noted for the 1327 patients in the overall population (1% vs 2% for toxic deaths), and somewhat lower than that for the 895 patient group from an earlier analysis (1% vs 1.5%).

4. The incidence of septic deaths for the 800 patients with normal baseline hepatic enzymes is no different from that of the 895 patient group from an earlier analysis (0.6% for both), but less than half that noted for the 1327 patients (0.6% vs 1.4%).

5. Patients with breast and ovarian cancer who received paclitaxel had markedly lower rates of grade 4 neutropenia, febrile neutropenia, and anemia as compared to any group receiving docetaxel. However, overall infection rates were comparable for the two agents.

6. The septic death rate for the 800 docetaxel-treated patients with normal baseline hepatic enzymes was comparable to that of the 812 paclitaxel-treated patients (0.6% vs 1%). However, the septic death rate on docetaxel for 282 second line breast cancer patients with "normal" baseline hepatic enzymes (1.4%) was 7-fold higher than the septic death rate for 471 second line breast cancer patients on paclitaxel (0.2%).

Hematologic Toxicity by Patient:
Comparison of Taxotere to Taxol

Endpoint	Taxotere[a]		Taxotere[a]: Baseline LFTs			Taxol: Phase 3 Breast		Taxol[b]
	Total N=1327	Breast N=455	All N=895	Elevated N=95	Normal N=800	175/3h N=229	135/3h N=229	Total N=812
Neutropenia	97%[c]	99%[d]	97%	97%	97%	90%	81%	90%
Neutropenia -grade 3/4	92%[c]	97%[d]	92%	95%	92%	-	-	-
-grade 4	76%[c]	92%[d]	-	-	-	28%	19%	52%
Febrile Neutropenia grade 4	15%	18%	19%	32%	17%	2%	2%	-
Infections	17%	22%	20%	26%	20%	23%	15%	30%
Thrombo-cytopenia	8%[c]	12%[d]	8%	16%	7%	11%	7%	20%
-grade 3/4	4%[c]		3%	8%	2%	3%	2%	7%
Anemia	90%[c]	-	90%	93%	90%	55%	47%	78%
-grade 3/4	9%[c]	-	9%	20%	8%	4%	2%	16%
Deaths								
-Toxic	26 (2.0%)	9 (2.0%)	13 (1.5%)	5 (5.3%)	8 (1.0%)	-	-	-
-Septic	19 (1.4%)	5 (1.1%)	5 (0.6%)	0	5 (0.6%)	0	1 (0.4%)	1%

[a] Taxotere at the initial planned dose of 100 mg/m²
[b] Taxol dosed at 135-300 mg/m², over 3 or 24 hr; G-CSF used in 4 studies, package insert
[c] N=Subset of 931 patients at the initial planned dose of 100 mg/m², Updated ISS, 11/7/94
[d] N=Subset of 228 breast cancer patients at the initial planned dose of 100 mg/m², Original ISS, 7/27/94

Non-Hematologic Toxicity:

The table below summarizes the major non-hematologic toxicities observed with docetaxel and paclitaxel. The most recent available data were included for the total evaluable patient population and for the evaluable breast cancer patient population treated at the initial planned docetaxel dose of 100 mg/m². The information on paclitaxel is derived from the package insert. The following should be noted:

1. Breast cancer patients treated with docetaxel had somewhat higher rates of mucositis, fluid retention, skin and neurosensory toxicity than the total evaluable patient population.

2. **Exclusion of patients with elevated hepatic enzymes at baseline does not lower the incidence of any of the major non-hematologic parameters.** Thus, the 800 patients with normal baseline hepatic enzymes have similar frequencies of non-hematologic toxicities as the total evaluable population (931 patients).

3. Patients with breast and ovarian cancer who received paclitaxel had:

- fluid retention with a frequency less than half of that reported for docetaxel; this toxicity consisted primarily of localized edema only; no patients discontinued paclitaxel because of fluid retention;
- lower rates of mucositis, and of elevations of hepatic enzymes while on treatment;
- skin toxicity and asthenia rarely reported, if at all; and
- comparable rates of acute hypersensitivity reactions, neurosensory toxicity, and gastrointestinal toxicity (nausea, vomiting, diarrhea, data not shown) as docetaxel.

Non-Hematologic Toxicity by Patient: Comparison of Taxotere to Taxol

Endpoint	Taxotere[a] Total N=931	Taxotere[a] Breast[d] N=228	Taxotere[a]: Baseline LFTs All N=895	Elevated N=95	Normal N=800	Taxol: Phase 3 Breast 175/3h N=229	135/3h N=229	Taxol[b] Total N=812
Mucositis	41%	54%	41%	52%	40%	23%	17%	31%
-grade 3/4	5%	11%	5%	13%	4%	3%	<1%	
Fluid Retention	52%[c]	64%	51%	53%	51%	-	-	21%
-severe	9%[c]	16%	10%	12%	10%	-	-	1%
Skin Tox	63%	72%	64%	68%	63%	-	-	rare
Neurosens	51%	61%	51%	52%	51%	70%	46%	60%
-severe	4%	5%	4%	5%	3%	7%	3%	3%
Asthenia	69%	72%	69%	67%	69%	-	-	none
HSRs	30%	28%	29%	25%	29%	36%	31%	41%
-severe	7%	5%	7%	7%	6%	0	<1%	2%
Inc LFTs:			-	-	-	-	-	
-Bilirubin	11%	11%						7%
-Alk Phos	42%	33%						22%
-SGOT	33%	36%						19%

[a] Taxotere at the initial planned dose of 100 mg/m²

[b] Taxol dosed at 135-300 mg/m², over 3 or 24 hr; G-CSF used in 4 studies, package insert

[c] N=1070 evaluable patients at the initial planned dose of 100 mg/m², Updated Specific Safety Analysis, 3/9/95

[d] N=228 breast cancer patients at the initial planned dose of 100 mg/m², Original ISS, 7/27/94

- **Summation, September 8, 1995**

Since the ODAC Meeting in December 1994, RPR has submitted supplemental safety data to its pending NDA # 20,449 on 1/18/95, 3/9/95, 5/23/95, 6/8/95, and most recently on 7/21/95. In addition, there have been twelve patient deaths reported to the RPR-sponsored IND and two deaths to the NCI-sponsored IND (no deaths were reported to the Agency between 7/22/94 and 1/8/95). Taken together, this data has heightened existing concerns regarding docetaxel-induced myelosuppression, treatment-related deaths, worsened performance status of responders, and the poor tolerability of fluid retention lasting several weeks to months.

Preliminary reports in 104 breast cancer patients premedicated with the proposed 5-day corticosteroid regimen suggest that these patients rarely discontinue treatment due to fluid retention. Note that while the overall incidence of fluid retention is not lessened with corticosteroid use, the incidence of symptomatic reactions may be lowered (20% vs 50% without premedication). These findings should be viewed with caution, given that the median cumulative docetaxel dose these premedicated patients have received is well below the median cumulative dose to onset of moderate/severe fluid retention (298 vs 490 mg/m^2 without premedication). Since many of these patients were still undergoing treatment at the time of these reports, additional follow-up on these patients will be of great interest.

No information has been provided regarding the tolerability of symptomatic fluid retention in patients who do not discontinue treatment. Nor is there any evidence as yet suggesting that corticosteroids shorten the duration of symptomatic fluid retention in patients with toxicity.

New concerns have now been raised regarding the severe myelosuppression, mucositis, and deaths reported among patients with minimally elevated serum bilirubin, SGOT, SGPT and alkaline phosphatase, particularly in the first cycle of docetaxel treatment. The contribution of underlying liver metastases to the toxicities observed in these patients remains unclear. Note, however, that exclusion of patients with liver dysfunction from the overall patient population does not alter the morbidity observed with docetaxel treatment in terms of the incidence of hematologic or non-hematologic toxicities. Toxic deaths and possibly, septic deaths may be reduced if only patients with normal liver function are considered. A similar trend may be apparent for second line breast cancer patients as well, although it is difficult to document since the patient numbers are smaller (i.e., only 15 of 301 had abnormal LFTs in the sponsor's latest analysis).

At present, the "at risk" patient population is not been well defined. For example, if the "at risk" population is conservatively defined as patients with any elevation of bilirubin and SGOT/SGPT > 1.5 x N, then 11% of second line breast cancer patients, or possibly, 35% of anthracycline-resistant patients could be defined as "at risk". The sponsor's definition (patients with elevation of alkaline phosphatase > 2.5 x ULN associated with SGOT and/or SGPT > 1.5 x ULN) would include only 4% of second line breast cancer patients. However, this

classification would exclude patients with isolated transaminase elevations, the very patients shown to have poor outcomes in the sponsor's initial report to the Agency.

For patients defined as "at risk" at baseline, possible options would be treatment with a lower starting dose as has been proposed, or complete exclusion. Current estimates of what the most appropriate dose should be are PK-derived and have not been confirmed clinically in second line breast cancer patients.

Moreover, there is insufficient retrospective clinical data to recommend appropriate, safe management of patients who develop one or more liver function abnormalities during docetaxel treatment. In second line breast cancer patients, elevations of SGOT/SGPT occurred in 25% of patients, elevations of alkaline phosphatase in 8% and of bilirubin in 9% during treatment. The sponsor's recommendation for 25-30% dose reductions is again, primarily PK-derived. There is clinical data for only 8 second line breast cancer patients with "elevated" LFTs who were dose-reduced from 100 to 75 mg/m^2. Their safety profile in later treatment cycles was extremely poor. The proposal to withhold treatment until elevated values fall below a certain point may not be practical if resolution is slow. Additional dose-finding studies must be performed to evaluate these issues in hepatically-impaired patients.

For second line breast cancer patients without liver impairment, the Japanese clinical experience with docetaxel doses of 60 mg/m^2 suggests that toxicity, particularly non-hematological toxicity, may be ameliorated without compromising tumor response rates. Given that one-third to one-half of second line breast cancer patients dosed at 100 mg/m^2 may require dose reductions for hematologic and non-hematologic toxicities, the choice of 100 mg/m^2 as the recommended dose in this patient population should be re-examined.

In conclusion, the safety data submitted to NDA # 20,449 do not support the conclusion that docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks has an acceptable *therapeutic index for the second line treatment of patients with locally advanced or metastatic* breast cancer. Full approval of docetaxel for the proposed indication cannot be recommended at this time.

Tumor response rate may be a valid surrogate endpoint for clinical benefit and serve as the basis for accelerated approval of minimally toxic drugs, such as hormonal agents. In the case of docetaxel, however, tumor response rate is not a surrogate for clinical benefit because of the overriding toxicity associated with its use in the target population.

8. Pre-ODAC Meeting with Sponsor, October 11, 1995

The sponsor requested a meeting with the Taxotere review team in preparation for the upcoming ODAC Meeting on October 17, 1995. At a meeting held on October 11, 1995, the sponsor indicated that it would like to narrow the proposed indication for Taxotere as treatment for "patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy". It was the sponsor's impression that a favorable risk:benefit argument for this patient population could be made, since treatment options were otherwise limited. A review of the literature showed that response rates for paclitaxel in anthracycline-resistant patients ranged from 6-50%, although the definitions of anthracycline-resistance in different studies varied.

The sponsor then presented selected slides in draft form that would address the safety profile in anthracycline-resistant patients according to baseline liver function, and evolution of performance status in responders and non-responders.

The sponsor was told that these analyses could be presented to ODAC on the assumption that they were accurate, and FDA would review these in depth after they were formally submitted to the NDA.

The sponsor also voiced a strong commitment to phase 4 clinical studies, post-marketing surveillance, and physician education.

9. ODAC Meeting, Octob. 17, 1995

Question 1. Are the three pivotal phase 2 trials evaluating docetaxel as therapy for anthracycline-resistant breast cancer adequate and well-controlled trials?

After Dr. Temple clarified the meaning of adequate and well-controlled trials (in the absence of phase 3 data), the vote taken was yes 7, no 0.

Question 2. Are the hematologic toxicities reported in anthracycline-resistant breast cancer patients acceptable?

Dr. Ingle, the primary reviewer on the committee for this application, stated that the hematologic toxicity was "substantial, but acceptable" if patients with liver dysfunction (defined as SGOT/SGOT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN) are excluded from treatment. The sponsor verbally concurred with the recommendation to exclude patients with liver dysfunction defined in this manner. Dr. Bunn, however, did not agree that the hematologic profile was acceptable. The vote was yes 6, no 1 (Dr. Bunn).

Question 3. The applicant has concluded that fluid retention has been ameliorated by

corticosteroid premedication and is no longer a major impediment to docetaxel treatment. Do you agree?

The committee stated that the data regarding the effects of corticosteroid premedication was "preliminary", but that the data indicated that fluid retention had been ameliorated (meaning reduced) by the premedication regimen. It was stressed that more studies were needed to address this issue. The vote was yes 7, no 0.

Question 4. From a safety standpoint, is the recommended starting dose of 100 mg/m² every three weeks justified as therapy in anthracycline-resistant breast cancer patients?

The issue of dose was considered by several members of the committee. The sponsor stated that 75 mg/m² might not be as efficacious as 100 mg/m² (in first line therapy) however, the confidence intervals for objective response rates in these two groups were overlapping. The data from Japan on 60 mg/m² apparently have not been confirmed by the sponsor, although they were presented in summary form in the original NDA and re-analyzed (by baseline liver function) in the July 1995 amendment. Thus, the conclusion reached by Dr. Gelber and others was to base the answer to this question on the 100 mg/m² data presented.

The committee stressed that more clinical studies at lower doses were needed. Should docetaxel be approved, the labeling would describe the safety profile of 100 mg/m² initially, and could be amended in the future as information on the safety and efficacy of lower doses in the target patient population could be verified and confirmed. The vote was yes 6, no 1 (Dr. Bunn).

Question 5. Is there agreement that elevations of hepatic enzymes (bilirubin, SGOT, SGPT, AP, or combinations thereof) either at baseline or during docetaxel treatment constitutes a significant risk in patients receiving docetaxel?

Based on available data, the vote was yes 6, no 0, abstaining 1.

If yes, how should such patients be characterized and managed? Is there sufficient evidence to recommend a dose that is safe in patients with liver dysfunction? Which patients should be excluded from treatment?

The committee recommended that patients with liver dysfunction defined as SGOT or SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN should be excluded from treatment.

Question 6. Given the 41% response rate, 2% CR rate, 5.9-month response duration, and constellation of severe hematologic and non-hematologic toxicities, is docetaxel approvable for the treatment of patients who are anthracycline-resistant defined as "disease progression during treatment of advanced disease or recurrence during adjuvant therapy"?

The vote for approvability for the indication in anthracycline-resistant breast cancer was yes 6, no 0, abstaining 1 (Dr. Bunn).

10. Reviewer's Conclusions Post-ODAC, October 20, 1995

- **Safety Concerns**

1. Exclusion of patients with combined transaminase and alkaline phosphatase abnormalities does not appreciably alter the safety profile of docetaxel in the remaining patients in the various populations presented.

2. Patients with isolated transaminase elevations as presented in the sponsor's March 1995 analysis were also at risk for the development of febrile neutropenia grade 3/4, infections grade 3/4, mucositis grade 3/4, and had a toxic death rate of 5% (all non-septic deaths). The toxic death rate for 800 patients with normal liver function in this analysis was 1%. Thus, patients with isolated transaminase elevations may require a dose reduction (this was also the sponsor's conclusion at the time).

3. Patients with elevation of bilirubin are also at increased risk for the development of grade 4 neutropenia, febrile neutropenia, thrombocytopenia, severe stomatitis, and toxic death.

4. Severe fluid retention, characterized as pronounced and not well-tolerated edema, generalized anasarca, effusion requiring urgent drainage, dyspnea at rest, tamponade, or pronounced abdominal distention (due to ascites), still occurred in 5% of patients receiving docetaxel at 100 mg/m^2, despite use of a 5-day dexamethasone premedication regimen. No severe cases were noted among 174 second line breast cancer patients treated with docetaxel 60 mg/m^2 without premedication in Japan. At the ODAC Meeting, it was learned that the Japanese data submitted to the NDA and re-analyzed in the NDA amendment (July 1995) had not yet been verified by the sponsor, although plans were underway to authenticate this information. If verified, this data should be submitted to the Agency for review.

5. The duration of fluid retention is protracted in the absence of premedication; its duration on the 5-day dexamethasone premedication regimen is unknown at this time.

6. It is imperative that prospective studies to determine optimal dose-finding, and to identify patients at risk for the development of increased toxicity are conducted.

- **Efficacy Results**

1. Verification of anthracycline-resistance for the pivotal studies TAX233, TAX267, and TAX286 was carried out using the sponsor's Table 1 of the data listings from each study report. Of the 134 patients enrolled on these trials, the sponsor could not document disease progression on prior anthracycline-based therapy in 7 patients, and 16 patients had received prior mitoxantrone, rather than prior anthracycline. Thus, there were, in fact, 106

anthracycline-resistant patients. The overall response rate (CR + PR) in this group was 40% (42/106). Response rates on docetaxel according to whether patients had disease responsive or unresponsive to prior anthracycline are shown below. There was no statistical evidence that response rates to docetaxel differed among patients who were previously responsive or unresponsive to anthracycline. (This conclusion is analogous to that published for paclitaxel by Seidman et al. and Wilson et al. [and personal communication with Dr. Wilson]).

Response to Prior Anthracycline	Response to Docetaxel in Pivotal Trials
Unresponsive to Anthracycline	35% (22/63)
-PD as best response	34% (18/53)
-Relapse during adjuvant therapy	40% (4/10)
Responsive to Anthracycline	47% (20/43)
-PR/CR, then PD	56% (5/9)
-NC, then PD	44% (14/32)
-Unknown response, then PD	50% (1/2)
RR in Unresponsive (35%) vs Responsive (47%), p=0.312	

2. The relative efficacy of docetaxel and paclitaxel in anthracycline-resistant breast cancer patients is difficult to estimate from reports in the literature, due to varying definitions of anthracycline-resistance among investigators, and varying doses/schedules of paclitaxel utilized. The ongoing phase 3 trial, TAX311, may answer the question of relative efficacy between the two agents in this setting, if sufficient numbers of anthracycline-resistant patients are enrolled. In the setting of metastatic breast cancer, where no standard life-prolonging or curative therapy exists, this reviewer supports the contention of O'Shaughnessy et al., JCO, 9: 1991, that if a "new drug were associated with more severe potentially life-threatening toxicity, ... comparison with a standard regimen would usually be needed to assess whether treatment resulted in inferior QOL or survival".

3. For the subset of patients having "PD as best response" to prior anthracycline, a preliminary comparison between the docetaxel-treated patients listed above (RR=34%, 18/53) and paclitaxel-treated patients on the Bristol-Myers Squibb randomized phase 3 trial was performed. For the latter study, the RR to paclitaxel 175 mg/m^2 over 3 hours in this subset of patients was 27% (8/30), with p=0.624 for the comparison, indicating no statistical difference. For this patient population, also compare the 32% RR (10/31, 95% CI: 18-40%) for paclitaxel 250 mg/m^2 over 24 hours (Seidman et al., 13, JCO, 1995) and the 50% RR (12/24, 95% CI: 29-70%) for paclitaxel 140 mg/m^2 over 96 hours (Wilson et al., 12, JCO, 1994). Thus, docetaxel, like paclitaxel, appears active in patients with *de novo* resistance to anthracycline.

11. Recommended Regulatory Action, October 20, 1995

Although this reviewer remains convinced that docetaxel demonstrates activity in second line breast cancer, including the subset of anthracycline-resistant patients, reservations persist regarding the safety of the 100 mg/m² dose in patients with normal liver function. In situations such as this in which there is no general agreement on what constitutes acceptable risk, the deliberations of the Oncologic Drugs Advisory Committee can be most helpful. On October 17, 1995, a majority of ODAC members (6-0-1 abstaining) recommended that TAXOTERE® be approvable for the treatment of anthracycline-resistant breast cancer prior to the completion of ongoing phase 3 trials, although it was stressed that there was a need for further study of this drug to determine the optimal dose clinically. A majority of ODAC members (6-1) deemed the hematologic toxicity "substantial, but acceptable" if patients with liver dysfunction (defined as SGOT/SGOT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN) were excluded from treatment. The sponsor verbally concurred with the recommendation to exclude patients with liver dysfunction defined in this manner. Fluid retention, the most common reason for treatment discontinuation for toxicity in the original NDA submission, was, in ODAC's judgment (7-0), ameliorated by the use of a 5-day dexamethasone premedication regimen. Thus, ODAC concluded that the overall risk:benefit ratio for TAXOTERE® in the anthracycline-resistant patient population was favorable.

TAXOTERE® (docetaxel) for Injection Concentrate, at a dose of 100 mg/m² over 1 hour every three weeks, is approvable for the treatment of "patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy". This decision is based on docetaxel's single agent activity in phase 2 trials evaluating 134 anthracycline-resistant patients (41% overall response rate, 2% CR rate, and 5.9-month response duration).

Before the application may be approved, however, it will be necessary for the applicant to submit the primary data in support of analyses presented at the October 17, 1995 ODAC Meeting, not previously submitted to the NDA, as outlined below. In addition, the applicant must submit a letter committing to the phase 4 studies as identified below, revised draft labeling, and introductory promotional material for this product.

Note that this review supersedes the May 1995 Medical Officer's Review of NDA # 20,449.

12. Deficiency List

The sponsor should submit the following documents:

a) Case report forms for the 15 second line breast cancer patients with combined abnormalities of transaminases and alkaline phosphatase

b) Case report forms for all second line breast cancer patients with baseline edema and/or

effusions

c) Tumor lesion measurements and sponsor's assessment for the 174 second line breast cancer patients treated in Japan; sponsor's assessment of anthracycline-resistance in this patient population. To expedite this submission, Japanese data could be submitted electronically, with minimal prior translation.

d) Detailed safety summary for all hematologic and non-hematologic toxicities observed in the 134 anthracycline-resistant patients on TAX233, TAX267, and TAX286, according to baseline liver function.

e) Assessment of performance status over time for responders and non-responders, as presented at the October ODAC Meeting. Sponsor's slides 61-65 should be submitted along with supporting electronic data.

In addition, the sponsor should clarify the following points:

a) Please explain the reporting of toxic deaths to IND given that no deaths were reported in the months preceding 1/95, while 16 deaths were reported between 1/95 and the present (as of 10/24/95). Please also comment on the nature of these recent deaths, the majority of which were non-sepsis-related. This is in contrast to the deaths reported to the NDA which were primarily sepsis-related.

b) Please clarify the number of toxic deaths that occurred among the 95 patients with transaminase elevations in the March 1995 safety analysis of patients with liver dysfunction.

c) Please describe the specific symptoms that were included in the designation of "severe asthenia" for each anthracycline-resistant patient with this toxicity. Please explain why there did not appear to be a correlation between the development of severe asthenia and deterioration in performance status in these patients.

d) Please clarify the incidence of severe infection for anthracycline-resistant patients. At the October ODAC Meeting, a 10% incidence of severe infection was reported in 13 of 134 patients. The individual study reports (TAX233, TAX 267, and TAX 286) mention that 45 of 56 infections were associated with grade 3 or 4 neutropenia. How many patients with normal liver function experienced such infections?

e) The next safety update should include the most recent information available on the cohort of patients premedicated with the 5-day dexamethasone regimen. This report should include the median number of treatment cycles, median cumulative dose to onset of moderate/severe toxicity, median cumulative dose to treatment discontinuation, rate of treatment discontinuation, and the duration of fluid retention. Please also describe patient compliance with the regimen, supportive measures used to treat fluid retention, evolution of performance

status during treatment, and response to docetaxel treatment.

f) We acknowledge the sponsor's commitment to conduct a physician education program. Please provide a detailed proposal for review.

13. Phase 4 Commitments

14. Product Labeling Comments

A. BOXED WARNING

The new second paragraph should read: TAXOTERE® should not be given to patients with bilirubin > ULN, or to patients with SGOT or SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN. Patients with elevation of bilirubin are at risk for the development of grade 4

neutropenia, febrile neutropenia, thrombocytopenia, severe stomatitis, and toxic death. Patients with combined abnormalities of transaminase and alkaline phosphatase are at risk for the development of febrile neutropenia, infections overall and severe, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values must be obtained prior to each cycle of TAXOTERE® therapy and reviewed by the treating physician.

The fourth paragraph (on severe hypersensitivity reactions) should read: "Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 7% of patients who received no premedication. These reactions resulted in immediate discontinuation in only 0.4% (4 of 1074) of patients and resolved after discontinuation of the infusion and the administration of appropriate therapy. TAXOTERE® must not be given to patients who have a history of severe hypersensitivity reactions to TAXOTERE® or to other drugs formulated with polysorbate 80.

A new fifth paragraph should read: Severe fluid retention, characterized by poorly tolerated edema, generalized anasarca, effusion requiring urgent drainage, dyspnea at rest, tamponade, or pronounced abdominal distention (due to ascites) occurred in 5% of patients despite use of a 5-day dexamethasone premedication regimen.

B. CLINICAL PHARMACOLOGY

The second paragraph should read: "The cytotoxic potency of docetaxel may result from its high affinity for microtubules". The second sentence should be deleted.

In the third paragraph, the table of *in vitro* activity of docetaxel in human tumor cell lines and references pertaining to it should be deleted. Delete the sentence, "In addition, docetaxel was found to be active on a number of cell lines overexpressing the *p*-glycoprotein which is encoded by the multidrug resistant gene."

In the seventh paragraph, the last sentence should read, "In patients with clinical chemistry data suggestive of mild to moderate liver function impairment [alkaline phosphatase > 2.5 x the upper limit of normal (ULN) concurrent with SGOT or SGPT > 1.5 x ULN, total body clearance was lowered by an average of 27%, and this patient population should be excluded from treatment.

C. CLINICAL STUDIES

This section should be revised to include only the results from the three pivotal phase II trials in anthracycline-resistant breast cancer, that is, the indication for which approval is based. Include survival data, along with response rate, response duration and time to progression. The definition of anthracycline-resistance should be provided.

In addition to efficacy parameters, a tabulation of key hematologic and non-hematologic adverse events noted in the 134 anthracycline-resistant patients breast cancer patients should be inserted here. The incidence of neutropenia (any and grade 4) febrile neutropenia (include definition), infections (any and severe), thrombocytopenia (any and grade 4), anemia, septic deaths, mucositis (any and severe), neurosensory toxicity (any and severe), skin toxicity (any and severe), fluid retention (any and severe), acute hypersensitivity reactions, asthenia (any and severe), myalgias, and non-septic deaths, should be noted for patients with "normal" and "elevated" LFTs at baseline. Definitions of "normal" and "elevated" LFTs should be provided.

D. INDICATIONS and USAGE

The indication was amended on October 11, 1995, to: TAXOTERE® (docetaxel) for Injection Concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

E. CONTRAINDICATIONS

The following should be added to the end of the second paragraph after "< 1,500 cells/mm³": "with a bilirubin > ULN, or with SGOT or SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN (see WARNINGS and DOSAGE ADMINISTRATION sections). Delete the sentence "TAXOTERE® should not be used in patients with severe liver impairment, since there are no data available in this patient population."

F. WARNINGS

This section as written is sketchy and should be revised to include "serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur" as discussed in 21 CFR 201.57.

PREMEDICATION REGIMEN: State that the optimal premedication regimen is not known but that all patients should be premedicated with oral corticosteroids. Note that dexamethasone does not alter the overall incidence of fluid retention. Text should read: "dexamethasone 16 mg per day for 5 days starting 1 day prior to TAXOTERE® administration in order to reduce the severity of fluid retention".

HEPATIC IMPAIRMENT: Text should read: "Bilirubin, SGOT or SGPT, and alkaline phosphatase values must be obtained prior to each cycle of TAXOTERE® therapy and reviewed by the treating physician. Patients with bilirubin > ULN, or patients with SGOT or SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN should not receive TAXOTERE®. Patients with isolated elevations of SGOT or SGPT > 1.5 x ULN are also at risk for excessive toxicity and a 25% dose reduction should be considered.

G. PRECAUTIONS

DRUG INTERACTIONS: Separate out those drugs which increase docetaxel clearance from those which decrease it.

HEMATOLOGY: The text should read:
In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOTERE®. Patients should not be retreated with subsequent cycles of TAXOTERE® until neutrophils recover to a level > 1500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³.

A 25% dose reduction during subsequent cycles is recommended following prolonged (seven days or more), severe (<500 cells/mm³) neutropenia, febrile neutropenia, or grade 4 infection in a TAXOTERE® cycle.

HYPERSENSITIVITY REACTIONS: Use of premedications should be re-iterated in this section.

CUTANEOUS: State the magnitude dose reduction recommended in patients with severe skin toxicity. State the frequency of treatment discontinuations due to skin toxicity.

FLUID RETENTION: State the incidence of moderate/severe edema, pleural effusions, pericardial effusions and ascites here. State the time to onset and resolution of fluid retention. The benefits of corticosteroid premedication in the 104 breast cancer patients should be mentioned here. Recommendations regarding supportive therapy should also be made.

NEUROLOGIC: State the magnitude dose reduction recommended in patients with severe neurologic toxicity. State the frequency of treatment discontinuations due to neurotoxicity.

PREGNANCY: Should read: Pregnancy Category D (see WARNINGS section).

PEDIATPIC USE: The sentence should read, "The safety and effectiveness of TAXOTERE® in pediatric patients have not been established.

H. ADVERSE REACTIONS

The table of adverse events should be updated for the 1028 patients with "normal" liver function tests. Septic and non-septic deaths should be included. The definition of "normal" should be provided. Move detailed discussion to WARNINGS or PRECAUTIONS sections as appropriate (see 21 CFR 201.57).

HEMATOLOGIC: Text should begin with the statement: "Bone marrow suppression was the major dose-limiting toxicity of TAXOTERE®". Anemia should be discussed in this section.

Reference should be made to the WARNINGS sections.

There have been four (?) fatal cases of gastrointestinal hemorrhage associated with coagulopathy and at least one death due to DIC (? correct number); deaths should be included under WARNINGS.

HYPERSENSITIVITY REACTIONS: Reference should be made to the WARNINGS section.

FLUID RETENTION: In the WARNINGS section, state the overall incidence of fluid retention, the incidence of moderate/severe reactions, and the median cumulative dose to onset of moderate/severe fluid retention regardless of premedication. State the benefits of the 5-day dexamethasone premedication. State the duration of fluid retention as reported for the TAX237 trial and for the logistic regression analysis in 90 patients with adequate follow-up. Reference should be made to the PRECAUTIONS section.

NEUROLOGIC: Available information on the reversibility of neurotoxicity should be provided.

HEPATIC: In the WARNINGS section, state the incidence of SGOT or SGPT values > 1.5 x ULN, of alkaline phosphatase > 2.5 x ULN, and of bilirubin > ULN, in the anthracycline-resistant breast cancer patient population. Adverse events related to the combination of transaminase and alkaline phosphatase abnormalities should be detailed here.

ASTHENIA: Define and state the incidence of severe asthenia.

OTHER CLINICAL EVENTS: Mention alopecia here.

I. DOSAGE AND ADMINISTRATION

Include: "For patients with locally advanced or metastatic carcinoma of the breast, TAXOTERE® at a dose of 100 mg/m² administered intravenously over 1 hour every three weeks has been shown to be effective after progression during anthracycline-based therapy for metastatic disease or relapse during anthracycline-based adjuvant therapy".

SPECIAL POPULATIONS: Patients with bilirubin > ULN, or patients with SGOT or SGPT > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN should not receive TAXOTERE®. Patients with isolated elevations of SGOT or SGPT > 1.5 x ULN may require an adjustment in dosage.

J. REFERENCES

A complete listing of references should be provided.

K. Patient Package Insert

A patient package insert should be provided outlining specific directions, precautions, warnings or safety information patients should know to take this drug safely (e.g., patients should be alert to the signs and symptoms of fluid retention, and to the need to take the premedication as prescribed).

Julie Beitz MD 10/24/95
Julie Beitz, MD Date

Robert Justice, M.D. 10/24/95
Robert Justice, MD Date

cc:
NDA # 20,449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

Addendum to Medical Officer's Review of NDA #20,449 TAXOTERE® (docetaxel)

Objective Responses on TAX286

The TAX286 study report was submitted without data listings on November 7, 1995, and reviewed in Section 10 (Medical Officer's Review of the original NDA). Data listings were requested and submitted on May 23, 1995. Because of the sponsor's decision to limit its indication to anthracycline-resistant breast cancer on October 11, 1995, it was necessary to review the responses for the 51 patients on this trial. These patients, along with the 83 patients on the TAX233 and TAX267 trials, are included among the 134 anthracycline-resistant patients on whom approval is based.

Altogether, there were 15 partial responses reported and confirmed for an overall response rate of 29% (using sponsor's Table 28, Vol II of the May 23, 1995 submission). Responses were primarily noted in skin and lymph nodes. Responses in lung (patients and in liver (patients were also noted. Nine responding patients eventually progressed on therapy, four discontinued due to toxicity, and two patients withdrew in response for undocumented reasons. The patients withdrawn for toxicity were:

edema, neurosensory toxicity;
edema, eczematous lesions arms and legs;
edema; and
paresthesias, vertigo, pain in hands and feet.

Julie Beitz MD 10/24/95
Julie Beitz, MD Date

Robert L Justice, MD 10/24/95
Robert Justice, MD Date

cc:
NDA # 20,449
HFD-150/Division File
HFD-150/J. Beitz
HFD-150/ R. Justice
HFD-150/ D. Pease

Pharm./Tox

APR 10 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum Review No. 9

NDA No. 20,449

Date(s) of Submission: March 25, 1996

Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer: Margaret E. Brower, Ph.D.

Date Review Completed: April 10, 1996

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Related INDs/NDAs: NDA 20-449, Addendum reviews/NDA, IND NDA 20262 (Taxol) IND

Class: Cytotoxic Antineoplastic Agent

Indication: Locally advanced or metastatic breast carcinoma

LABELLING REVISIONS

The proposed labelling revision provided by Rhone Poulenc for the labelling of Taxotere (**OVERDOSE** section) has been accepted by Pharmacology. However, the following changes should be incorporated:

1. Page 4, line 7 of CLINICAL PHARMACOLOGY section:

Change to: . . . Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The only information submitted to the agency which specifically addresses this "uniqueness" is an abstract (Peyrot et al., 1993). An abstract is not sufficient information to claim this "unique"

property since there is no data available to evaluate.

2. Page 10, lines 5 and 6 of PREGNANCY section:

Change to: . . . that TAXOTERE is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

3. Page 13, continuing paragraph from previous page under CARCINOGENICITY-MUTAGENICITY-IMPAIRMENT OF FERTILITY:

Change to: . . . testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at i.v. doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/8 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Neurotoxicity associated with paralysis, non-extension of hind limbs and axonal and myelin degeneration was observed in mice following 5 daily doses of 10mg/kg taxotere. The overdose section of the label addresses primarily single dose studies. Therefore, we accept your change to 48mg/kg.

RECOMMENDATIONS

Labelling should be revised as indicated above.

Margaret E. Brower, Ph.D.
Pharmacologist
April 10, 1996

cc:
Original NDA
/Division File HFD-150
/MBrower--Awaiting archival NDA 4/4
/JDeGeorge--Subm 3/29/96, retur 4/4
/JBeitz
/DPease

4/12/96

FEB 8 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum Review No. 8

NDA No. 20,449

Date(s) of Submission: December 4, 1995

Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer: Margaret E. Brower, Ph.D.

Date Review Completed: December 12, 1995

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Related INDs/NDAs: NDA 20-449(Primary review/ taxotere, Addendum reviews/taxotere 1,2,3,4), IND IND . NDA 20262 (Taxol)

Class: Cytotoxic Antineoplastic Agent

Indication: Locally advanced or metastatic breast carinoma, locally advanced or metastatic non-small cell lung cancer

LABELLING REVISIONS

The proposed labelling revisions provided by Rhone Poulenc for the labelling of Taxotere have been accepted by Pharmacology with the exception of the following (changes underlined):

1. The original calculation for paragraph 1, pg 16 was correct at <u>1/15</u> and should not be changed to 1/20. This is based on a conversion factor of 20 for the dog. [0.375mg/kg

taxotere in dogs X 20 (conversion factor to mg/m^2)/100 mg/m^2 (proposed clinical dose)]

2. The paragraph at the top of pg 24 should read:
In mice, lethality was observed following single iv doses that were ≥154mg/kg (about 4.5 times the recommended human dose on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs and myelin degeneration was observed in mice at 10mg/kg (about ½ the recommended human dose on a mg/m^2 basis). In male and female rats, lethality was observed at 20mg/kg (about equal to the recommended human dose on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

RESPONSE TO DEGRADATE ISSUE

BACKGROUND

Nondegraded taxotere is known to be a neurotoxicant. Pathological examination of mice (study # A-92-641) administered a single iv dose (95mg/kg) of taxotere indicated severe destruction of nerve fibers of the spinal cord, sciatic and tibial nerves and demyelination of nerve fibers within 15 days of dosing. Nerve destruction was lessened by study day 92, although complete recovery did not occur.

The question therefore is how much additional neurotoxicity is produced by the degradates?

The original requested limit of degradant RPR 112248 was 0.5% (7/27/94). Previous data on the level of this degradant in batches used for clinical trials indicated 0-0.3% with mean of 0.09%. The sponsor indicated that the concentration was "very low and stable" and the relationship between RPR 112248 and adverse events had not been analyzed.

The original requested limit of degradant RPR 110928 is 1%. 0-0.7% (mean of 0.4%) was previously indicated as the range of this degradate in clinical batches. The sponsor indicated that neurotoxicity was not a prognostic factor (specific data were not submitted).

Concern regarding the neurotoxicity of RPR 112248 and RPR 110928 was initiated following a review of the 40% degradate single-dose lethality study in mice (study # RPR/RD/CRVA/SM 93-0357) and 40% degradate 5-day lethality study in mice (RPR/RD/CRVA/SM93-0430) in which neurotoxicity (as exhibited by non-extension of hindlimbs and paresis of hindlimbs) was exhibited with greater incidence and severity in mice administered the degraded taxotere solution (30% ↑ in neurotoxicity as exhibited by nonextension of hindlimbs and 90% ↑ in paresis of hindlimbs in mice administered single doses of 40% degraded taxotere equivalent to animals administered nondegraded taxotere). The certificate of analysis of the 40% degraded solution listed only the 2 major degradates (RPR 73077 and RPR 70617) with an additional indication of " 2-3.5% undisclosed degradation products". When the sponsor was asked to submit a listing of

the undisclosed degradation products, it was indicated that degradate quantities were a rough approximation and specifics were unavailable. Additional acute toxicity studies indicated that animals administered RPR 70617 and RPR 73077 did not exhibit neurotoxicity and were less or equally toxic to taxotere. No additional data were submitted for RPR 112248 and RPR 110928. Since the increased neurotoxicity of the degraded drug was not a result of the two major degradants (toxicity compared to taxotere), additional data on the two degradants of concern (RPR 112248 and RPR 110928) were requested.

The certificate of analysis for the 6% degraded taxotere (study # RPR/RD/CRVA/SM 94-0054) was not provided. Neurotoxicity (as exhibited by absence of hindlimb extension and paresis of hindlimbs) was similar in ♂ administered nondegraded or 6% degraded taxotere and slightly increased in ♀ administered the 6% degraded material. The administration of the LD solution (60% below the dose at which neurotoxicity was observed) produced no indication of neurotoxicity from degraded or nondegraded solutions.

Since the initial data for batches used in clinical trials (presented above) indicated that 2X the mean level of degradant in these batches were within the requested limit of the degradant, the degradant issue was deferred to clinical data to support requested levels without additional pharm/tox testing. The sponsor was requested to (1) correlate level of degradant found in clinical batches with adverse neurological response associated with these batches and (2) provide a list of degradates with proposed rationale for grouping them according to rate of degradation.

1. Degradant RPR 110928- The question asked that Rhone Poulenc provide the data from which it was concluded that the degradate was not a prognostic factor for the onset of neurotoxicity. The model calculation submitted indicates that there is no association between the incidence of neurotoxicity in 256/644 patients (39.7%) and the concentration of degradant RPR 110928. Individual patient data were not provided.

2. Degradant RPR 112248- The requested limit for this degradate was 0.5%. The current data indicates that the maximum level of the degradate in clinical batches was 0.91% (note that this is above requested limit); a table with data from 7 patients exposed to 0.8% was presented (see background paragraph). Previously submitted data indicates that 2/7 (29%) of these patients experienced neurotoxicity which is within the incidence of neurotoxicity reported in anthracycline-resistant patients (65%); however, 4/7 patients (57%) withdrew from the study due to disease progression and death which is >2X that observed in pivotal trials (20%). These patients may have been taken off study prior to observation of neurotoxicity. There is no information on 1/7 patients. It is necessary to provide data on a larger number of patients in order to ascertain neurotoxicity and death as a possible result of neurotoxicity (See Medical Officer review attached). Concern was conveyed to the sponsor via fax on 12/26/95 by the Medical Officer.

Based on preclinical data, requested limits appear to be acceptable. However, we refer the sponsor to two additional questions prior to committing to limits requested for RPR 110928 (1%) and RPR 112248 (0.5%).

RECOMMENDATIONS

The following questions should be addressed:

1. Was the complete subset provided for degradate RPR 112248 or are there any other identifiable patients who were exposed to ≥0.8%?

2. The concentration of degradate RPR 112248 was indentified in clinical batches up to 0.91%. Why was it not identified in the certificate of analysis of degraded material in the 6% degradate study in mice (study # RPR/RD/CRVA/SM 94-0054) or the 40% degradate single-dose lethality study in mice (study # RPR/RD/CRVA/SM 93-0357)?

In addition, labelling should be revised as indicated on page 1-2 of this review.

Margaret E. Brower, Ph.D.
Pharmacologist
December 13,1995

cc:
Original NDA
/Division File HFD-150
/MBrower
/JDeGeorge
/JBeitz
/DPease

2/8/96

D [illegible]

FEB 8 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum Review No. 7

NDA No. 20,449

Date(s) of Submission: May 23, 1995

Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer(s): Margaret E. Brower, Ph.D.

Date Review Completed:

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5 ß, 20-Epoxy- 1,2 a, 4, 7 ß, 10 ß, 13 a-hexahydroxytax- 11 -en-9-one 4- 10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Additional Preclinical Studies Received:

RPR/RD/CRVA/SM 94-0054 RP 56976 (6% Degraded Solution) and RP 56976 (Solution of Non-degraded Material): Single-Dose Intravenous Lethality Study in Mice. Conducted byRhone-Poulenc Rorer, Centre de Recherche de Vitry-Alforville, Alforville, France in 1994 according to OECD and Japanese GLP.

Methods:

species: Crl:CD-1(ICR)BR strain (5 mice/sex/group) [Different strain from previous studies]
drug: Non-degraded taxotere or 6% degraded solution of taxotere
dosage: 75, 120mg/kg in ♂; 65, 100mg/kg in ♀ [control group administered PS80 vehicle diluted in 5% glucose solution at concentrations of 10% (♀) or 12% (♂)
route: Single iv dose, 14 day recovery
age, wt.: 6 weeks; 22-24g♂; 17-19g♀

Taxotere (batch FCH 158) was stored at 4°C for 23 months resulting in a 6% degraded solution; ♀ were administered 2.6 (65mg/kg) and 4.0 mg/ml (100mg/kg) and ♂ were administered 3.0 (75mg/kg) and 4.8mg/ml (120mg/kg). Corresponding solutions of nondegraded taxotere (batch 15PROC92325) were administered to separate groups of animals.

Degradate RPR 110928 was listed in the analysis reference of degraded solution in a concentration of 0.4%; degradate 112248 was not identified.

Results:
Mortality:

	Males		Females	
	Dose (mg/kg)	Morality	Dose (mg/kg)	Mortality
Control	0	0/5	0	0/5
Undegraded Taxotere	75	0/5	65	0/5
	120	3/5	100	0/5
6% Degraded Taxotere	75	0/5	65	0/5
	120	2/5	100	2/5

Mortality was increased in HD ♀ administered 6% degraded taxotere (40%) as compared to the undegraded drug; mortality was not increased in ♂. Mortality occurred 1 day following dosing.

Clinical observations:

Convulsions, reduced motor activity, dyspnea, prostration and ataxia were observed for 4 days in HD ♂ and ♀ administered degraded and nondegraded taxotere and 3/5 controls. In addition, 1/5 LD♂ administered the nondegraded drug exhibited transient convulsions. The incidence of absence of spontaneous hind limb extension and paresis of hind limbs was observed throughout the recovery period in HD animals administered degraded and nondegraded taxotere and was slightly increased in HD animals administered the degraded drug.

Incidence of neurotoxicity in mice administered degraded and nondegraded taxotere						
	Males			Females		
	Dose(mg/kg)	Absence of hindlimb extension	Paresis of hindlimb	Dose(mg/kg	Absence of hindlimb extension	Paresis of hindlimb
Control	0	0/5	0/5	0	0/5	0/5
Non-degraded taxotere	75	0/5	0/5	65	0/5	0/5
	120	2/2	2/2	100	3/5	0/5
6% degraded taxotere	75	0/5	0/5	65	0/5	0/5
	120	3/3	3/3	100	3/3	1/3

Body Weight:

Body weights of HD ♂ administered degraded and nondegraded taxotere were depressed from 4-22% and 8-19%, respectively, from study days 3 to 15 when compared to concurrent controls. Body weights of LD ♂ were depressed 9 and 12% for degraded and nondegraded animals. respectively, on study day 8; body weights were similar to concurrent controls on days 3 and 15. Body weights of HD ♀ administered degraded taxotere were depressed 9-13% with 13%

depression on study day 8 and slight recovery to 9% depression on day 15; body weights of ♀ administered nondegraded taxotere were depressed 7-8% with full recovery in body weight by day 15. Body weights of LD ♀ administered nondegraded taxotere were similar to concurrent controls.

A-92-641 **Report on Neurotoxicological Study of RP 56976 in Mice.**
Conducted by GLP status of study not reported. *Individual data were not reported.*

Methods:

species: ♂ CD_2F_1 (Crj: CDF_1, SPF) strain (10mice/control group; 35mice/treated group) [Different strain from previous studies]
drug: Nondegraded taxotere (lot # CB05546) in PS 80 diluted with 5% glucose [stability of stock solution indicated to be 5 hours]
dosage: 95 mg/kg [control group administered PS80 vehicle]
route: Single iv dose, 119 day recovery
age: 6 weeks

Results:

Mortality and clinical observations:

There were 3/35 deaths in taxotere-treated animals (2 animals died immediately following dosing). Nonextension of hindlimbs was observed in all treated animals from study days 4-30 and days 35-70 with 1 animal exhibiting nonextension to study termination; nonextension was most severe on days 15-20. Decreased motor activity was observed in 21 treated animals from study days 3-27. Abnormal gait was observed in 8 treated animals from days 12-22.

Body Weight:

Body weight gain of treated animals was depressed on study day 8; weight gains began to recover following day 8. No further information was provided.

Behavioral Examination:

20/33 treated animals were not able to remain on the rotating rod for 60 seconds on study day 14; 2 treated animals continued to fail the examination on day 119. 5/33 treated animals showed abnormality with the suspension test on day 14; animals recovered the examination by day 58. "Incidental significance " was reported between dosed and control animals for the test of hindlimb grip strength on day 28.

Pathological Examination:

Animals sacrificed during the study exhibited atrophy of thymus, testes and epididymides.

Destruction of nerve fibers of the spinal cord, and severe destruction of sciatic and tibial nerves was reported in treated animals on day 15. Myelination of nerve fibers was reported to be lessened or absent. Destruction of nerve fibers of the spinal cord was reported to be more severe by day 29; severe destruction of nerve fibers and absence of myelination was again reported. Destruction of nerve fibers of sciatic and tibial nerves lessened by day 59; spinal cord destruction remained similar. Destruction of spinal cord, sciatic and tibial nerve fibers was lessened by study

92, although not recovered when compared to concurrent controls. No individual data were reported.

Electron Microscopic Examination:

Degeneration and condensation of axoplasm and swelling of axons were observed in nerves of the spinal cord of treated mice on study day 15. Basal lamina of nerve fibers was loosened and detached from Schwann cells. The study author indicated that early stage regeneration of nerve fiber (few axons surrounded by basal lamina and few axons with thin myelin sheath) was observed by study day 15.

CONCLUSIONS:

Neurotoxicity, as measured by absence of hindlimb extension and paresis of hindlimbs, was similar in ♂ administered nondegraded or 6% degraded taxotere. Using the same method of examination, neurotoxicity was slightly increased in ♀ administered the 6% degraded material.

Based on preclinical data, requested degradate limits appear to be acceptable. However, we refer the sponsor to two additional questions prior to committing to limits requested for RPR 110928 (1%) and RPR 112248 (0.5%).

RECOMMENDATIONS:

The following questions should be addressed:

1. Was the complete clinical subset provided for degradate RPR 112248 or are there any other identifiable patients who were exposed to ≥0.8%?

2. The concentration of degradate RPR 112248 was indentified in clinical batches up to 0.91%. Why was it not identified in the certificate of analysis of degraded material in the 6% degradate study in mice (study # RPR/RD/CRVA/SM 94-0054) or the 40% degradate single-dose lethality study in mice (study # RPR/RD/CRVA/SM 93-0357)?

Margaret E. Brower, Ph.D.
Pharmacologist
Decembe. 21, 1995/January 25, 1996

cc:
Original NDA
/Division File HFD-150
/MBrower
/JDeGeorge
/JBeitz
/DPease

OCT 2 4 '95

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum Review No. 6

NDA No. 20,449

Date(s) of Submission: July 21, 1995

Information to be conveyed to sponsor: Yes (X) No ( )

Reviewer: Margaret E. Brower, Ph.D.

Date Review Completed: August 28, 1995

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Related INDs/NDAs: NDA 20-449(Primary review/ taxotere, Addendum reviews/taxotere 1,2,3,4), IND , IND NDA 20262 (Taxol)

Class: Cytotoxic Antineoplastic Agent

Indication: Locally advanced or metastatic breast carinoma, locally advanced or metastatic non-small cell lung cancer

LABELLING ISSUES

Labelling changes were submitted to the sponsor with the primary NDA review on ~January25, 1995. However, labelling changes were not incorporated in the Labelling Update dated July 21, 1995 and submitted July 26,1995. The following changes must be incorporated.

1. *Delete* 3 paragraphs, page 4, line 4 under CLINICAL PHARMACOLOGY *which begins. . .*
. . and ending with . . .

2. **CONTRAINDICATIONS** pg.8 *Delete* paragraph 3 of Contraindications (TAXOTERE may cause fetal harm. . .)

3. **WARNINGS** pg 10 *Insert* the following as the final paragraphs of the section:

Pregnancy

TAXOTERE can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses equal to or greater than 0.3 and 0.03mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that TAXOTERE is embryotoxic and fetotoxic characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay. Doses indicated above did not produce maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.

4. *Delete* paragraph under Carcinogenicity, Mutagenicity, and Impairment of Fertility on pg 12, *replace with*:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No studies have been conducted to assess the carcinogenic potential of TAXOTERE. Taxotere has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K1 cells and in the *in vivo* micronucleus test in the mouse. However, it did not induce mutagenicity in the Ames test, or the CHO/HGPRT gene mutation assays. TAXOTERE produced no impairment of fertility in rats when administered in multiple iv doses of up to 0.3mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis) . However, decreased testicular weights were reported. This correlates with findings of a 10-cycle (dosing 1X every 21 days for 6 months) toxicity study in rats and dogs in which testicular atrophy or degeneration was observed at iv doses of 5mg/kg in rats (about 1/3 the recommended human dose on a mg/m^2 basis) and 0.375mg/kg in dogs (about 1/15 the recommended human dose on a mg/m^2 basis). Increased frequency of dosing in rats produced similar effects at lower dose levels.

5. *Delete* current pregnancy labelling for Category X (pg 12) under **PRECAUTIONS**, *replace* with the following:

Pregnancy Category D (see **WARNINGS**)

6. *Delete* paragraph Nursing Mothers on pg 13, *Replace with*:

It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from TAXOTERE in nursing infants, mothers should discontinue nursing prior to taking the drug.

7. *Include* as final paragraph of **OVERDOSE** section.

In mice, lethality was observed following single oral doses that were ≥156mg/kg (about 4.5 times the recommended human dose on a mg/m^2 basis); neurotoxicity associated with paralysis, nonextension of hindlimbs and myelin degeneration was observed in mice at 10mg/kg (about ⅛ the recommended human dose on a mg/m^2 basis). In male and female rats, lethality was observed

at 64 and 121mg/kg, respectively (about 4 and 7 times, respectively, the recommended human dose on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

Recommendation

The pharmacology/toxicology section of the labelling for Taxotere is approvable with the above revisions.

Margaret E. Brower, Ph.D.
Pharmacologist
August 28, 1995

cc
Original NDA
/Division File HFD-150
/Beitz
/Pease
/DeGeorge
/Brower (revised 10/23/95)

10/27/95

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DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum Review No. 5

NDA No. 20,449

Date(s) of Submission: August 17, 1995

Information to be conveyed to sponsor: Yes( ), No (X)

Reviewer: Margaret E. Brower, Ph.D.

Date Review Completed: August 28, 1995

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Related INDs/NDAs: NDA 20-449(Primary review/ taxotere, Addendum reviews/taxotere 1,2,3,4), IND IND NDA 20262 (Taxol)

Class: Cytotoxic Antineoplastic Agent

Indication: Locally advanced or metastatic breast carinoma, locally advanced or metastatic non-small cell lung cancer

Additional Preclinical Study Submitted:

BOZO/R-576 Teratological Study in Rats Treated Intravenously with RP-56976.
Conducted by
GLP status not reported.

species:	Crj:CD(SD)SPF rats (60♂, 160♀), 13 weeks of age, BW/♀: 259-322g
drug:	Taxotere, Lot No. GVR 1093
dosage:	0.3, 1.0, 3.7 mg/kg/day dosed on 3 successive days including gestational days 6-8, 9-11, 12-14, and 15-17
route:	iv

LD, MD, and HD dams dosed on gestation days 12-14 exhibited vaginal hemorrhage and paleness of the extremities with death of 2/9 MD dams of this dosing period on gestation day 17. HD dams dosed on gestation days 9-11 also exhibited paleness of extremitites with death of 2/10 ♀ on day 17; death was attributed to hypothermia. Emaciation was observed in MD dams dosed on gestation days 9-11 and 12-14, and in HD dams dosed on gestation days 6-8, 9-11, and 12-14.

Maternal body weights were depressed up to 6, 32, 28, and 11% in MD ♀, and 34, 38, 44, and 24% in HD♀ dosed on gestation days 6-8, 9-11, 12-14, and 15-17, respectively, when compared to concurrent controls. Maternal food consumption was depressed inconsistently throughout the study duration from 48-89% in MD ♀ and 37-90% in HD ♀ when compared to concurrent controls; depression of food consumption was dependent on dosing schedule. Microscopic observations in dosed animals included atrophy of the thymus, hypertrophy or atrophy of the spleen, and pale livers.

The following table illustrates the increase in the number of embryo-fetal deaths and decrease in the number of live fetuses from dams dosed with taxotere. The embryo-fetal death rate was ~100% in MD and HD ♀ dosed on gestation days 9-11 and 12-14, and HD ♀ dosed on gestation days 6-8. Body weights of live fetuses were depressed 18-21% in the LD(day12-14) group, 15-17% in the MD (day12-14 and 15-17) groups, and 26-28% in the HD (day 15-17) group. The number of corpora lutea and implantations were similar in dosed and control ♀.

External Examination of F_1 Fetuses from Dams Treated Intravenously with Taxotere

Dose (mg/kg)	Dosing Period (gestation days)	No. of resorbed or dead fetuses			No. of live fetuses	Fetal Body Weight mean (g)	
		Total	Early Resorb	Late Resorb		Male	Female
control	6-17	7	7	0	146	3.90	3.70
0.3	6-8	7	6	1	119	3.92	3.73
	9-11	44	41	3	119	3.71	3.31
	12-14	52	43	9	87	3.23	2.94
	15-17	12	12	0	149	3.85	3.56
1.0	6-8	15	14	1	145	3.65	3.47
	9-11	164	164	0	0	---	---
	12-14	106	104	2	3	3.27	---
	15-17	13	10	3	147	3.34	3.17
3.7	6-8	138	137	1	6	2.71	3.19
	9-11	139	139	0	0	---	---
	12-14	122	116	6	0	---	---
	15-17	7	6	1	132	2.83	2.72

External malformations of fetuses included gastroschisis in 2/74 MD (day6-8) fetuses, omphalocele accompanied by brachyury and anal atresia in 1/2 HD (day6-8) fetuses and thoracogastrochisis accompanied by talipes varus in 1/2 fetuses from the same litter. The

historical incidence of these malformations was not indicate Increased skeletal variations were exhibited in the cervical ribs of 18/74 MD (day6-8) fetuses; reduced ossification was exhibited in 73/74 MD (day6-8), 77/77 MD and 67/67 HD (day15-17) fetuses. There were no visceral abnormalities.

Taxotere was maternally toxic at doses ≥1.0mg/kg (6mg/m^2). The highest incidence of embryo-fetal deaths occurred in dams administered doses ≥1.0mg/kg (6mg/m^2) during gestation days 9-14.

Recommendation

The pharmacology/toxicology section of the labelling for Taxotere should incorporate the study reviewed above.

Margaret Brower

Margaret E. Brower, Ph.D.
Pharmacologist
August 28, 1995

cc
Original NDA
/Division File HFD-150
/Beitz
/Pease
/DeGeorge
/Brower

10/28/95

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum 4 to NDA

NDA No. 20,449

Date(s) of Submission: January 30, 1995
Received by Reviewer: February 27, 1995 (Chemistry submission)

Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer(s): Margaret E. Brower, Ph.D.

Date Review Completed: May 8, 1995

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5 ß, 20-Epoxy- 1,2 a, 4, 7 ß, 10 ß, 13 a-hexahydroxytax- 11 -en-9-one 4- 10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Issue: Degradation products of taxotere/ Additional submitted data

Degradation products of RP 56976 (RP 73077, RPR 110928, RPR 108771, RP 70617 and RPR112248 +X): Single-dose intravenous lethality study in mice (RPR/RD/CRVA/SM 94-0087) Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France, April, 1994

The accelerated degradation of a stock solution of RPR 108771(oxidation product of RP 56976) resulted in a solution containing the major and minor degradates of taxotere. The sponsor indicated that since direct degradation of RP 56976 does not result in sufficient amounts of the degradates and many of the products are difficult to isolate individually, the degradates would be studied as a mixture resulting from the degraded oxidation product.

RP 73077 was indicated to be the major degradate of RPR 108771 (indicated to be the secondary degradate of docetaxel in previous studies and product specs) with a concentration of 20.5mg/ml. Minor degradates reported for this study included RPR 110928, RPR 108771, RPR 70617 and RPR 112248 + X at concentrations of 5.1, 1.2, 0.6, and 0.2mg/ml, respectively. Based on these individual concentration levels and the total calculated concentration reported to be 40mg/ml, an additional unknown with a concentration of 12.4mg/ml, has not been reported in this mixture.

Degraded RPR 10877 was administered to CD_2F_1/CrlBR mice (5 mice/sex/group) at doses of 80 or 120mg/kg (240 and 360 mg/m^2) per iv infusion (degradate solutions of 3.2 and 4.8mg/ml prepared from stock solution; dosing volume, 25ml/kg; rate of administration, 1ml/min). RPR 70377, the major degradate of the oxidation product, was administered at the same dose levels in "pure" form as a standard for comparison. Two vehicle controls were administered: 5%glucose containing 12% polysorbate 80 and 5%glucose containing 8% polysorbate 80, corresponding to the respective concentrations of polysorbate administered to the dosed groups.

Measurements and observations

Daily	Mortality, clinical observations
Predosing and days 3, 8, and 15	Body weight

Macroscopic and microscopic examinations were not performed.

Mortality and clinical observations

Deaths occurred in 2/10 (1male, 1 female) HD mice administered RP 73077 and 2/10 (males) HD mice administered the degradate mixture within 30 minutes of dosing. Deaths were also observed in 2/10 concurrent controls (1 accidental death on day 3). There were no deaths in LD animals.

Convulsions, reduced motor activity, dyspnea and prostration were observed immediately following dosing of HD animals for a period of approximately 2 hours. Low dose animals and concurrent controls from both groups exhibited reduced motor activity for a period of 30 minutes. Red colored urine was observed sporadically in control and treated animals as a result of polysorbate administration.

Body weights

There were no significant changes in body weights of dosed animals.

Sponsors' conclusion:

The mixture of degradation products and RP 70377 have comparable toxicity. Since RP 70377 is less toxic than taxotere, it is unlikely that the presence of the degradation products will modify the toxicity of taxotere.

Study deficiencies:

1. No comparison of degradates to positive control (nondegraded taxotere) demonstrating relative toxicity.
2. Macroscopic and microscopic observations were not conducted.

Taxotere Degradates

	Mouse [a]				Human [b]		
Degradate	Conc. of Total (mg/mL)	Dosed Conc. (mg/kg)	Dosed Conc. (mg/m^2)	Comments	Proposed Conc. of Total(%)	Proposed Dose (mg/kg)	Propos Dose (mg/m2
70617	0.6	2.0	6.0	no neurotox; = toxic/tax; LD_{10}= 363mg/m^2	4	0.1	4
73077	20.5	64.3	192.9	no neurotox; <toxic/tax; LD_{10}= 513mg/m^2	2.5	0.0625	2.5
110928	5.1	16	48.0	no data[c]	1	0.025	1
108771	1.2	3.8	11.4	no data	no spec requested		
112248 +X	0.2	0.6	1.8	no data[c]	0.5(112248)	0.0125	0.5
73079				no data	no spec		
101118				no data	no spec		
102049				no data	no spec		
66779				no data	no spec		
102512				no data	no spec		
104952				neurotoxic; >toxicity/ taxotere	no spec requested		
104953				<toxic/ taxotere	no spec requested		

a Individual degradate data from Study No. RPR/RD/CRVA/SM 94-0087 (no histopathology)
b Basis: 100mg/m^2 proposed human dose

c Degradates of concern based on 40% degradate studies (Study Nos. RPR/RD/CRVA/SM 93-0357 and RPR/RD/CRVA/SM 93-0430)

Submission received from sponsor dated May 10, 1995 indicated the limit of quantification for each of the products of degradation to be 0.1%; the sponsor indicated the limit of detection to be 0.2% during the telecon of May 5, 1995.

Conclusions and Recommendations:

1. Comparison of the individual degradate doses administered to mice and doses proposed clinically indicate that mice received higher doses than those requested for drug product specification on a mg/m^2 basis. However, the study from which these concentrations were determined did not demonstrate relative toxicity to nondegraded taxotere and did not perform macroscopic or microscopic observations. There was no indication of clinical examination for neurotoxicity in these animals.

2. Even though neurotoxicity was increased in the 40% degradation studies (Study Nos. RPR/RD/CRVA/SM 93-0357 and RPR/RD/CRVA/SM 93-0430) as compared to undegraded taxotere, histopathology was also not performed.

3. In order to provide data for unanswered questions and to set limits of degradants for approvability if requested clinical data are not forthcoming, Pharm/Tox has requested the following study to be performed.

Recommended additional study to Rhone Poulenc on 5/5/95 (telecon):

Repeat of degradant study (RPR/RD/CRVA/SM 94-0087) conducted with 5 daily doses; study should indicate quantities of each degradant with detailed analytical methodology used to determine concentrations.The study must demonstrate relative toxicity of degradants and undegraded taxotere (positive control). The mouse strain used in previous studies should be repeated (CD_2F_1). Clinical observations for hindlimb paralysis and nonextension of hindlimbs, and histopathology of the sciatic nerve should be included.

Margaret E. Brower, Ph.D.
Pharmacologist/Toxicologist
May 22, 1985

cc:
Original NDA
/Division File HFD-150
/MBrower Reviewed 5/8/95, resubmitted 5/22/95
/JDeGeorge 5/8/95
/JBeitz
/DPease

1157 - 5/24/95

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum 3 to NDA

NDA No. 20,449

3-27-95 4-3-95

Date(s) of Submission: March 30, 1995, April 10,1995
Received by Reviewer: April 6, 1995, April 13, 1995, May 1, 1995

Information to be conveyed to sponsor: Yes( ), No (X)

Reviewer(s): Margaret E. Brower, Ph.D.

Date Review Completed: April 12, 1995, April

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Additional Preclinical Studies Submitted:

12-Cycle toxicity study in cynomolgus monkeys (each cycle consisting of a single intravenous infusion every 3 weeks) over a 9-month period. Report No. RPR/RD/CRVA/SM 92-0292. 1994.

Pulmonary toxicity of different formulations in male rats following a single-dose intravenous administration. Report No. RPR/RD/CRVA/SM 94-0098. 1994.

4-Week intravenous toxicity study of polysorbate 80 in rats. Study No. RP931221994.1994

Toxicology review:
12-Cycle toxicity study in cynomolgus monkeys (each cycle consisting of a single intravenous infusion every 3 weeks) over a 9-month period. Report No. RPR/RD/CRVA/SM 92-0292.

The study was conducted at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1994; the study was not conducted according to GLP. Taxotere (batch #FCH 162; purity 100% in a 40mg/ml stock solution of polysorbate 80) was administered to cynomolgus monkeys (3 animals/sex/group) at doses of 0, 25, or 50mg/m^2 per iv infusion (dosing

volume 1.4, 2.0-2.6, and 4.3-4.9ml/kg, rate of infusion 1ml/min) once every 3 weeks for a total of 12 doses.

Measurements and observations

Daily	Mortality, clinical examination
One week prior to necropsy (control and LD)	Complete physical examination with particular attention to potential presence of edema
Weekly	Body weight
Pretreatment, 6-7 days, and 3 weeks following each infusion	Hematology, clinical chemistry

Plasma drug concentrations
Blood samples were obtained for plasma drug concentrations following the first and eighth infusion (9 study intervals); results were not reported.

Data on plasma drug concentrations received from Rhone-Poulenc on 5/1/95 following request: Plasma levels were determined on day 1 immediately following dosing and 24 hrs following dosing in LD and HD monkeys. Immediately following dosing, plasma levels ranged from ug/ml and ug/ml in males and females administered 25mg/m^2/day, respectively; plasma levels ranged from ug/ml and ug/ml in males and females administered 50mg/m^2/day, respectively. Plasma levels of 0.46, 0.82, and 0.86 reflected those animals with edema at the infusion site. Plasma levels of taxotere were not detected 24 hours following dosing in males or females.

Plasma levels were also determined on pooled blood samples at 5, 15, 30 min, and 2, 6, 10 and 24 hours following dosing of LD animals. Plasma levels were 0.63 and 0.57ug/ml in males and females, respectively, 5 mins following dosing. Fifteen mins following dosing, plasma levels decreased to 0.11 and 0.17ug/ml in LD males and females, respectively. Taxotere was not detected at 30 mins following dosing. Taxotere appears to rapidly disappear from the circulation.

Mortality

Due to severe toxicity, monkeys administered a single dose of 50mg/m^2 were removed from the study; 4/6 monkeys (3 males, 1female) were sacrificed moribund on study days 8, 9, 15, and 16. One male administered 25mg/m^2 was sacrificed moribund on study day 123 due to a severe injury to the right paw. Animals which completed the study were sacrificed 3 weeks following the final treatment.

Clinical observations

Within 2 weeks following the first infusion, 4/6 monkeys (3 males, 1female) administered

50mg/m^2 exhibited reduced motor activity, hyporeactivity, severe hypothermia, and severe diarrhea; multiple cutaneous lesions were observed in two of the animals (1/sex). Ataxia and tremors were exhibited in 1HD male and female, respectively. No edema was observed following the first treatment.

Moderate to severe diarrhea was observed up to 5 days following each 25mg/m^2 infusion in up to 4/6 animals for a duration of up to 8 days. Vomiting was observed sporadically following infusion in two LD animals; one control was observed to vomit on one occasion. Facial erythema was exhibited following infusion in one LD and control animal. No edema was observed.

Body weights and food consumption

Body weights of HD monkeys were depressed 9-18% when compared to pretest weights. Body weights of LD monkeys were depressed 5-10% following the first infusion when compared to pretest weights; body weight gains remained lower than control weight gains in male monkeys.

Food consumption was determined qualitatively. Food consumption was depressed in HD monkeys until sacrifice and in monkeys administered 25mg/m^2 following the first infusion only.

Hematology

Red cell indices (red cell counts, hgb, hct) were depressed up to 26% when compared to pretest values in one HD male sacrificed moribund on day 15; red cell indices of other HD monkeys were similar to pretest values. Leukocytes were depressed 36-93% in HD animals when compared to pretest values following the initial infusion.

Red cell indices were depressed up to 30% in LD animals when compared to pretest values within 1 week following each infusion; associated depressions in reticulocyte counts (up to 80%) were observed in these animals. Males were effected to a greater extent as compared to females. Partial hematological recovery associated with reticulocytosis was exhibited in week 3 following each infusion period. Leukocytes were depressed 70-80% in these animals when compared to pretest values following each infusion; lymphocyte and neutrophil counts were depressed approximately 62 and 99% of pretest values, respectively. Rebound hyperplasia of white cells occurred during week 3 following each infusion period. Platelet counts appeared to follow a similar pattern.

Clinical chemistry

Cholesterol and glucose levels were increased 30-50% and up to 74% respectively in LD animals when compared to pretest values within 1 week of infusion; levels returned to control range within 3 weeks of infusion.

Organ weights

Organ weights of HD animals were not measured. Absolute thymic and pituitary weights of LD monkeys were slightly depressed; absolute liver, lung, heart, thyroid, prostate, uterus, ovarian, and spleen weights were increased as compared to concurrent controls. Increased

absolute weights ranged up to 45%; relative weights of these organs were slightly increased. There were no correlating macroscopic findings, histopathological observations were not performed.

Macroscopic observations
Macroscopic observations were unremarkable. There was no evidence of edema.

Histological examinations were not performed.

Pulmonary toxicity of different formulations in male rats following a single-dose intravenous administration. Report No. RPR/RD/CRVA/SM 94-0098. 1994.

The study was conducted at Rhone-Poulenc Rorer, Centre de Recherche de Vitry, Alfortville, France in 1994 according to GLP. Taxotere (batch # FCH 160, purity 98.1%) was administered iv to Sprague-Dawley rats in an 80mg/ml non-filtered polysorbate solution, a 80mg/ml filtered (0.22um) solution, and a 40mg/ml filtered (0.22um) solution; formulations containing concentrations of 1 and 2 mg/ml taxotere were prepared from these solutions. Dose levels were 10 and 20 mg/kg/day in taxotere-treated animals; controls received 5% glucose solution containing 5% polysorbate or 0.9% NaCl solution containing 5% polysorbate.

A previous single-dose iv toxicity study in rats (RPR/RD/CRVA/SM 700) conducted at doses of 10, 20, 30, and 40mg/kg taxotere resulted in single cell necrosis in the lung. The formulation used was prepared by dilution of an 80mg/ml non-filtered polysorbate stock solution in 5% aqueous glucose. Since these changes were not observed in subsequent multidose studies at less concentrated (40mg/ml) and filtered polysorbate solutions, the pulmonary changes were considered by the study author to be a result of precipitation of taxotere during dilution of the non-filtered stock solution and subsequent accululation of particles in the lung. The purpose of this study was to investigate the pulmonary toxicity of intravenous formulations of taxotere prepared from different stock solutions. Dose levels of 10 and 20mg/kg corresponded to dose levels which produced pulmonary changes in the earlier study.

Measurements and Observations

Daily	Mortality, clinical observations
Weekly	Body weight
Day 4 and day 29	Sacrifice 3 and 28 days following dosing; organ weights, macroscopic examination and histopathology of lungs and testes

Visual Appearance of administered solutions

Following administration of formulations, visual appearance of 80mg/ml filtered and non-filtered solutions appeared cloudy and contained a precipitate, whereas the 40mg/ml filtered solution appeared clear.

Mortality and clinical examination

No mortality occurred during the study. Alopecia was observed in all HD animals.

Body weight

Body weights of LD rats were depressed 19-26% from study days 8 to 28 when compared to concurrent controls. Body weights of HD animals were concurrently depressed 29-37% during this same study duration.

Organ weights

Depressions in lung weights were dose-related; absolute and relative lung weights of HD animals were ≈12% lower than weights of control and LD animals. There were no other organ weights measured.

Macroscopic and microscopic observations

Only male rats were examined microscopically; in addition, histopathology was restricted to lungs and organs with macroscopic changes (testes).

Soft and/or small testes were observed in 13/30 LD and HD animals which correlated with tubular degeneration of the testes observed histologically.

Lung changes (necrosis, abnormal mitosis of alveolar mononuclear cells on day 4 and increased alveolar macrophages on day 29) were observed in 5/5 LD and HD animals administered the 80mg/ml non-filtered polysorbate solution and sacrificed on day 4 and 4/5 and 3/5 animals sacrificed on day 29. One of five HD rats administered the 40mg/ml filtered polysorbate solution and sacrificed on day 4 exhibited lung necrosis and 1/5 LD animals of this same group sacrificed on day 29 exhibited increased macrophages.

Intravenous administration of taxotere prepared from non-filtered stock solutions which contain precipitate produce pulmonary histopathologic changes.

4-Week intravenous toxicity study of polysorbate 80 in rats. Study No. RP931221994. 1994.

The study was conducted at according to GLP. Polysorbate 80 (lot GW930080) supplied by Rhone-Poulenc Rorer, Japan and used as the vehicle for taxotere, was administered to Crj:CD(SD) rats (10 rats/sex/group) at doses of 0, 150, 300, and 600 mg/kg per iv infusion (dosing volume, 10mg/kg; rate of infusion, 1 ml/min) once daily for 4 weeks. Doses were determined based on a preliminary study in which polysorbate 80 was administered iv at doses between 100 and 600mg/kg.

Data was not submitted in tabulated or graphic format.

Measurements and observations

Daily	Clinical signs
Twice weekly	Body weight, food consumption
Study week 4	Urinalysis
Study termination	Hematology, clinical chemistry, myelogram, gross pathology, organ weights, histopathology

Mortality and clinical observations

No mortality occurred during the study. Beginning on study day 5, irregular respiration and decreased movement were observed immediately following dosing in 3/5 and 2/5 male and female animals, respectively. Animals recovered within 40 mins of dosing.

Body weights and food consumption

There were no changes in body weight and food consumption between treated animals and concurrent controls.

Hematology

Hemoglobin concentration was reported to be significantly depressed in HD females only; numerical data was not provided. Decreased mean corpuscular hemoglobin concentrations (MCHC) were observed in MD and HD females. Myelograms indicated a significant increase in basophils of HD males, numerical data were not provided. There was no reported changes in the hematological parameters of other dosed animals. Polysorbate has been confirmed to induce hemolysis.

Clinical chemistry and urinalysis

Bilirubin levels were reported to be depressed in LD and MD males; depressed levels were not dose-dependent. No other blood chemistry changes were observed in dosed animals. Numerical data were not provided. Urinary specific gravity of HD males was significantly decreased.

Macroscopic and microscopic observations, and organ weight changes

There were no macroscopic changes observed. Adaptive changes to polysorbate included foamy swelling of Kupffer cells of liver, swelling of cells of the reticuloendothelial system of the spleen, associated with increased splenic weight, and vacuolation of the proximal tubular epithelium of the kidneys in all dosed animals. Slight extramedullary hematopoiesis was observed in 1/5 MD males and females and 3/5 HD males and females. Eosinophilic crystals were observed in the proximal tubular epithelium of the kidneys of MD and HD males.

Conclusions:

The cynomolgus monkey was used as a model for the investigation of fluid retention observed in man. Clinical and macroscopic observations indicated no evidence of edema. Hematological indices were depressed in a similar manner as compared to other species administered taxotere (rats, dogs). Studies of plasma levels of taxotere indicated rapid elimination from the circulation (30 min). The potential toxicity and fluid retention properties of the vehicle component of taxotere (polysorbate 80) were studied in rats; there was no evidence of edema although swelling of cells of the liver, reticuloendothelial system and kidney were observed.

Filtered and nonfiltered formulations of taxotere were administered to rats in order to assess pulmonary toxicity. Twenty percent (1/5) animals administered the 40mg/ml filtered polysorbate solution (clinical formulation) exhibited lung necrosis.

Recommendations:

Even though the reviewed studies did not elucidate the mechanism of fluid retention in humans, the monkey model was considered to be the model of interest for this consideration. The sponsor should submit the edema data using the mouse model when it becomes available. In addition, G. Herman, Ph.D., DRT Pharmacology/Toxicology, has forwarded a protocol for the study of taxotere-induced fluid retention to Rhone Poulenc Rorer in order to obtain the clinical formulated product for use in this research. The sponsor has not yet submitted a reply.

As a result of the above pulmonary toxicity study, the lung tissue will be examined for possible lung necrosis during the abovementioned study.

Margaret Brower

Margaret E. Brower, Ph.D.
Pharmacologist/Toxicologist
April 12, 1994
May 19,1995

cc:
Original IND
/Division File HFD-150
/MBrower Submitted 4/12/95; review returned 5/16/95; resubmitted 5/19/95
/JDeGeorge JJ V 5/21/95
/JBeitz
/DPease

JAN 25 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum 2 to NDA

NDA No. 20,449

Date(s) of Submission: July 27, 1994
Received by Reviewer: August 21, 1994
Information to be conveyed to sponsor: Yes( ), No (X)

Reviewer(s): Margaret E. Brower, Ph.D.
C. Joseph Sun, Ph.D.

Date Review Completed: October 21, 1994

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Hypersensitivity in guinea pigs

Anaphylactic shock in the guinea-pig; Study No. ST/CRVA/IRSM N500

Hartley guinea pigs were administered ip taxotere in a polysorbate 80/ethanol (50/50) vehicle solution at doses of 0.25 or 0.50mg/kg in four sensitizing treatments over a 7-day interval in order to evaluate the anaphylactogenic activity of the drug. Fourteen days following the first sensitizing treatment, the animals were challenged by a single iv dose containing the same drug concentration. Control animals received the vehicle or ovalbulmin (positive control). No anaphylactogenic activity was observed at either dose level of taxotere.

Margaret E. Brower, Ph.D.
Pharmacologist/Toxicologist

cc: 1572
Original NDA
/Division File
/MBrower
/ D.Pease

/JSun
/JDeGeorge
/JBeitz
/DPease
/ATaylor

12/24/67

N. Leone

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum 1 to NDA

NDA No. 20,449

Date(s) of Submission: July 27, 1994

Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer(s): Margaret E. Brower, Ph.D.

Date Review Completed: October 21, 1994

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5 ß, 20-Epoxy- 1,2 a, 4, 7 ß, 10 ß, 13 a-hexahydroxytax- 11 -en-9-one 4- 10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Issue: Degradation products of taxotere

Degradation product/ sponsor limit requested (limit of degrada.prod. in clinical trial infusion)	Toxicology data	Results (Undegra Taxot LD_{10} =285-468mg/m2) mouse model
RPR 70617 to 4% (<0.3%)	Acute (single iv) toxicity 28 day observation	LD_{10} = 121mg/kg (363mg/m2); no neurotox; equally toxic to taxotere
RPR 73077 to 2.5% (0.2-0.3%)	Acute (single iv) toxicity 27 day observation	LD_{10} = 171 mg/kg (513mg/m2); LD50 = 230mg/kg; no neurotox; less toxic than taxotere
RPR 110928 to 1% (<0.1%)	No data	
RPR 112248 to 0.5% (<0.1%)	No data	

RPR 104952	Acute (single iv)toxicity 21 day observation	LD_{10} =90mg/kg(270mg/m2); deaths on day 1; neurotox signs(absence of hindlimb extension reflex@ 210mg/m2,convulsions@300mg/m2, paresis@360mg/m2; absence of reflex and paresis persisted to study termin; more toxic than taxotere
RPR 104943	Acute (single iv)toxicity 21 day observation	LD_{10}=200mg/kg(600mg/m2); convulsions (1/20); less toxic than taxotere

One single-dose lethality and one 5-day lethality study were submitted using a stock solution of taxotere stored for 11 days at 45°C; degradation was indicated to be 40%. Primary degradation products were indicated to be RPR 70617 (37-39.5% of single-dose study solution; 36.6-37.6% of five-dose study solution) and RPR 73077 (0.2-0.3% of single-dose study solution; 0.4% of five-dose study solution). Undesignated degradation products equalled 2.7-3.4% and 2.1-2.3% of single- and five-dose study solutions, respectively.

RP 56976 (40% degraded) single-dose iv lethality study in mice with a 28-day observation period Study No.RPR/RD/CRVA/SM 93-0357

CD2F1 mice were administered iv solutions of taxotere (40% degraded following 11 days of storage at 45°C) at doses of 61, 80, 106, and 140mg/kg (183, 240, 318, 420mg/m2). Animals were dosed one time and observed for an additional 28 days. Mortality was primarily on study day 1 and was continued to day 12.

Concentrations of taxotere and degradation products combined were 2.44, 3.20, 4.24, and 5.6mg/ml for the 4 dose levels. The concentration of the degraded portion of the doses were 0.976, 1.28, 1.7, and 2.24mg/ml (based on 40%degradation). The average amount of unidentified degradate/degradates were 2.0% of the above concentrations, ie. 0.02
8, 0.037, 0.049, and 0.065mg/ml (based on 5 sample analyses). The remaining 38.5% of the degradate concentration was composed of RPR 70617 and 73077, found to be less toxic or equally toxic to taxotere.

Mortality:

mg/kg	mortality rate
14% PS80	6/20(♂+♀, day1-3)
10 6%PS80	0/20
61	0/20
80	0/20
106	9/20(♂+♀, day 1-12)
140	20/20(♂+♀, day 1-3)

The 10.6 and 14% PS80 vehicle solutions correspond to the PS concentrations used in the 106 and 140mg/kg taxotere doses, respectively. Convulsions occurred immediately following dosing; ataxia, prostration, and dypsnea were also observed at this time and increased in incidence and severity with increase in dose level. Absence of extension of hindlimbs was exhibited in 20/20 mice administered 61 and 80 mg/kg, respectively, and 12/12 surviving mice administered106mg/kg; paresis of hindlimbs was also exhibited in these surviving mice from study day 10 to study termination. Absent hindlimb extension was observed from study day 6 to day 20 at the low dose, and extended to study termination at 80 and 106mg/kg.

Body weights of surviving animals were depressed 3-4%, and 7-12% at 80 and 106mg/kg, respectively, from study days 1 to 8; body weights increased between days 8 and 29. Animals were not submitted to gross or microscopic examination.

LD_{10} NA
LD_{50} ~106mg/kg

RP 56976 (40% degraded): 5-day iv lethality study in mice with a 4-week observation period Study No.RPR/RD/CRVA/SM93-0430

CD_2F_1/CrlBR mice were administered iv stock solutions of taxotere (40%degraded following 11 days storage at 45°C) at doses of 15, 21, 29, or 41 mg/kg(45, 63, 87, 123mg/m2) in PS80 +5% glucose (4.1%PS80). Control animals received the polysorbate vehicle. Animals were dosed for 5 days and observed for an additional 29 days.

Concentrations of taxotere and degradation products combined were 0.6, 0.84, 1.16, and 1.64mg/ml for the 4 dose levels. The concentration of the degraded portion of the doses were 0.24, 0.336, 0.464, and 0.656mg/ml (based on 40%degradation). The average amount of unidentified degradate/degradates were 2.2% of the above concentrations, ie.0.00528, 0.00739, 0.0102, and 0.0144mg/ml (based on 5 sample analyses). The remaining 37.5% of the degradate concentration was composed of RPR 70617 and 73077, found to be less toxic or equally toxic to taxotere.

Mortality:

mg/kg	mortality rate
0	0/20
15	0/20
21	2/20 (♂, day 8-17)
29	13/20(♂-♀, day 8-12)
41	19/20(♂+♀, day 7-10)

Clinical signs included absence of hindlimb extension in all dosed animals, and paresis of hindlimbs at 21, 29 and 41mg/kg. Additional findings included head edema, dyspnea, and prostration; all findings increased with duration of dosing and were dose-related. The absence of hindlimb reflex reversed in LD animals by the end of the observation period.

Body weights were depressed up to study day 15; depressions were 13-16%, 24%, 28-31%, and up to 32% in surviving animals administered 15, 21, 29, or 41mg/kg degraded taxotere. Body weights remained depressed following recovery.

	♂	♀
LD_{10}	20	24
LD_{50}	25	30
HNLD	7.5	10.5

Acute lethality studies previously reviewed for taxotere (undegraded):

Study No. 89/RHS058/0539 PS80+ethanol-single dose
LD_{10}= 95mg/kg
LD_{50} >156mg/kg
Mortality: 1/20 @95mg/kg
1/20 @156mg/kg

Dose (mg/kg)	Nonextension of hindlimbs	Paresis of hindlimbs
74	1/20	0/20
95	10/19	3/19
121	14/20	0/20
156	18/19	13/19

Histopathology:
Pale areas of heart in 9/19mice @156mg/kg; untreated control incidence 6/20
Small testes at 74, 121, 156mg/kg

Study No. RPR/RD/CRVA/SM 553 (9/91) PS80- single dose
LD_{10}=115 (101-130)mg/kg in ♂
LD_{50}=138 (126-150)mg/kg in ♂; 64-95mg/kg in ♀

Mortality (N= 10/sex) in control and treated mice

dose level (mg/kg)	# deaths (day of death)
121(♂)	1(d1), 1(d7)
156(♂)	6(d1), 1(d7), 1(d14)
control(♀)	1(d1)
64(♀)	1(d1), 1(d11)
95(♀)	7(d1), 1(d2), 2(d8)
121(♀)	10(d1)
156(♀)	10(d1)

Nonextension and paresis of hindlimbs at all doses

Study No. 90/RHS 059/0177 (7/90) PS80+ ethanol-single dose

Mortality: 3/20(@156mg/kg
Clinical signs:
Nonextension of hindlimbs @ 48, 95, 156mg/kg, paresis of hindlimbs @156mg/kg
Histopathology:
Axonal degeneration of sciatic nerve and myofibril degeneration @48,95,156mg/kg

No five-day lethality study available with docetaxel and PS80 without addition of ethanol.

Study No.89/RHS061/0919 (3/90)
Five-day lethality study of docetaxel in PS80 + ethanol
LD_{10}= 20mg/kg, combined sex (60mg/m^2)
LD_{50}= 30mg/kg, combined sex (90mg/m^2)

Delayed neuromotor changes: non-extension, paresis and swelling of hindlimbs from days 6-8; non-extension exhibited in all dose groups, paresis @ 54 and 64mg/m2.

COMPARISON OF TAXOTERE AND DEGRADED TAXOTERE LETHALITY IN MICE (MG/KG)

		NONDEGR TAX (PS80 +ETOH)	NONDEGR TAX (PS80)	DEGR TAX (PS80)
SINGLE DOSE	LD_{10}	95	115	<106
	LD_{50}	>156	138	>106
FIVE-DAILY DOSE	LD_{10}	20	NA	20-24
	LD_{50}	30	NA	25-30
	HNL D			7.5-10.5

Comparisons of incidences of neuromotor changes in mice in single-dose and five-dose studies

Study	Dose (mg/kg/day)	Incidence of NEHL[1]	Incidence of paresis of HL	Days of onset-recovery of NEHL and paresis
Single dose (PS80+etoh)	74	0/20	0/20	4 -
	95	10/19	3/19	9-11 9
	121	14/20	0/20	6-12 -
	156	18/19	13/19	7-T[2] 8-T
Single dose (PS80)	64	8/19	-	7-13 -
	95	8/12	1/12	8-28 10-28
	121	9/9*	1/9	4-28 3-6
	156	3/4*	3/4	7-28 8-28
Single dose (40% degra)	61	20/20	0/20	6-20 -
	80	20/20	0/20	6-T -
	106	12/12*	12/12	6-T -T[3]
	140	-*	-[4]	
Five dose (PS80+etoh)	15	14/20	0/20	6-17 -
	18	20/20	1/20	6-30 13
	21.6	20/20	11/20	6-33 8-22
	26	20/20	20/20	6-33 8-20
	31.2	17/20	3/20	6-33 8-33
	37.5	18/20	15/20	6-33 8-33
Five dose (40% degra)	15	19/20	0/20	8-26 -
	21	19/20	16/19	8-T 8-T
	29	20/20	18/20	8-T 8-T
	41	19/19	18/19	5-T 8-T

1 Non-extension of hindlimbs
2 To study termination
3 Onset not specified; continued to study termination
* Decrease in total number of animals due to mortality
4 Dose-related increased severity of convulsions in all animals immediately following dosing

Single- dose studies reported precipitation of drug at the time of dosing. In a single-dose study in which mice were administered 10, 48, 95, and 156mg/kg(30, 144, 285, and 468mg/m^2) taxotere iv, myelin degeneration of the sciatic nerve was observed 4 days following dosing at levels ≥48mg/kg; axonal degeneration was observed at the HD. Body spasms and paralysis of the hindlimbs were concurrently observed. Twenty-nine days following dosing at levels ≥95mg/kg, axonal degeneration and degeneration of the sciatic nerve continued to be observed. In a 5-day dosing study in which mice were administered 2, 10, 20, and 30mg/kg (6, 30, 60, and 90mg/m^2) taxotere iv, axonal degeneration of the sciatic nerve and schwann cell proliferation were observed at doses as low as 10mg/kg; myelin degeneration was observed at 20mg/kg.

Summary

In the single dose and five dose studies, mortality appears to be similar following dosing with non-degraded taxotere in PS80+etoh, non-degraded taxotere in PS80 alone, or 40% degraded taxotere. In single dose studies, neurotoxicity is exhibited with greater severity following dosing with 40% degraded taxotere; animals exhibited convulsions at all doses following dosing and 20/20 mice exhibited nonextension of hindlimbs at a lower dose and earlier in time following dosing (61 mg/kg at day 6) when compared to other single-dose studies. Taxotere in PS80 appeared to display similar neurotoxicity to taxotere in PS80+etoh following a single dose. Following five daily doses, 40% degraded taxotere appeared to exhibit increased neurotoxicity (greater incidence of paresis of hindlimbs and nonextension of hindlimbs) as compared to taxotere in PS80+etoh.

Recommendation:

Sponsor must submit a listing of the undisclosed degradation products (2-3.5%) contained in the 40% taxotere degration batches.

Margaret Brower

Margaret E. Brower, Ph.D.
Pharmacologist/Toxicologist
October 21,1994

Response to Recommendation:

Rhone Poulenc Rorer (Meg Martin) responded to the recommended listing of degradation products contained in the 40% taxotere degradation studies on 11/16/94 She indicated that all degradate quantities listed in these studies "should be interpreted as a very rough approximation". This is interpreted to indicate that the specific quantities of indicated degradates as well as the possible presence of additional degradates contained in these studies is unknown.

Additional data on degrad .e composition and toxicity is forthcoming

cc:
Original IND
/Division File
/MBrower Reviewed 10/21/94, resubmitted and updated 5/9/95
/JDeGeorge
/JBeitz
/DPease

5/13/95

JAN 25 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original, Review No. 1

NDA No. 20,449

Date(s) of Submission: July 27, 1994
Received by Reviewer: August 21, 1994
Information to be conveyed to sponsor: Yes(X), No ( )

Reviewer(s): Margaret E. Brower, Ph.D.
C. Joseph Sun, Ph.D.

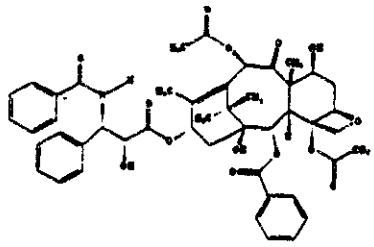
Date Review Completed: October 21, 1994

Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: Taxotere Other Names: Docetaxel, RP56976

Chemical Name: 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Structure:



Molecular Weight: 861.9

Related INDs/NDAs: IND IND NDA 20262 (Taxol)

Class: Cytotoxic Antineoplastic Agent

Indication: Locally advanced or metastatic breast carinoma, locally advanced or metastatic non-small cell lung cancer

Clinical Formulation: Single dose vials containing 20mg or 80mg taxotere in polysorbate 80

Route of Administration: 1-hour iv infusion

Previous Review(s), Date(s) and Reviewer(s):
Original Review 11/28/90 AW Coulter
Review #2 11/25/92 AW Coulter
Review #3 6/17/94 CJ Sun

Studies Reviewed in this NDA:
Pharmacology
1. In vitro antitumor cytotoxicity
2. In vivo antitumor activity
3. Mechanism of action
4. In vitro and in vivo effects of metabolites
5. In vitro and in vivo effects of degradation products

Toxicology
1. 4-Week intravenous toxicity study of RP56976 in rats; Study no.RPR/RD/CRVA/SM 698
2. 3-Cycle toxicity study in rats (each consisting of a single intravenous administration of 21 days) over a period of 6 weeks followed by a 4-week reversibility period; Study no. RPR/RD/CRVA/SM 92-0118
3. RP 56976 - 10-cycle toxicity study in rats (each cycle consisting of a single intravenous infusion every 3 weeks) over a 6-month period followed by a 1-month reversibility period. Study No. RPR/RD/CRVA/SM 92-0026, Vols 1.34-1.39.
4. RP 56976 - 10-cycle toxicity study in dogs (each cycle consisting of a single intravenous infusion every 3 weeks)over a 6-month period followed by a two-month reversibility period. Study No. RPR/RD/CVRA/SM 92-0239, Vols 1.42-1.44.
5. Fertility and general reproduction study of RP 56976 administered intravenously to CRL:CD BR VAF/+rats (segment 1 evaluation) Study No.DS 92-090 Vols. 1.47- 1.48.
6. RP 56976 Intravenous teratology study in rats with postnatal development phase. Study No.RPR/RD/CRVA/SM 710. Vol 1.49.
7. Teratology study of RP 56976 in the rabbit by the intravenous route. Study No. RPR/RD/CRVA/SM 707. Vol.1.50.
8. Intravenous peri and post-natality (segment III) study in rats with reproductive performance of the F1 generation. Study No. RPR/RD/CRVA/SM 92-0117. Vol 1.5.
9. In vitro gene mutation test of RP 56976 on Escherichia coli strain WP2 uvr A Study No. RPR/RD/CRVA/SM 637 Vol.1.51
10. Chromosome aberration test in Chinese Hamster Ovary cells (CHO-K1) Study No. ST/CVRA/IRSM 508 Vol. 1 51
11. Effect of RP 56976 on the distribution of CHO-K1 cells in the cell cycle phases Study No. ST/CRVA/TOX 407 Vol. 1.51
12. Hypoxanthine-guanine phosphoribosyl transferase gene mutation test in Chinese Hamster Ovary cells (CHO-K1) Study No.RPR/RD/CRVA/SM 550 Vol. 1.51

13. Bone-marrow micronucleus test in the mouse by intravenous route
Study No. RPR/RD/CRVA/SM 544 Vol.1.51
(Several additional toxicology studies reviewed but not included in data below)

Pharmacokinetics
1. RP 56976 Toxicokinetics after intravenous administration to beagle dog once every 21 days over 28 weeks (0.1, 0.375 and 1.5mg/kg) Study No. IBP/Biodyn. No 1773, Vol 1.54.
2. RP 56976 Toxicokinetics after intravenous administration to rats once every 21 days over 28 weeks (0.2,1 and 5mg/kg) Study No. IBP/Biodyn. No. 1774; Vol 1.53.
3. Pharmacokinetics (absorption, distribution, metabolism, and excretion)

Impurities
1. Acute intravenous toxicity study of RP70617 in the mouse Study no. RPR/RD/CRVA/SM 672 Vol 1.45
2. RP73077: Single dose intravenous lethality study in mice with a 27-day observation period Study no. RPR/RD/CRVA/SM 93-0065 Vol 1.45

Studies Not Reviewed in this NDA:
1. Local intravenous, paravenous and intra-arterial tolerance in rabbits; Document No. 5.75

Studies Previously Reviewed (Appendix 1):
Original review:
1. Acute intravenous lethality study in the mouse; Study No. 89/RHS 058/0539
2. Acute toxicity study by intravenous administration to beagle dogs followed by an eight week observation period; Study No. 90/RHS 048/0115
3. Five-day subacute intravenous lethality study in the mouse; Study No. 89/RHS 061/0919
4. Five-day subacute intravenous toxicity study in the mouse; Study No. 90/RHS062/0336
5. Toxicity study by intravenous administration to beagle dogs for five days followed by an eight week observation period; Study No. 89/RHS 049/1124
6. Toxicity study by intravenous administration to beagle dogs every 21 days over 12 weeks followed by a further 8-week observation period; Study No. 90/RHS050/0690
7. Preliminary results of experimental anti-tumor activity of RP 56976; Study No. ST/CRVA/BIOL 135
8. In vivo evaluation of RP56976 against murine tumors; Study No. ST/CRVA/BIOL 134
9. In vitro mutagenicity: Ames test (Salmonella typhimurium); Study No. ST/CRVA/IRSM 508
10. Micronucleus test in chinese hamster ovary cells (CHO-K1); Study No. ST/CRVA/TOX 407

Review No. 2
1. Preliminary results of experimental anti-tumor activity of RP 56976; Study No. ST/CRVA/BIOL 135
2. Lethality study in the mouse by intravenous route; Study No. RPR/RD/CRVA/SM 55
3. Sensitization in the rabbit; Study No. RPR/RD/CRVA/SM 563

4. RP 56976 and its vehicle solution (100% polysorbate 80); In vitro study of the compatibility and hemolytic potential with human blood; Study No. RPR/RD/CRVA/SM 562

Review No. 3
1. Acute intravenous toxicity study of RP56976 in rats with four-week observation period; RPR/RD/CRVA/SM 700
2. Acute intravenous toxicity study in the mouse; Report No. 90/RHS/ 059/0177

Note: Portions of this review were excerpted directly from the sponsor's submission.

Pharmacology
In vitro antitumour cytotoxicity

Antiproliferative activity and cytotoxicity in tumour cell lines: Cytotoxicity of docetaxel was evaluated in several murine and human long term cell culture lines (P388 murine leukemia, SV ras murine fibrosarcoma, Calc 18 human breast adenocarcinoma, HCT 116 human colon adenocarcinoma, T24 human bladder carcinoma and human epidermoid carcinoma). IC_{50} values of docetaxel ranged from 4 to 35 ng/ml. The cytotoxic effects were greater on proliferating than on non proliferating KB human epidermoid carcinoma cells. These effects were found both time and concentration dependent on proliferating cells . In comparison with paclitaxel, docetaxel was more cytotoxic (1.3-12 fold) a result that could be explained by its more potent activity on microtubules .

Resistance: A paclitaxel-resistant mouse macrophage cell line, J774.2/paclitaxel (J774-TAX-50), was used to evaluate the cross-resistance to docetaxel . This cell line displays the MDR phenotype with the amplification of P-glycoprotein (P-gp). Docetaxel was about 5-fold more potent than paclitaxel in inhibiting the replication of the J774.2/paclitaxel cell line. Five cell lines expressing the classic MDR phenotype involving both the expression of resistance to vincristine or etoposide and overexpression of P-gp (MCF-7/VCR6E, MCF-7/VCR/DXR, CEM/VLB1000, CHO/CHRC5, and CHO/DOCE-R) proved cross resistant to docetaxel. However, six other sublines known to significantly overexpress P-gp and to show only some resistance to vincristine and to etoposide (CHO/AUX-10E, CHO/DXR-101, CHO/DXR-1011, SKOV3/DXR-10, Susa/VPC3 and Susa/VPC4) showed a lack of cross-resistance to docetaxel. There was a lack of cross-resistance to 5-fluorouracil or to cisplatin in certain cell lines(COLO/5-FU-R and LOVO/5-FU-R) established by colony forming assay methodology after 24h drug exposure. The antiproliferative action of docetaxel was also studied and compared to paclitaxel in a variety of freshly explanted human tumor cells at clinically achievable plasma concentration. Cytotoxicity of docetaxel and paclitaxel was observed against breast, lung, ovarian, colorectal cancer and melanoma tumor colony forming units. Twenty-nine specimens were found more sensitive to docetaxel than paclitaxel while only 13 were more sensitive to paclitaxel than to docetaxel. These data indicate that cross-resistance between these two agents was incomplete .

In vivo antitumour activity

Docetaxel was administered by the intravenous route (i.v.) except when otherwise stated.

Murine tumour models:

B16 melanoma: Docetaxel and paclitaxel were tested by an intermittent schedule (days 4, 6, 8, 10) . The highest non-toxic dosage of docetaxel was 13.4 mg/kg/day. This dosage was highly active. In comparison, the highest non-toxic dosage of paclitaxel was 21.7 mg/kg/day. This dosage was found marginally active. T/C were equivalent for both compounds at equitoxic dosage (T/C = 0%) but docetaxel gave a 2.6 higher log cell kill than paclitaxel.

Evaluation of two docetaxel formulations: Docetaxel formulated in ethanol : polysorbate 80, 50 : 50 v/v, or in polysorbate 80 alone, was administered to mice bearing early stage s.c. B16 melanoma using an intermittent schedule (days 3, 5 and 7). Both formulations were found equally active.

Colon tumours:

Colon adenocarcinoma 38: Docetaxel was found highly active with a T/C equal to 0% and cures at optimal dosage against early stage C38. For advanced stage C38, docetaxel was given on days 14, 16 and 18. The highest non-toxic dose was 26.8 mg/kg/injection. There were 5/5 complete regressions, but no cures on day 60. The compound was found active. The dosages below the H.N.T.D. retained activity.

Colon adenocarcinoma 51: Docetaxel was injected on days 3, 5 and 7 against early stage colon adenocarcinoma 51. At the H.N.T.D.(12.7 mg/kg), T/C was 2.4%, indicating a high level of activity. The tumour growth delay was 22.5 days and the log cell kill total was 2.3. Mice bearing advanced stage tumours were also treated on days 10, 12, and 14. At the H.N.T.D. - 15.2 mg/kg/injection - the tumor growth delay was 17.2 days and the log cell kill was 1.7.

Colon carcinoma 26: Docetaxel was found marginally active using a daily schedule of day 1 through to 4. The highest dosage tested was 5 mg/kg and gave a 33% T/C.

Pancreatic ductal adenocarcinoma 03: Cures were obtained at optimal dosage against early stage P03. For advanced stage P03, mice with measurable tumours were treated on days 22,

24, 26 and 28. At the highest non-toxic dose, 18 mg/kg, the agent was found to be active. There were 6/6 partial regressions, among which 5/6 complete regressions.

Lewis lung carcinoma : Docetaxel was injected on days 3 through to 7 in animals bearing s.c. early stage Lewis lung carcinoma (3LL). The H.N.T.D.(23.2 mg/kg), was active with a 5.6% T/C corresponding to a 1.23 log cell kill. The dosage below the H.N.T.D. retained activity. Lewis lung carcinoma cells (10^6) were also grafted intramuscularly on day 0. Mice were treated with 5 mg/kg on days 1 through to 4. On day 21, the percentage of inhibition of metastasis was 82% indicating good activity.

Mammary tumors:

Mammary adenocarcinoma 13/C: Docetaxel was found highly active on early stage mammary adenocarcinoma 13/C with a T/C equal to 0% and a 4.3 log cell kill total. For advanced stage, the treatment was delayed until day 14 and docetaxel was administered on days 14, 17 and 20. The highest non-toxic dose was 15 mg/kg. The tumor growth delay was 23.9 days and the log cell kill total was 2.8 .

Mammary adenocarcinoma 16/C: Docetaxel was injected on days 3, 5 and 7. At the H.N.T.D.(15 mg/kg), the tumor growth inhibition was 0% which indicates a high level of activity. The tumour growth delay was 12.7 days and the log cell kill total was 2.4.

Mammary adenocarcinoma 17/A: Docetaxel was administered on days 3 and 8. The highest dose tested (40 mg/kg) was found inactive with a 59% T/C.

Mammary carcinoma 44: Docetaxel was found marginally active using an intermittent schedule days 3, 5 and 7. The H.N.T.D. was 22 mg/kg and gave a 39% T/C.

Other solid tumours: Marginal activity was detected on Glasgow osteogenic sarcoma. The tumour growth inhibition was 27% at the highest non-toxic dose. Docetaxel was found inactive on M5076 histiocytosarcoma with tumour growth inhibition of 51%.

P388 leukemia: Docetaxel was given daily on days 1 through to 4 by the i.v. route in mice bearing P388 leukemia. The H.N.T.D. was 23.2 mg/kg and active.

L1210 leukemia: Docetaxel was given i.v. on days 1 through to 4 in mice bearing L1210 leukemia. The H.N.T.D. was 21.7 mg/kg and was active. The dosage below HNTD still observed activity.

Leukemias with acquired resistance: Docetaxel has been shown to be inactive and cross-resistant with doxorubicin and vincristine-resistant P388 leukemias, and with cisplatin and BCNU-resistant L1210 leukemias, at the highest non-toxic dosages.

Human tumor xenografts in mice: Docetaxel was evaluated in nude (NCR-Nu) mice bearing subcutaneously (sc) implanted CX-1 or KM20L2 (colon carcinomas), LX-1 (lung carcinoma), MX-1 (mammary carcinoma), and SK-MEL-2 (melanoma) xenografts. Other evaluations included OVCAR-3 (ovarian carcinoma) xenografts implanted intraperitoneally (ip). Docetaxel was administered iv every 4 days for three injections except in one OVCAR-3 experiment in which the drug was given ip three times at 7-day intervals. The highest dosage used (50 mg/kg/dose) was toxic in all experiments. The maximally tolerated dosage varied between 22 and 33 mg/kg/dose. Therapeutic responses among those xenografts ranged from clinically important long-term tumor-free survivors (MX-1, SK-MEL-2 and OVCAR-3) to tumor growth delays (CX-1, LX-1, and KM20L2) of various durations. These results are indicative of a broad spectrum of antitumour activity for docetaxel. Five additional human ovarian cancer lines grafted s.c. in nude mice were evaluated (Ov.Pe, Ov.Sh, FMa, FKo, MRI-H-207). At the maximum tolerated dose of 15-20 mg/kg administered as 2 i.v. injections, 1 week apart, docetaxel was found active in 4/5 of these human ovarian cancer lines. Docetaxel was found, active against the cisplatinum insensitive Ov.Pe tumor, more effective than cisplatin, cyclophosphamide and doxorubicin in FMa, and active in MRI-H-207 and Ov.Sh but less than cisplatin, cyclophosphamide and doxorubicin. It was found inactive against FKo.

Schedule of administration:

Docetaxel was administered i.v. by three different schedules against the docetaxel sensitive advanced colon adenocarcinoma 38.

Intermittent schedule (day 14 and 18): The H.N.T.D. was 40.3 mg/kg. The agent was found active with 4/5 complete regressions of colon adenocarcinoma C38. There was no cure on day 60 and a 1.6 log cell kill total.

Intermittent schedule (days 14, 16, 18): The H.N.T.D. was 26.8 mg/kg. It was found active with 5/5 complete regressions of colon adenocarcinoma C38 and a log cell kill total of 1.6.

Twice daily schedule for 5 consecutive days (day 16 through 22, 2 x/day): The H.N.T.D. was 5 mg/kg. It was found active but there were no regressions of colon adenocarcinoma C38. Based on these results, docetaxel is considered schedule-independent.

Mechanism of action:

Effects on DNA, RNA and protein synthesis: Docetaxel (100 μg/ml) reduced by 50% the biosynthesis of DNA, RNA and protein in P388 cells as judged by the decreased incorporation of radiolabelled precursors in the cellular DNA, RNA and proteins. Paclitaxel (200 μg/ml) was found slightly less potent than docetaxel on DNA and RNA synthesis and as active on protein synthesis. These data suggest that docetaxel was not a potent inhibitor of DNA, RNA and protein synthesis.

Effects on microtubules/tubulin system: Docetaxel has been shown to promote the assembly of tubulin into stable microtubules. Docetaxel has been found slightly more active than paclitaxel as a tubulin assembly promoter and as a microtubule stabilizer. As an inhibitor of microtubules depolymerization, docetaxel was approximately twice as potent as paclitaxel.

Docetaxel also assembled tubulin under conditions in which polymerization would not normally occur. The thermodynamic process of taxoid induced assembly of tubulin was similar for both docetaxel and paclitaxel. Docetaxel competed with paclitaxel for the same binding site on microtubule with a 1.9 times higher effective affinity. Docetaxel induced a larger decrease of the critical concentration than paclitaxel : the GTP-tubulin critical concentration is 0.05 mg/ml and 0.1 mg/ml in the presence of docetaxel and paclitaxel, respectively. Similarly, the docetaxel induced assembly of GDP-tubulin required a critical concentration of tubulin 2.1 times lower than that of paclitaxel. The tubulin polymers generated by paclitaxel differed structurally from those generated by docetaxel.

Cellular effects: The cytotoxicity of docetaxel is probably related to microtuble-mediated mitosis arrest. The effects of taxoids on the cell cycle were analyzed by flow cytometry, using five human cell lines (KB, CEM, LAUDI, and HeLa) and a rodent cell line (CHO-K1). There was an accumulation of cells in mitosis.

Cellular uptake and efflux: Uptake and efflux studies were performed on P388 leukemia cells *in vitro* with docetaxel and paclitaxel. Uptake experiments revealed that a 3-fold higher intracellular concentration of docetaxel was obtained as compared to paclitaxel , for the same initial extracellular concentration (0.1 μM). Thus, the efflux of paclitaxel from P388 cells was found to be 3-fold more rapid than that of docetaxel.

In vitro and in vivo effects of metabolites: The IC_{50} value of RPR 104952 in P388 leukemia cells was 0.34 μg/ml, which indicates that it is about 30-fold less cytotoxic than docetaxel (IC_{50} = 0.01 μg/ml). With RPR 104943, no activity against murine P388 leukemia cells was detected for concentrations up to 10 μg/ml, which means that it was at least 140-fold less cytotoxic than docetaxel. In in vivo antitumor model (B16 melanma), RPR 104952 was found

inactive against this tumor with a 115% T/C at the highest non-toxic dose (7.7 mg/kg administered on days 5, 7 and 9 post tumor implantation). RPR 104943 was also found inactive against B16 melanoma, with a 146% T/C at the highest dosage tested (32.2 mg/kg/injection on days 5, 7 and 9). RPR 104952 was found to be more toxic than the parent compound whearas RPR 104943 was less toxic than the parent compound in this animal model.

In vitro and in vivo effects of degradation products: The cytotoxicity of two docetaxel degradation products, RP 70617 and RP 73077, was evaluated *in vitro* against P388 leukemic cells. RP 70617 (IC_{50} = 0.055 μg/ml) was 1.8-fold less cytotoxic than docetaxel, whereas RP 73077 (IC_{50} = 0.038 μg/ml) was found 3.2-fold less cytotoxic than docetaxel (IC_{50} values = 0.012 μg/ml). In B16 melanoma bearing mice, RP 70617 was found modestly active at optimal dosage (30 mg/kg, x 5) with a log10 cell kill total of 0.92. RP 73077 was also found modestly active at the highest dosage tested (32.2 mg/kg x 3) with a log10 cell kill total of 0.85.

Secondary Pharmacological effects

Neuropharmacologic activity:

Behaviour: In the rat, at the dose of 10 mg/kg i.v., docetaxel did not induce any gross behavioural changes in comparison with its vehicle. Administered at doses up to10 mg/kg i.v., docetaxel also did not modify the behaviour, the neurologic state or affect the autonomic nervous system, as assessed by the Irwin-type scale, up to 240 min after administration, in comparison with the vehicle .

Spontaneous locomotor activity: Docetaxel had no effect on spontaneous locomotor activity in rats at single doses up to 10 mg/kg i.v..

Body temperature: It had no effect on body temperature in rats at doses up to 10 mg/kg i.v.

Electrocorticographic effects: Administered to rats in ethanol/polysorbate 80 / 5% aqueous glucose mixture (4/4/92, v/v/v), docetaxel (10 mg/kg i.v.) decreased the main parameters quantifying the electrocorticogram activities only in the first hour post-drug administration, in comparison with its vehicle. Seven days later, for both the vehicle-treated group and the docetaxel-treated group, no differences were seen.

Effect on electroshock- and pentylenetetrazole-induced convulsions: At doses up to 10 mg/kg i.v., docetaxel had no effects on the convulsions induced in the rat by an electroshock or by

pentylenetetrazole administration, in comparison with its vehicle.

Effect on hexobarbital-induced sleep: Docetaxel (3, 10 and 30 mg/kg i.v.,) did not modify the seative effect of hexobarbital in mice, in comparison with its vehicle.

Cardiovascular effect:

The action potential profile of the papillary muscle of guinea pigs was not changed by docetaxel at concentrations up to 30 uM.

Rat: In anesthetized or conscious rats, docetaxel, in polysorbate 80/ethanol (50/50, v/v, Formulation N° 1) and diluted in 5% aqueous glucose solution, did not affect heart rate and carotid artery blood pressure,at 9 mg/kg i.v. infused over 30 min .Docetaxel in polysorbate 80 / ethanol (50/50, v/v, Formulation N° 1) did not modify, at a dose of 9 mg/kg i.v. (over 30 min), in anesthetized pithed rats, vascular responses to the stimulation of adrenergic (after i.v. noradrenaline or electrical stimulation), angiotensin II (after i.v. angiotensin II) or serotoninergic (after i.v. serotonin) receptors, in comparison with its vehicle. It, at the same dose over 30 min, neither modified the vascular responses to the stimulation of muscarinic (after i.v. acetylcholine) or histaminergic (after i.v. histamine) receptors, in comparison with its vehicle .

Rabbit: In conscious rabbits, docetaxel infused i.v. at 3 mg/kg over 60 min was devoid of effects on blood pressure, heart rate and hematocrit, but at 9 mg/kg i.v. it produced moderate hypotensive effects (23 % decrease in mean arterial pressure) of short duration, in comparison with its vehicle .

Conscious dogs and pentobarbital-anesthetized dogs: Docetaxel infused at the dose of 1.5 mg/kg i.v. over 60 min in 1 animal produced a decrease in mean arterial blood pressure. This hypotension was accompanied by tachycardia , increase in hematocrit, plasma histamine levels and increase in QRS (20-38 ms) and QTc (70-83 ms) intervals. The vehicle of docetaxel (polysorbate 80/ethanol 50/50, v/v, Formulation N°1) evoked the same effects on blood pressure, hematocrit and plasma histamine levels, when infused for 60 min except the effect on ORS and QTcinterval. However, such EKG effects were not observed following 360 minute infusion. Other parameters (total peripheral reistance, coronary resistance, cardiac output and left ventricular end diastolic blood preesure) were found to be depressed in the pentobarbital-anethstized dogs treated with vehicle. Similarly, in the halothane-anesthetized Beagle dog, polysorbate 80 infused i.v. at 10, 20 and 40 mg/kg over 1 h (in amount equivalent

to that coadministered with docetaxel at 0.375, 0.75 and 1.5 mg/kg), produced same vehicle-induced caridovascular effects.

Bronchopulmonary resistance, compliance and respiratory rate :

In urethane-anesthetized guinea-pigs, docetaxel at i.v. doses up to 3 mg/kg infused over 30 min did not modify bronchopulmonary resistance and compliance throughout a 60-min period. A decrease (41%) in the respiratory rate occurred 30 min after the end of the infusion of 3 mg/kg i.v., and this effect can be attributed to the vehicle, since it also decreased by 31% this parameter.

Gastrointestinal activity: The gastrointestinal transit was slightly increased (15%) in conscious mice treated with a single dose of docetaxel (50 mg/kg i.v.), in comparison with its vehicle. In conscious rats treated with docetaxel dissolved in polysorbate 80 at i.v. doses up to 10 mg/kg, 30 min before charcoal gavage, the intestinal transit of charcoal was not changed, in comparison with the corresponding vehicle.

Genito-urinary activity: In water-loaded rats, docetaxel (1, 3 and 10 mg/kg i.v.) did not modify urine output, pH, urinary Na^+, K^+, Cl^- and protein excretion during the 3- and 24-h periods following its administration, in comparison with its vehicle.

Anti-inflammatory/Analgesic activity: In rats, in the paw pressure test, docetaxel (1, 3 and 10 mg/kg i.v.) had no analgesic effect, in comparison with its vehicle.

Immunoactivity: In vitro, docetaxel dissolved in ethanol and diluted in a culture medium showed a preferential inhibitory activity on mouse T murine lymphocyte lineage (inhibition of proliferation and of interleukin-2 and interleukin-3 release, after concanavalin A stimulation, $IC_{50} = 10^{-7}$ M). However, it had little or no effect on murine macrophage activation. In vivo, docetaxel, given to mice at repeated daily doses (3 to 20 mg/kg i.v. or i.p.) prior to or after *Listeria monocytogenes* or *Klebsiella pneumoniae* challenge, had no significant immunosuppressive activity, in comparison with its vehicle.

Receptor binding profile and functional effects on receptors : Docetaxel dissolved in ethanol at concentrations up to 10 µM lacked significant affinity (< 30%) *in vitro* for several receptors present in brain tissue membranes (rat, guinea-pig). These receptors were muscarinic, dopaminergic D-A2, serotoninergic [5-HT-1, 5-HT-2] , benzodiazepine, α-1-, α-2-,β - adrenoceptor, Na^+ channel, Ca^{++} channel, H-1 histamine, and opiates. Docetaxel at concentrations up to 10 µM modified neither the basal tone, nor its responsiveness to the different agonists (acetylcholine, histamine or barium chloride) studied in isolated guinea pig ileum preparation..

Interation with other drugs: Docetaxel was evaluated, in vivo against transplantable tumors in mice, in combination with each of the six drugs : cisplatin, doxorubicin, vincristine, etoposide, cyclophosphamide and 5-fluorouracil. Of these six two-drug combinations, three were found to have modest to marked therapeutic synergism : etoposide, cyclophosphamide, 5-fluorouracil. Absence of synergism was observed with cisplatin and doxorubicin. Synergism with vincristine was equivocal.

Summary of pharmacology

In vitro docetaxel is a potent inhibitor of cell replication and was found to be cytotoxic against both murine and human tumour cell lines. Cytotoxicity of docetaxel studied in a variety of human tumor biopsies revealed sensitivity of breast, lung, ovarian, colorectal and melanoma tumor colony forming units.

Docetaxel mechanism of action is similar to that of paclitaxel. Docetaxel has been shown to induce assembly of microtubule bundles but does not alter the number of protofilaments in microtubules. In addition, docetaxel was more active as a promoter of the assembly of microtubule polymerization and approximately twice as potent as paclitaxel, as an inhibitor of microtubule depolymerization. As predicted by these properties, docetaxel was found to act as a mitotic spindle poison and to induce a mitotic block. Uptake and efflux studies showed that P388 leukemia cells could accumulate 3 times more docetaxel than paclitaxel. Thus the higher cytotoxic potency of docetaxel may be explained by the combination of its high affinity for microtubules, high achievable intracellular concentrations and slow cellular efflux.

Docetaxel was tested *in vivo* against tumours representing a variety of tissue types and behaviour patterns. At maximum tolerated i.v. dosages, docetaxel had a good spectrum of efficacy against murine transplantable solid tumours. Twelve out of the fourteen tumours tested responded to docetaxel with a clear dose response relationship.

Docetaxel was found highly active against the fast growing B16 melanoma. It was observed that the total log cell kill was 2.5 times greater for docetaxel than for paclitaxel, at equitoxic dosages. Docetaxel was found active against the three colon tumours tested (C26, C38 and C51). It was able to induce 100% cure rate of early stage disease and complete regressions of advanced stage colon adenocarcinoma C38. Docetaxel was able to effect complete regression of advanced stage pancreatic adenocarcinoma 03. It was active against 3/4 mammary tumors evaluated (MA13/C, MA16/C, MA44). Docetaxel was also found active to a lesser extent against a variety of other tumours, Lewis lung carcinoma, Glasgow osteogenic sarcoma (GOS), and the P388 and L1210 leukemias. It was, however, found inactive against M5076 histiocytosarcoma, and mammary adenocarcinoma M17/A.

Docetaxel was found active i.p. and i.v. against s.c. implanted tumors, indicating that it crossed physiological barriers.

Docetaxel belongs to the schedule-independent drug category. The schedule of administration did not influence the total dosage that can be administered *i.e.*, the maximum tolerated dose does not vary markedly between a split dose schedule or an intermittent schedule.

Docetaxel has been shown to be inactive and cross-resistant with doxorubicin and vincristine-resistant P388 leukemias, and with cisplatin - and BCNU-resistant L1210 leukemias. However, in vitro, it was found that cross-resistance was not automatically observed in sublines expressing the MDR phenotype and that there was a lack of cross-resistance to 5-fluorouracil or to cisplatin in certain cell lines, which may have clinical implication.

Docetaxel has also been found active against 10/11 human tumour xenografts models in mice, one at an early stage (OVCAR-3), and nine at an advanced stage (CX-1, KM20L2, LX-1, MX-1, SK-MEL-2, Ov.Per, Ov.Sh, F.Ma and MRI-H-207). Long term survivors were obtained with mice bearing OVCAR-3, SK-MEL-2 and MX-1.

Docetaxel was evaluated in vivo in combination with 6 clinically useful antitumor drugs. Three of the combinations demonstrated therapeutic synergism (5-fluorouracil, cyclophosphamide, etoposide). The effects seen with docetaxel-vincristine were equivocal.

Docetaxel appears to be well tolerated at the level of various vital systems. At a dose of 10 mg/kg i.v., it lacks activity in routine central nervous system tests performed the rat. No potentiation of hexobarbital-induced sleep time in mice is observed up to the dose of 30 mg/kg i.v. of docetaxel. *In vitro*, docetaxel does not inhibit any significant effect on transmembrane action potential up to a concentration of 30 µM in guinea-pig cardiac tissues. Docetaxel appeared to be tolerated in conscious and anesthetized rats (up to 9 mg/kg infused over 30 min) and conscious rabbits (up to 9 mg/kg infused over 30 min). However, in the conscious and the anesthetized dog (pentobarbital or halothane), the vehicle of docetaxel containing polysorbate 80 induces well known marked cardiovascular effects (decreases in diastolic and systolic arterial pressures, and in total peripheral resistance, increases in hematocrit and in plasma histamine levels). These appear also with docetaxel up to the dose of 1.5 mg/kg when injected with the same quantities of polysorbate 80, either over 60 min (conscious or anesthetized dogs) or 360 min (conscious dogs). Prolongations of QRS and QTc interval were only seen at 60 min infusion of docetaxel. In the anesthetized guinea-pig, the vehicle of docetaxel containing polysorbate 80 induces a decrease in the respiratory rate which is also obtained after a dose of 3 mg/kg i.v. of docetaxel injected with the same quantities of polysorbate 80.

Docetaxel, at a dose of 50 mg/kg i.v., increases slightly the gastrointestinal transit of the conscious mice but is without effect in the conscious rat, at a dose of 10 mg/kg i.v..

Docetaxel had no effects on diuresis and in the paw pressure test (analgesy test) in the rat up to a dose of 10 mg/kg i.v.. *In vitro*, docetaxel induces an inhibition of proliferation of T murine lymphocyte lineage but has no marked effect on murine macrophage activation. In mice, docetaxel up to a dose of 20 mg/kg i.v.had no effect on the survival of animals with bacterial challenge. Docetaxel lacked activity for several receptors of rat and guinea-pig brain membranes up to 10 M muscarinic, dopaminergic D-A2, serotoninergic (5 HT-1, 5 HT-2), α-1, α-2, β-adrenoceptors, Na^+ and Ca^{--} channels, H-1 histamine and opiates and at 1 μM for benzodiazepine receptors. It has no activity on isolated guinea-pig ileum preparations up to 10 μM.

Pharmacokinetics

RP 56976 Toxicokinetics after intravenous administration to beagle dog once every 21 days over 28 weeks (0.1, 0.375 and 1.5mg/kg) Study No. IBP/Biodyn. No 1773, Vol 1.54.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer Recherche-Developpement Institut de Biopharmacie, Cedex, France in 1992-1993. The study was intended to compare plasma levels of taxotere immediately following infusion and 24h following first (day 1) and final (day 190) infusion of beagle dogs administered 0.1, 0.375 and 1.50mg/kg taxotere iv once every 3 weeks over 6 months for a total of 10 doses. In addition, the study was intended to determine change in plasma concentration with time, determine the relationship between plasma level and dose, and investigate sex-related differences in plasma levels (see Study No. RPR/RD/CVRA/SM 92-0239, 10-cycle toxicity study in dogs over a 6-month period followed by a two-month reversibility period reviewed under Toxicology. Multiple doses.).

MD males received double doses of taxotere (0.75mg/kg) on infusion day 1; this was not indicated in the 6-month reversibility study. The study authors indicated that these dose concentrations were normalized prior to determining mean plasma levels.

All 24h plasma samples and plasma samples obtained following the final infusion of LD animals were indicated to be less than the limit of quantitation. Plasma levels of 2/5 LD males and1/5 LD females following infusion on day 1 were also below the limit of quantitation.

Levels of taxotere in plasma were independent of animal sex and day of treatment regardless of dose administered. Following the infusion periods, plasma levels increased with dose over the range of the doses administered. Following the first infusion, mean plasma levels ranged from 0.083 (males) to 0.105ug/ml (females) in LD animals, 0.32 (females) to 0.78ug/ml (males) in MD animals, and 1.86 (males) to2.06(females) ug/ml in HD animals. Following the final infusion, plasma levels ranged from 0.23 (males)to 0.29(females) ug/ml in MD animals and 1.61(females) to 2.15(males)ug/ml in HD dogs. When MD male concentrations were normalized and male and female concentrations were calculated as a unit of 10 animals, mean plasma levels were determined as indicated below.

End of Injection Concentrations (ug/ml) (♂+♀)

Dose (mg/kg)	Day 1	Day 190
0.1	0.07±0.05 n=10	ND
0.375	0.36±0.12 n=10	0.26±0.12 n=10
1.50	1.96±0.44 n=10	1.88±0.48 n=10

RP 56976 Toxicokinetics after intravenous administration to rats once every 21 days over 28 weeks (0.2,1 and 5mg/kg) Study No. IBP/Biodyn. No. 1774; Vol 1.53.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer Recherche-Developpement Institut de Biopharmacie, Cedex, France in 1992-1993. The study was intended to compare plasma levels of taxotere immediately following infusion and 0.5 and 24h following first (day 1), the fifth (day 85), and the tenth (day 189) infusion of Sprague-Dawley rats administered 0.2, 1 and 5mg/kg taxotere iv once every 3 weeks over 6 months for a total of 10 doses. In addition, the study was intended to determine change in plasma concentration with time, determine the relationship between plasma level and dose, and investigate sex-related differences in plasma levels (see Study No. RPR/RD/CRVA/SM 92-0026, 10-cycle toxicity study in rats over a 6-month period followed by a 1-month reversibility period reviewed under Toxicology. Multiple Doses).

Twenty-four hour plasma samples of rats at all dose levels and plasma samples of LD animals following all infusion periods were indicated to be less than the limit of quantitation. Plasma levels were also below the limit of quantitation 0.5h following all infusion periods in MD males and following the first and tenth infusion period in MD females.

Plasma levels in MD males were found to be slightly below those of females on infusion days 1 and 5; plasma levels in HD males were slightly below those of females on infusion days 1 and 10. Day of treatment effect for HD animals resulted from lower plasma levels on infusion day 1 as compared to days 5 and 10; study authors indicated that this effect on infusion day 1 may have been due to belated sampling times following dosing. This indication was strengthened by results of a previous pharmacokinetics study in rats administered 5mg/kg over 3 cycling periods in which plasma levels were similar following infusion on day 1 (2.52ug/ml, ♂) and day 42 (2.45ug/ml,♂). Plasma levels increased with dose over the range of doses administered as indicated in the table below. Plasma levels followed a supralinear curve; increases ranged from 1.5 to 2X the increase in dose level.

Mean Plasma levels (µg/ml) of RP 56976 (n = 5, except* n = 4)

Sex	males					
DOSE	day 1 1st adm.		day 85 5th adm.		day 189 10th adm.	
mg/kg	EI	0.5 h	EI	0.5 h	EI	0.5 h
0.2	*	*	*	*	*	*
1	0.09 ± 0.03	*	0.19 ± 0.07	* *	0.23 ± 0.09	* *
5	0.92 ± 0.07	0.14 ±0.03	2.50 ± 0.50	0.28 ± 0.06	2.45 ± 0.89	0.21 ± 0.12
Sex	females					
DOSE	day 1 1st adm.		day 85 5th adm.		day 189 10th adm.	
mg/kg	EI	0.5 h	EI	0.5 h	EI	0.5 h
0.2	*	*	*	*	*	*
1	0.24 ± 0.17	* *	0.28 ± 0.05	0.05 ± 0.03	0.21* ± 0.07	* *
5	1.56 ± 0.36	0.13 ±0.03	2.36 ± 0.50	0.27 ± 0.03	3.06 ± 0.62	0.23 ± 0.09

* = too many values < LOQ to calculate mean

Pharmacokinetics (absorption, distribution, metabolism and excretion)

Docetaxel was administered intravenously to animals, either as a bolus at pharmacological doses to the mouse or as an infusion at toxicological doses to rats, rabbits and dogs. It was administered in polysorbate 80/ethanol (50/50 V/V) or polysorbate 80 alone, diluted with 5% glucose or 0.9% sodium chloride. [^{14}C-3 propionate]-docetaxel was used. The total radioactivity content of the different biological samples was determined by liquid scintillation. For radiolabelled compounds, samples were analysed by a high performance liquid chromatography system with an on-line radioactivity detection. Unlabelled-docetaxel was measured in plasma, urine and tissues by high performance liquid chromatography (HPLC). For some of the pharmacokinetic and toxicokinetic studies in dogs, the routine limit of quantitation in plasma and urine was 40 ng/ml, while this limit increased to 100 and 200 ng/ml in smaller samples (mouse studies). In rat and some dog pharmacokinetic and toxicokinetic studies, the limit of detection was 20 ng/ml in plasma .

Absorption:

Single dose

Mice

UNLABELLED COMPOUND: Pharmacokinetic studies were performed in non-tumour bearing mice and in colon adenocarcinoma 38 tumour bearing mice. Tumour bearing mice received i.v. bolus doses of either 39 mg/m^2, 66 mg/m^2, 111 mg/m^2 or 186 mg/m^2 docetaxel. Non-tumour bearing mice received an i.v. administration of 111 mg/m^2 docetaxel. This dose corresponds to the highest non toxic dose in mice. After administration of a 111 mg/m^2 i.v. dose the plasma pharmacokinetic parameters in the tumour bearing and the non tumour bearing mice are listed below:

Parameter	With Tumour		Without Tumour
	Plasma	Tumour	Plasma
C_0 (μg/ml)[1]	51	-	54
Cmax (μg/ml)	28 [2]	3.97 [3]	50
AUC (h.μg/ml)	17.1	44.0[4]	24.4
t1/2 (h)	1.18	21.7	1.12
CL_t (l/h/kg)	2.2	-	1.5
V_{ss} (l/kg)	2.2	-	1.6

1) C_0 = calculated concentration at the end of injection
2) first sampling time after dosing (5 min)
3) tmax = 10 min
4) $AUC_{0\text{-}24h}$

Tumor pharmacokinetics: The maximal tumour levels were obtained at times ranging from 5 min to 30 min. and were proportional to the dose. The AUC (0-24h) varied from 17 to 71 h.μg/g and was linearly related to the dose. Docetaxel levels in tumour decreased slowly, with the terminal elimination half life ranging from 21 to 35 hours. High tumour levels were maintained over time and 24 hours after drug administration tumour concentrations were 0.65, 0.56, 1.29 and 1.90 μg/g for doses of 39, 66, 111 and 186 mg/m^2, respectively. These tumour levels were higher than the IC_{50} of the human cell lines, KB cells (epidermoid carcinoma, 0.01 ug/ml) and T24 cells (bladder carcinoma, 0.04 ug/ml). Tthe docetaxel clearance from tumours was lower than that from both plasma and normal tissues, resulting in increased exposure, with tumour AUC 2.5 to 4 fold higher than that in plasma.

RADIOLABELLED COMPOUND: Blood and plasma levels of radioactivity in mice had similar kinetic profiles. They decreased according to a three-exponential model, with a very rapid distribution phase (first half-life <0.1h) and a slow elimination phase (27h half-life).

Rats:
UNLABELLED COMPOUND: Pharmacokinetics were studied after single intravenous bolus administration of docetaxel in male rats at doses of 15-120 mg/m^2. Blood samples were taken up to 6 hours post-dosing. The AUC increased in proportion to the dose from 0.57 h.μg/ml to 2.52 h.μg/ml in the dose range 15 to 60 mg/m^2. The AUC for 120 mg/m^2 was 9.36 h.μg/ml. Higher AUC was due to its lower clearance (2.14 l/h/kg vs 3.97-5.51 l/h/kg) at this dose level. Docetaxel disposition in the rat was biphasic, as in the mouse and in the dog, with a fast distribution half life, $t_{1/2\alpha}$ ranging between h and an elimination half life between 0.78 h and 1.66 h. These are close to the values observed in mice.

RADIOLABELLED COMPOUND: After administration of a 30 mg/m^2 dose, blood and plasma radioactivity levels decreased rapidly (first half-life <0.11 h). The terminal plasma

was 43-49 h. AUC values of parent docetaxel and total radioactivity were similar, indicating the level of circulating metabolites is negligable.

Dog:

UNLABELLED COMPOUND: The pharmacokinetics of docetaxel were studied in dogs receiving a single intravenous dose of 30 mg/m². Blood samples were collected for 6 hours, and urine samples up to 24 hours after drug administration. The plasma level versus time curve was fitted according to a two-compartment model, a rebound phase occurring between 0.5 and 1.5 hour post administration (in 3 of the 4 animals) suggested the possibility of enterohepatic cycling. Elimination half life was 6.6 h. Volume of distribution was 9.1 l/kg. Plasma clearance (Clt) was 0.93 l/h/kg.

End of infusion plasma levels of docetaxel were determined in an acute toxicology study in dogs, given 15-140 mg/m² as an i.v. infusion of 24 to 31 minutes. The observed plasma levels ranged between 0.27 μg/ml (15 mg/m²) and 3.2 μg/ml (140 mg/m²).

Comparative pharmacokinetic parameters in mice, rats and dogs are shown below:

	MOUSE NTBA[1]	RAT	DOG
	111 mg/m²	30 mg/m²	30 mg/m²
C_{max}(μg/ml)	50 (5 min)[2]	4.1 (2 min)[2]	3.5 (end infusion)
$AUC_{0-\infty}$ (h.μg/ml)	24.4	0.91	1.7
$t_{1/2}$ alpha(h)	0.12	0.02	0.07
$t_{1/2}$ beta(h)	1.12	0.78	6.6
V_{ss} (l/kg)	1.5	4.0	9.1
Cl (l/h/kg)	1.6	5.5	0.9

[1] NTBA = Non Tumour Bearing Animals
[2] first sampling time

In comparison, following PK data for human trial were obtained: dose, 70-100 mg (44-62.5 mg/m²) ; Cmax, 1.9-3.6 ug/ml; AUC, 2.8-5.9 ug.h/ml; CL, 17-27 l/h/m² (or 0.45-0.72 l/h/kg); Vss, 16-149 l/m² (or 0.4-4 l/kg). The mg/m²-corrected AUCs for mouse, rat and dogs were 0.22, 0.03 and 0.06 ug.h/ml, respectively, and for human was 0.063-0.08 ug.h/ml.

RADIOLABELLED COMPOUND: Following i.v. infusion of ^{14}C-docetaxel at 15 mg/m² to dogs, radioactivity plasma levels declined in a similar manner in both sexes, without any evidence of a rebound effect. The three-phase elimination half-lives were 0.23-0.3, 2-2.4 and 50-63 hours. Blood concentrations of drug-derived radioactivity were greater than corresponding plasma levels, suggesting preferential uptake by blood cells.

Multiple doses:

Mouse: Docetaxel was administered intravenously to mice bearing colon adenocarcinoma 38

at doses of 39-186 mg/m² every two days for a total of three injections. At the dose of 111 mg/m², blood, tumour and tissue samples were drawn over 48 hours (10 samples), whereas for the other dose levels only 3 samples were taken over 4 hours. In plasma, at the 111 mg/m² dose, there was a trend toward lower AUC values and shorter terminal half-life (β) after repeated administration as compared to the single dose data from a previous study. This was due to higher body clearance following repeated administration (CLt = 2.2 l/h/kg in the single dose study and 3.2 l/h/kg on day 5 of the multiple dose study) and shorter elimination half-life (β half-lives were 1.80 h on day 1 and 0.77 h on day 5). Unlike the single administration, after three administrations the tumour docetaxel concentrations were not proportional to the dose.

Rat: During a toxicological study in rats, docetaxel (15-60 mg/m2) was given once every 21 days over 3 cycles. The sex or day of treatment had no influence on docetaxel plasma levels. However, the plasma levels increased with dose in a nonlinear fashion, in agreement with the data of the single dose study. In a second toxicological study, rats were treated with docetaxel at the doses 1.2-30 mg/m² once every 21 days over 28 weeks . The end of infusion plasma levels increased with the administered dose. For the 30 mg/m² dose, end of infusion plasma levels on day 85 and day 189 were similar to the levels observed on day 1 and day 42 of the previous toxicokinetic study, indicating of no drug accumulation and no induction of inhibition.

Dog: Docetaxel (3-15 mg/m²) were given every day during 5 days in the course of a toxicologicalstudy, plasma concentrations at the end of infusion increased with the infused dose. When docetaxel was given (7.5-30 mg/m2) once every 21 days over 12 weeks, docetaxel plasma levels were lower on day 85 than on day 1. Following table summarizes the plasma levels (ug/ml) obtained in the three toxicological studies.

Dose	Single Acute Dose	5-Day Repeated Dosing		Single Dose Every 21 Days (5 Courses)	
(mg/m²)	1st dose	1st dose	5th dose	1st course	5th course
3	-	0.11	0.08	-	-
6	-	0.18	0.17	-	-
7.5	-	-	-	0.20	0.16
15	0.27	0.97	0.54	0.65	0.33
30	0.54	-	-	1.71	1.23
50	1.08	-	-	-	-
70	1.82	-	-	-	-
140	3.19	-	-	-	-

In another toxicological study, dogs were treated once every 21 days for 10 cycles. Plasma levels were independent of sex and duration of treatment. On the last day of treatment (day

190), mean plasma levels were 0.26 and 1.88 μg/ml for the 7.5 and 30 mg/m² doses.

Rats:
RADIOLABELLED COMPOUND: Male rats were given 30 mg/m² of ^{14}C-docetaxel i.v. once a week for four administrations . Blood and plasma samples were taken 0.5 and 24 hours after each administration. Blood and plasma radioactivity levels decreased with a similar profile until 168 h: at first rapidly and then more slowly with a terminal plasma half-life of 41 h. Blood levels were always higher than plasma levels, suggesting preferential uptake by blood cells. A trend to accumulation was observed in plasma levels of radioactivity, though the terminal half-lives obtained after single or repeated doses were very similar.

Plasma protein binding
Plasma Radioactivity binding to plasma proteins in mice (111 mg/m²) and rats (30 mg/m²) was above 84 % for both species.

In vitro protein binding: Plasma protein binding of ^{14}C-radiolabelled docetaxel was assessed in vitro using the ultrafiltration technique in the concentration range μg/ml (μM),corresponding to values observed in animal studies and clinically relevant in humans. Plasma protein binding ranged between 70% and 95% and appeared to decrease in the order mouse (85-95%) > dog (83-89%)> human (81-83%)> rat (70-76%). Additional study result indicated that albumin, α1-acid glycoproteins and lipoproteins contributed to the binding of docetaxel in human plasma.

Distribution

Mouse
Single dose, unlabelled compound: Five minutes after administration of the drug, docetaxel was mainly located in liver and kidney, with concentrations of μg/g (times the plasma concentration). Heart, lung and spleen levels were as high as plasma levels, while tumour concentrations were lower. No docetaxel could be detected in the brain.

Whole-body autoradiography: An i.v. bolus dose of 111 mg/m² of ^{14}C - doxcetaxel was injected. The observed distribution indicated biliary excretion and gastric radioactivity secretion. High concentrations were observed in the spleen and bone marrow. Radioactivity in muscle was substantial up to 1 hour, especially in myocardium. High levels were also detected in the pancreas, salivary glands, hypophysis and Harder's gland. Concentrations were very low in testes and slightly higher in the ovaries and preputial gland. No radioactivity was detected in the CNS. However, radioactivity in the cervical and dorsal nerve roots was visible up to the last time point studied (168 h). Lymph nodes and thymus radioactivity levels were moderate. Substantial levels were obtained in the thymus up to the last time point studied (168 h).
In the female pigmented B6D2F1 mouse, no radioactivity binding to melanin was observed.

Rat

Single dose: After an i.v. infused dose of 30 mg/m², the tissue distribution of radioactivity appeared similar to those reported in mice. Low levels were detected in adipose tissue, blood, sciatic nerve and eyes. Biliary excretion and gastric radioactivity secretion were possible in the rat. High concentrations were observed in the spleen and bone marrow. The radioactivity in the myocardium was significant (around three times that of other muscle). High levels were also detected in various glandular structures. Concentrations of radioactivity were observed in females (ovary and uterus at 0.5h and 3h post-dose), whereas the radioactivity levels were very low in testes, low in epididymis and intermediate in the prostate. For these three tissues, the corresponding levels remained stable over the 24 hour period. The thymus exhibited low but persistent concentrations of radioactivity. The brain had the lowest concentrations of radioactivity, indicatiing limited crossing of the blood-brain barrier. Docetaxel and/or radioactive drug-derived products were also shown to distribute into the lymphatic system.

Multiple dose: Male rats were given four intravenous administrations of 30 mg/m² ^{14}C-docetaxel once a week. High radioactivity concentrations were found in the lungs, liver, kidneys, small intestine wall, in hematopoietic organs (the spleen, bone marrow and thymus) and in various glandular structures. Organ radioactivity concentrations decreased rapidly after the last administration (from 0.5 to 168 hours) with the exception of the testes and the thymus. After the last administration, tissue/plasma ratios increased steadily up to 48 or 168 hours post-administration to reach high values (> 300) in prostate, lungs, pituitary, thymus, spleen, liver, aorta, Harder's gland, epididymis, urinary bladder and thyroid.

Distribution in the pregnant rat: The tissue distribution data obtained in pregnant rats were similar to non-pregnant rats. The highest radioactivity concentrations were found in the lungs, liver, small intestine wall, kidneys, in hematopoietic organs (the spleen and bone marrow) and in various glandular structures. A precipitation of labelled product may have occurred in the lungs. There appeared to be limited distribution across the placenta. Concentrations of radioactivity in foetuses were generally far lower than in maternal tissues, the highest level being found in the foetal liver.

Milk transference in the lactating rat: After a single intravenous administration of 30 mg/m² on day 10 of lactation to the lactating rat, peak concentrations of radioactivity occurred at 1 hour post-dose in both milk (0.11 ug/ml) and plasma(0.35 μg eq/ml). From 4 to 24 hours post-dose, milk radioactivity concentrations were of the same order as those observed in plasma: the milk/plasma ratio increased slightly with time (from 0.3 at 1 hour post-dose to 1.7 at 24 hours post-dose) and plasma AUC $_{(0\text{-}24h)}$ was 1.4 times higher than that obtained for the milk. This appearance of radioactivity in milk is consistent with data from the distribution study in the pregnant rat. High values of the tissue/plasma ratio were observed in the mammary gland, following administration on day 18 of gestation (ratio~50 at 24 hours post-administration).

Metabolism

Liver subcellular fractions in vitro: The metabolism of docetaxel has been studied in mouse, rat, dog and human liver subcellular fractions. Docetaxel was metabolized by microsomal monooxygenases from all four species. UDP-glucuronosyltransferases and cytosolic glutathione S-transferases from rat and human liver did not appear to metabolize docetaxel.
Incubations with radiolabelled compound showed the formation of four peaks in microsomes from all species, respectively representing **V+VI**; **VII**; **XI** and **XIII+XIV+XV**. **IV** was detected in human liver microsomes and **XVI+XVII** in dog and human liver microsomes. Together these metabolites represented virtually all metabolites resulting from biotransformation of the *tert*-butylester group. C-oxidation apparently accounted for about 62 to 77% of docetaxel biotransformation in the four species (total of **VI**, **V** and **VII**), with the rest generally accounted for by the same reaction on the 7-epimer RP 70617 or resulting from epimerisation of the metabolites.

Isolated perfused rat liver : ^{14}C-Docetaxel disposition was studied in isolated perfused rat livers. Docetaxel was administered at doses of 0.48 mg and 4.8 mg, giving rise to initial perfusate concentrations of 5 and 50 μM (4 and 40 μg/ml). After administration at 5 μM, circulating radioactivity decreased rapidly and accounted for 5% of the dose at 30 minutes and 3% at 180 minutes. Hepatic clearance was confirmed by a corresponding biliary clearance, as the majority of the radioactivity (78.9%) was detected in the bile 60 minutes after administration.
Five major peaks, **IV**, **V+VI**, **VII**, **XI** and **XIII+XIV+XV**, accompanied by docetaxel were detected in bile.

Mouse: Metabolites were analyzed in biological samples, obtained from non-tumour bearing mice given 111 mg/m^2 of ^{14}C docetaxel.

Plasma: Parent compound represented 55-90% of total plasma radioactivity. Two peaks, representing **V+VI** and **VII**, each accounting for 5 to 15% of the plasma radioactivity.
Faeces: In the 0-24 h faeces, which contained 59% of the administered dose in the male mouse, the three peaks **V+VI**, **VII** and **XVI+XVII** (RPR 104943) represented 20.6%, 17.2% and 8.9%, respectively of the administered dose. These metabolites accounted for 75 to 80% of the compounds excreted in faeces. Unchanged docetaxel in faeces represented only 2% of the dose.
Urine: About 15 metabolites were present in urine, each accounting for less than 0.6% of the administered dose.

Rat: Metabolic profiles were determined in biological samples given a 30 mg/m^2 intravenous infusion of ^{14}C-docetaxel. Bile samples were obtained from bile duct cannulated rats. No difference was observed according to sex in these studies.
Plasma: In plasma, the parent compound was the only detected substance.
Bile: Biliary excretion accounted for 64-72% of administered dose. Unchanged docetaxel represented 2% of the dose, together with about 20 other compounds, among which metabolites **IV**, **V**, **VI** and **VII** accounted for respectively 5.3%, 6.0%, 7.5% and 7.9% of the administered dose. Metabolites **X**, **XI**, **XII** and **XIII**, the latter three being the 7-epi analogues of the major

biliary metabolites, were also present, with each accounting for 2 to 5% of dose.
Faeces: About 20 compounds were found in faeces. Unchanged docetaxel accounted for 11% of administered dose. The main metabolites were **VI** accounting for about 20% of dose, and **V**, **VII** and **XVI** , each accounting for about 6% of dose. The overall metabolic profile in faeces was similar to that in bile-duct cannulated rats.
Urine: Parent compound in urine acounted for about 1% of dose, together with RP 70617. The main metabolite was **I** which accounted for about 50% of the overall detected compounds in urine.

Rabbit: Metabolic profiles were determined in biological samples given a 6 mg/m² intravenous infusion of ^{14}C-docetaxel . No difference was observed according to sex.
Plasma: Parent compound was the only substance detected in plasma.
Faeces: About 85% of the dose was recovered in the 0-168h faeces. The parent compound accounted for an average of 11.6% of the dose. About 20 metabolites were found, the most important being **VI** accounting for almost 20% of the dose. Thus *tert*-butyl oxidation is also the main pathway in the rabbit.
Urine: Small amounts of parent compound and RP 70617 were present. Metabolites **I** and **XIX** (unidentified) were the main compounds, respectively accounting for 35% and 25% of the compounds detected in urine.

Dog: Metabolic profiles were analyzed in biological samples from beagle dogs given a 15 mg/m²intravenous infusion of ^{14}C docetaxel. No difference according to sex was observed.
Plasma: The parent compound was the principal circulating substance. The presence of small quantities of metabolites **V+VI**, resulting from *tert*-butyl hydroxylation, and **XXVIII** were also detected.
Liver and bile: Docetaxel and metabolites **V+VI** in liver tissue represented 4.2% and 3.7% of the administered dose with, in addition, four minor metabolites. The two peaks were also detected in the biles , representing an average of 4.4% and 7.4% of the dose, respectively. Metabolites **VII** and **XXVIII** in 3-hour bile represented 1% of the dose.
Feces: In the 0-72 h faeces, docetaxel and **V+VI** represented about 15% and 33% of the administered dose, respectively. Other metabolites, which included **VII, XI, XIII+XIV+XV, XVI+XVII** and **XXVIII** represented from 1 to 3.3% of the dose.
Urine: Fifteen metabolites were detected. The most abundant constituents were docetaxel, **V+VI** and **XXVI**.
Thus metabolites from the *tert*-butyl oxidation pathway (**V, VI, VII, XI, XIII**) constitute the majority of docetaxel biotransformation the dog.

The major metabolic pathway of docetaxel consisted of oxidations of one of the methyl groups of the *tert*-butylester moiety. This leads first to the alcohol derivative **VI** (RPR 104952). Further oxidation leads to a putative aldehyde, which cyclizes to give two diastereoisomeric hydroxy-oxazolidinones (**V** and **VII**). Oxidation of the aldehyde intermediate gives the corresponding acid derivative, which yields the cyclized oxazolidinedione derivative **XVI** (RPR 104943). A minor pathway is C-oxidation in the para position of the phenyl group of the side chain, leading to the hydroxylated compound **VIII** (RPR 107840). Another minor metabolic pathway results from epimerisation at position 7 of the taxane ring, leading to RP 70617. This compound may result

from chemical degradation of docetaxel. The 7-epimers of the metabolites VI, V and VII ; the alcohol-derivative XII and the diastereoisomeric hydroxy-oxazolidinone compounds XI and XIII have also been isolated. The metabolic pathway is proposed below:

Docetaxel (RP56976) .

Enzymology of docetaxol metabolism: Both *in vivo* and *in vitro* data have shown that docetaxel is principally metabolized by monooxygenases. Studies on cytochrome P450 isoenzymes were performed.

Effect of inducers in rat liver microsomes: Dexamethasone had the most significant effect on docetaxel biotransformation rate, and - to a lesser degree - 3MC, phenobarbital and clofibrate. Thus, docetaxel appeared to be mainly metabolized by cytochrome P450 3A isoenzymes.

Effect of inducers in the isolated perfused rat liver: The effect of enzyme induction by 3-methylcholanthrene (40 mg/kg/d for 2 days), phenobarbital (80 mg/kg/d for three days) and dexamethasone (50 mg/kg/d for three days) in the rat on ^{14}C-docetaxel metabolism and excretion in the isolated perfused liver was studied at the high dose of 50 μM. Compared to controls, 3-MC increased principally elimination in the form of parent drug and the alcohol VI. Phenobarbital had no effect on parent drug, but increased elimination in the form of VI (hydroxy) and V, VII and XI, all cyclized aldehydes. Dexamethasone actually decreased parent drug and VI excretion, while elimination of the aldehyde VII and the putative carboxylic acid IV were increased. These results, in agreement with the findings in induced rat liver microsomes, indicated that several inducible rat liver enzymes may be involved in docetaxel metabolism. The effect of 3-MC appears to be limited to the first hydroxylation step, phenobarbital induces metabolism as far as the cyclized aldehydes and dexamethasone the whole pathway, including the carboxylation.

Inhibition studies in human liver microsomes: The effect of several specific inhibitors of cytochrome P450 isoenzymes on docetaxel biotransformation in human liver microsomes was

studied. Ketoconazole, troleandomycin, nifedipine and erythromycin were able to inhibit docetaxel biotransformation, indicating a major role of P450 isoenzymes of the CYP3A subfamily in human metabolism.

Enzyme induction activity in mouse and rat:
Mouse: Mice (n=18/sex/dose) received 30 mg/m² docetaxel for five days. Control groups received the vehicle alone. Compared to controls, docetaxel did not significantly modify the parameters : liver weight, microsomal protein, total cytochrome P-450, the P450-catalyzed activities ethoxy- and pentoxyresorufin O-dealkylase (EROD and PROD) and aniline hydroxylase (AH) and the conjugation enzyme activities p-nitrophenol glucuronidation (GT-pNP) and cytosolic glutathione S-transferase (GST). Bilirubin glucuronidation (GT-bili) was slightly increased (+50%) in both sexes. Therefore, docetaxol had no enzyme induction activity in mouse.
Rat: Rats (n=6/sex/dose) were treated with 30 mg/m² docetaxel for five days (cumulative dose 150 mg/m²). None of the parameters mentioned above were modified in female rats. In male rats an increase in relative liver weight and a decrease in aniline hydroxylase (-22%) were the only changes observed. These results indicated that docetaxel was not an enzyme inducer in rat.

Excretion:
Mouse, rat, rabbit and dog: In these four species, radioactivity was predominantly excreted by faecal route: on average 83 to 92 % of the administered dose within 96 or 168 hours with most of it occurring during the first 48 hours. Urinary excretion only accounted for 3 to 9% of the administered dose. Pulmonary excretion of radioactivity was neglegible: less than 0.05% of the dose in 48 hours in mice and rats and not detectable in dogs. This finding indicates the relative stability of the position of radioactive labelling towards final degradation in the form of $^{14}CO2$. Radioactivity tissue retention at the end of the collection period, investigated in mice and rats, accounted for 0.5 to 0.8 % of the dose in mice (96h) and for 4 to 5 % in rats (168h).

Biliary excretion and enterohepatic cycling in rat: Excretion in bile (65-72% of administered dose) of total radioactivity in the rat bearing an indwelling biliary catheter. Enterohepatic recirculation in rats was low: 12.7% of the radioactivity infused (in the duodenum was reabsorbed over 24 hours.
Repeated doses in rats: Urine and faeces were collected daily during the repeated doses (30 mg/m² once a week on days 0, 7, 14 and 21) and up to 168 hours after the last administration. Radioactivity was largely excreted by fecal route (82.7% of the total administered dose). Urinary excretion only accounted for 9.6% of the total administered dose.

Summary of pharmacokinetics
Absorption: In mice, docetaxel showed a dose proportionality of plasma Cmax, plasma AUC and tumour AUC with the i.v. administered dose (39 to 186 mg/m²). No effect of sex and/or tumour presence on pharmacokinetics was observed. Tumour AUC was 2.5 to 5 times that of plasma. Tumour half-life of docetaxel (21.7h) was considerably longer than in other tissues (2.2-4.5h) and plasma (1.2 h). Repeated administration to mice caused a slight decrease in tumour AUC was observed on day 5. This did nor appear to be caused by enzyme induction, as no significant effect was observed on liver drug-metabolizing enzymes in mice and rats treated with docetaxel at 30

mg/m²/day for five days. In the rat, plasma docetaxel half-lives were comparable to that in the mouse. Docetaxel pharmacokinetics in the dog were characterized by half-lives of 4 min and 6.6 hours and a plasma clearance of 0.93 l/h/kg. The main difference in comparison to the mouse was a larger distribution volume (9 l/kg). However, mouse had the highest mg/m²-corrected AUC among three species.

Distribution: In the mouse, docetaxel was detected in most tissues, including tumour tissue, but not in the central nervous system. Distribution studies in mice and rats showed distribution in the following tissues: liver, bile, intestine and gastric contents, spleen, myocardium, bone marrow, pancreas and salivary glands. Radioactivity was detected in fetal tissues and milk, but not in the central nervous system. Levels in genital organs were relatively higher in females than in males. Upon repeated administration to the rat, tissue retention in lungs, prostate and epididymis, thymus and pituitary was observed.
Plasma protein binding of the radiolabelled compound was high in mice and rats *in vivo* (84-89%). Binding to plasma proteins *in vitro* was also high in mouse (89-95%), rat (70-76%), dog (83-89%) and man (79-83%).
Taxotere would not be effective for treatment of brain cancer since the drug does not cross the blood-brain barrier.

Metabolism: Several studies have shown that docetaxel was mainly eliminated by hepatic metabolism and that only a minor fraction of the dose is excreted in the form of parent drug.
Oxidation of the *tert*-butyl group of docetaxel represented the majority of biotransformation in all four species (mouse, rat, rabbit and dog), with the rest resulting from the same reaction on the 7-epimer, RP 70617, or from epimerisation of the metabolites. In all four species the metabolites from the *tert*-butyl oxidation pathway (**V, VI, VII and XVI**) represented the large majority of fecal metabolites, with the alcohol derivative, **VI**, being the most abundant one. Only in the mouse were metabolites of docetaxel detectable in plasma. The main enzymes involved in docetaxel metabolism are monooxygenases (Phase I enzymes). Cytochrome P-450 isoenzymes of the CYP3A subfamily were mainly responsible for docetaxel biotransformation in human and rat. Therefore, possible metabolic drug-drug interactions were likely to occur with potent CYP3A inhibitors such as ketoconazole.
A study in humans has shown the predominance of the *tert*-butyl oxidation pathway in humans, with metabolites **VI** and **XVI** being the most abundant compounds in faeces. The studied animal species are good models for human metabolism of docetaxel. Since docetaxel was the main circulating compound and that the major metabolites were less active than docetaxel indicates that parent drug analysis is an appropriate index for pharmacokinetic/ pharmacodynamic studies of this drug.

Excretion: Docetaxel was largely excreted by the faecal route in mice, rats, rabbits and dogs. Excretion in humans has also been shown to be in large majority in the faeces . Urinary excretion of parent drug or radioactivity was always low (< 10% of the dose). Biliary excretion of radiolabelled docetaxel-derived compounds was important. Plasma pharmacokinetics in the dog indicated a possible rebound effect. In the rat entero-hepatic cycling of radioactivity was not important.

Toxicology

Single Dose (Degradation Products)

Acute intravenous toxicity study of RP70617 in the mouse Study no. RPR/RD/CRVA/SM 672 Vol 1.45

Groups of 10 (5♂,5♀) CD2F1 mice were administered a single iv dose of RP70617 in polysorbate 80; doses ranged from 59-121mg/kg (177-363mg/m2). Signs of dyspnea, reduced motor activity, and hunched posture were exhibited in females administered 363mg/m2 from study day 9 to 28. One female with clinical signs of dyspnea and prostration was euthanized on study day 7. There were no drug-related changes in body weights or histopathology in male or female animals.

RP73077: Single dose intravenous lethality study in mice with a 27-day observation period Study no. RPR/RD/CRVA/SM 93-0065 Vol 1.45

Groups of 10 (5♂, 5♀) CD2F1 mice were administered a single iv dose of RP73077 in polysorbate 80; doses ranged from 154-327mg/kg (462-981mg/m2). Five of five males and females administered 327mg/kg taxotere died on study day 1 following dosing; 1/5 males and 2/5 females administered the equivalent polysorbate 80 vehicle concentration also died during the study suggesting the vehicle may have acted in conjunction with taxotere to produce the mortality at the highest dose. Deaths also occurred to a lesser degree in other dose groups: 257mg/kg (2/5♂,4/5♀), 201mg/kg (2/5♂), 154mg/kg (1/5♀). Associated clinical signs included reduced motor activity, ataxia, prostration, and dyspnea. There were no changes in body weights. Microscopically, male mice exhibited bilateral hypocellularity and atrophy of seminiferous tubules and small testes.

Multiple Doses

RP 56976 - 10-cycle toxicity study in rats (each cycle consisting of a single intravenous infusion every 3 weeks) over a 6-month period followed by a 1-month reversibility period. Study No. RPR/RD/CRVA/SM 92-0026, Vols 1.34-1.39.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Department Securite du Medicament, Alfortville, France in 1993. Taxotere (batch # OP9-PROC 92226; purity 100%; in a 40 mg/ml stock solution of polysorbate 80) was administered to Sprague-Dawley CD Crl:CD(SD)BR rats (15animals/sex/group) at doses of 0.2, 1.0, or 5.0mg/kg per iv infusion (1.2, 6, and 30mg/m^2, dosing volume, 10ml/kg; rate of infusion, 1ml/min), once every 3 weeks over 6 months for a total of 10 doses (days 1, 22, 43, 64, 85, 106, 127, 148, 169, 189). Rats were 7 weeks of age at study initiation; male weights ranged from 235-305g and female weights ranged from 184-242g. The saline control group was dosed with a 0.9%NaCl solution and the vehicle control group with a 1.25% polysorbate 80 solution in 0.9%NaCl. Five animals/sex/group were observed for 1 month following the dosing period for reversibility of toxic effects. Five satellite groups of 5/sex/dose were used for plasma drug toxicokinetic determinations (see toxicokinetics review).

Measurements and Observations

Daily	Mortality, clinical examination
Weekly	Body Weight, food consumption
Pretreatment	Ophthalmology (+examination of 5/15rats/sex following ninth infusion [day 169]
Day 2 and Week 3 following each treatment, study termination	Hematology, clinical chemistry
Post treatment 5 and 10 + study term (day 87,191,213)	Urinalysis
Post treatment and post reversibility	Organ weights, gross pathology, histopathology

Mortality and clinical observations

No drug-related mortality occurred during the study. One MD male was sacrificed moribund on day 153 as a result of hindlimb weakness; malignant lymphoma was exhibited upon histopathological examination but was not considered to be related to dosing. One MD female of the satellite group (pharmacokinetics study) died on day 127; cause of death was not indicated.

Following the third week of infusion, the length and number of muzzle hairs of HD animals was reduced or absent; incidence was increased in males. Dyspnea and paraparesis were observed sporadically in 1/15 HD and MD males, respectively.

Body weight and food consumption

Body weights of HD males and females were significantly depressed following each infusion; body weight gains were observed during the 2nd and 3rd weeks following dosing but weights remained depressed in these animals throughout the study. Body weights of HD males were depressed 7-15% following cycles 1-5 when compared to concurrent controls and 17-21% following cycles 6-10. Body weights of HD females were depressed 8-9% following cycles 1-5 when compared to concurrent controls and 10-14% following cycles 6-10. Body weights of these animals were depressed up to 22 and 15% in males and females, respectively, when compared to concurrent controls; weights did not recover during the 4 weeks following dosing. Weights of LD and MD animals were similar to those of concurrent controls throughout the study.

Food consumption of HD males and females was depressed up to 35% and 29%, respectively, following dosing when compared to concurrent controls; consumption of MD males and females was depressed up to 18 and 11%, respectively, when compared to concurrent controls. During the 2 weeks following each dosing interval, the food consumption recovered and was similar to that of concurrent controls.

Ophthalmology

There were no drug-related changes observed during the study.

Hematology

Administration of taxotere was associated with depressions in red cell indices/reticulocytes, platelets, and white cell counts in MD and HD males and females throughout the study when compared to concurrent controls; hematological measurements were conducted 2 days following dosing. Red and white cell indices appeared to recover between dosing intervals. RBC counts were depressed up to 10% and 15% in HD males and females, respectively; MD animals were effected to a lesser extent. Hgb and hct were depressed up to 9% in HD males and 10% in females of this group. Reticulocyte counts were depressed from 73-85% and 74-83% in HD males and females, respectively, and 28-60% and 26-41% in MD males and females, respectively, when compared to concurrent controls. Following the 4th dosing interval (day 64), the depressions in red cell indices did not appear to increase in severity.

Platelet counts were depressed from 35-50% and 30-54% in HD males and females, respectively, when compared to concurrent controls, and up to 16% in MD animals. Platelet counts of one HD female (animal #92-108-170-F05) were significantly lower (4to7fold) than other females of that dose group from initiation of dosing to day 108, following the sixth dosing interval; platelet counts of other animals were similarly depressed throughout the dosing period. WBC counts were depressed from 47-63% in HD males, with significant reductions in eosinophils, lymphocytes, and monocytes. The white cells of HD females were depressed 49-80% when compared to concurrent controls, with significant reductions in lymphocytes.

Hematological parameters recovered during the 4 weeks following dosing; adverse effects on hematological indices have been reported to occur with drugs of this therapeutic class (Calabresi and Chabner, 1990. Goodman and Gilman's, The pharmacological basis of therapeutics). There were no changes in the indices of LD animals.

Bone Marrow

Hypocellularity of the bone marrow of the sternum and femur was observed in 10/10 HD males and females, and 4/10 MD males and females following dosing. This finding correlated with the depressed red cells, white cells, and platelets observed in these groups as noted above. Following recovery, bone marrow findings from mid- and high-dose animals were comparable to concurrent controls.

Clinical Chemistry

Levels of AST were consistently increased in HD males and females when compared to concurrent vehicle controls following dosing with taxotere; levels recovered to pretest values between dosing intervals and during the 4 weeks following dosing. Enzyme levels increased 23-63% and 13-56% in HD males and females, respectively. It was interesting to note that increases were observed in various enzyme parameters of vehicle control animals when compared to saline controls.

Levels of glucose were consistently increased from 13-23% in HD females and sporadically increased from 9-15% in HD males. Levels recovered to pretest values between dosing intervals. Other variations were also sporatically observed in these animals throughout the study. The clinical chemistry parameters of MD and LD animals were similar to those of concurrent controls.

Urinalysis

There were no drug-related changes in the urinalyses of dosed animals.

Necropsy

Macroscopic observations. HD males exhibited soft and/or small testes following dosing (2/10, 5/10, respectively) and recovery (1/5, 3/5, respectively). These observations correlated with histopathological findings of necrosis of the epididymides and seminal vesicles, and atrophy and spermatocyte degeneration of the testes in these animals. Other incidental changes were not considered to be related to dosing.

Organ Weights. Changes in organ weights following 6 months of taxotere treatment consisted of significantly depressed absolute and relative testicular weights following dosing and recovery. Absolute testicular weights were depressed 28 and 37% following dosing and recovery, respectively, when compared to concurrent vehicle controls. Relative testicular weights were depressed 10 and 22% following dosing and recovery, respectively. These findings correlated with the histopathological observations of increased severity of testicular degeneration following the recovery period. Other organ weight changes (increased relative weights at the HD) were related to decreased body weights.

Microscopic observations. Malignant lymphoma was exhibited in several organs of one MD male which was sacrificed moribund on day 153; histology was not performed on the MD female which died on day 127.

Mid- and high-dose males and females exhibited significant pathologies associated with the anti-mitotic properties of taxotere treatment; findings were most pronounced in testes, epididymides, seminal vesicles, and bone marrow. Following dosing, necrosis was exhibited in the epididymides and seminal vesicles of 10/10 and 7/10 HD males, respectively; atrophy of the seminiferous tubules and spermatocyte degeneration of the testes was exhibited in 4/10 and 9/10 HD males, respectively. Following the recovery period, drug-related necrosis of the epididymis (3/5) and atrophy of the testes (3/5) persisted in males of this group. Cellular necrosis was also observed in the lacrimal glands, liver, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, thymus, and uterus of HD, and to a lesser extent, MD males and females. Increased karyomegaly (7/10) and cytomegaly (5/10) were also observed in the lacrimal glands of HD males; following the recovery period, cellular necrosis and increased karyomegaly and cytomegaly persisted in the lacrimal glands of these animals. Prominent paracortical histiocytes were observed in the mesenteric lymph nodes of MD (3/9, males) (3/10, females) and HD males (9/10) and females (8/10) following dosing; the study author considered this finding to be a secondary effect (lymphatic drainage) related to increased single cell necrosis of the gastrointestinal tract. All other microscopic findings were a result of venipuncture technique or were considered incidental and common for rats of this age and strain.

The major target organs of taxotere following 6 months of dosing were the lympho-hematopoietic system and the testes.

RP 56976 - 10-cycle toxicity study in dogs (each cycle consisting of a single intravenous infusion every 3 weeks)over a 6-month period followed by a two-month reversibility period. Study No. RPR/RD/CVRA/SM 92-0239, Vols 1.42-1.44.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Department Securite du Medicament, Alfortville, France in 1993. Taxotere (batch # FCH 162 and OP9-PROC92226) in 40mg/ml stock solutions of polysorbate 80 was administered to beagle dogs (5 animals/sex/group) at doses of 0.1, 0.375, or 1.5mg/kg per iv

infusion (2, 7.5, 30 mg/m^2; dosing volume, 12ml/kg; rate of infusion, 5ml/min) once every 3 weeks (days 1, 22, 43, 64, 85, 106, 127, 148, 169, 190) for a total of 10 infusions over a 6-month period. The first stock solution (GRV 1013), prepared with the first batch identified, was used to administer infusions 1-6; a second stock solution (GRV 1035) was used to administer infusions 7-10. Dogs were 16-17 months of age at study initiation; weights ranged from 9.3-12.3kg. The vehicle control group received polysorbate (PS) 80 diluted in a 0.9%NaCl solution, resulting in a 3.3% PS 80 solution corresponding to the PS solution used in the HD group.Two animals/sex/group were observed for 2 months (days 198-247) following the dosing period for reversibility of toxic effects.

Measurements and Observations

Daily	Mortality, clinical examination, food consumption
Weekly	Body weight
Pretreatment & 2X following 1st, 5th, 10th infusion (immediately following +24h later)	ECG, arterial BP, body temperature
Pretreatment & 1X following 5th, 10th infusion, 1X during reversibility	Ophthalmology
Following 1st, 10th infusion +24h later	Plasma drug determinations (see pharmacokinetics for review)
Pretreatment, 1 day + every week following each infusion, wk 1+8 of reversibility	Hematology, coagulation, clinical chemistry
Pretreatment, 1 day following 10th infusion, 1X following reversibility	Urinalysis
Post treatment & post reversibility	Organ weights, gross pathology, histopathology

Mortality and clinical observations

No drug-related mortality occurred during the study. Severe diarrhea was exhibited in 1-4/5 HD males and MD and HD females during and up to 1 week following each infusion period; bloody stool was observed in 7/10 HD males and females following the first infusion and 2-3/10 HD males and females sporadically following subsequent treatment. Three HD males and one HD female were most consistently affected; in addition, one LD female exhibited bloody feces up to 19 days following 4th, 6th and 7th infusions. Vomitus containing blood was observed in 3/10 HD males and

females 4-5 days following the second infusion; increased respiratory rate was exhibited in 1-2/5 LD and MD females following infusion 3 to 10. Alopecia was exhibited in HD animals from study week 4 to study termination. A number of clinical observations (facial erythema and edema, generalized erythema, lacrimation, agitation following infusion followed by somnolence, involuntary defecation, increased respiratory rate, and EKG, arterial and BP changes) were exhibited in control and dosed animals and were considered to be vehicle-related (PS 80) changes; PS 80 is known to act as a nonspecific histamine releaser in dogs when administered iv. Thickening of the ears of HD dogs following edema are indicated to be an additive effect of taxotere and the vehicle.

Body weight and food consumption

Body weights of HD males and females were depressed 9-10% following the first and second infusion when compared to concurrent controls and 7-9% when compared to pretreatment weights. Individual weights of these animals varied from 0 to 13% during this time. Body weights of these HD animals were similar to pretreatment weights from the third infusion to the end of the dosing period; weights were depressed up to 7% in males and 11% in females when compared to concurrent controls during this time. Following the tenth infusion, body weights were depressed up to 17% in HD males when compared to concurrent controls and in control and HD females when compared to pretreatment weights; the study author indicated that this was due to the low body weight of animals retained for the reversibility period. Body weights of MD and LD animals were similar to those of concurrent controls.

Food consumption of HD animals was severely depressed or absent following each dosing infusion throughout the study; the absence of food consumption was most prolonged following the first treatment (study days 1-8). Food consumption recovered by the second week following each infusion in these animals. Food consumption of LD and MD animals was similar to that of concurrent controls.

Electrocardiography

Immediately following taxotere infusion and continuing for 24 hours, heart rates of dosed and control animals increased up to 59% above pretreatment rates. These increased rates were considered to be a result of the polysorbate 80 vehicle which has been reported to induce this effect secondary to histamine release (Budden et al., 1978. Arzneimittelforschung, 28,1586)
Additional EKG readings were recorded for one LD (animal #27) and one HD(animal #39) female 48 and 72 hours following the first infusion. Sporadic changes in the EEG of these animals was not considered to be a result of dosing with taxotere.

Arterial Blood Pressure and Body Temperature

Arterial blood pressure of dosed and control animals was depressed up to 50% below pretreatment pressure immediately following taxotere infusion; this effect was considered to be a result of the hypotensive effect of polysorbate 80 vehicle.

The body temperature of control and dosed animals was depressed up to 2.3 degrees below pretreatment temperatures; this effect was considered to be a result of the hypothermic effect of polysorbate 80 vehicle. Temperatures recovered 24 hours following dosing.

Ophthalmology

Alopecia and purulent discharge of the eyelids were exhibited in 2/5HD males and 5/5

HDfemales; this effect was considered to be a result of the increase in viscosity of lacrymal secretions in these animals. The changes were less severe following the recovery period. There were no opthalmological findings in LD or MD animals.

Hematology

Administration of taxotere was associated with depressions in red cell indices/reticulocytes, platelets, and white cell counts in MD and HD males and females when compared to concurrent controls; hematological measurements were conducted 1 day following infusions. Males appeared to be affected to a greater extent when compared to females. Changes in red cell parameters (with the exception of reticulocytes), and platelets were greater at the beginning of the treatment schedule. White cells were depressed throughout the study in a dose-related manner. Recovery of hematologic indices was observed 2 weeks following each treatment period.

Following the first infusion (study day 2), red cell indices (RBC, Hgb, Hct) were depressed 8-10% and 4% in HD males and females, respectively. Reticulocyte counts were depressed 90% in MD and HD males and 40% in HD females when compared to concurrent controls. Platelet and WBC counts were depressed 27-39 and 28-32% in HD and MD males; WBC were depressed 43% in HD females when compared to control animals. RBC indices (with the exception of reticulocytes) were mildly depressed (10-15% in HD males and <5% in HD females) from study day 9 to study termination. Reticulocytes were depressed 45-65% in HD males and up to 25% in HD females when compared to concurrent controls during this time. Platelets were depressed 17% in HD males on day 9; following the third infusion to study termination, platelets were only mildly affected (8% depression) when compared to concurrent controls. WBC were depressed 40-50% in HD males and females following each infusion; lymphocytes and neutrophils were affected to the greatest extent. There were no drug-related hematological effects in LD animals.

Bone Marrow

Hypocellularity of the bone marrow of the sternum was observed in 5/5 HD males and females following dosing. This finding correlated with the depressed red cells, white cells, and platelets observed in these groups as noted above. Following recovery, bone marrow findings from HD animals were comparable to concurrent controls.

Clinical Chemistry

Levels of AST were consistently increased in HD males and females when compared to concurrent contols following dosing with taxotere; levels recovered to pretest values between dosing intervals. On day 2, enzyme levels increased 2.6-fold and 4.7-fold in HD males and females, respectively. On day 9, enzyme levels increased 3.5-fold in HD animals of both sexes; levels were similarly increased following infusions throughout the study. Increased AST was not associated with changes in ALT; however, increases in alkaline phosphatase (25-40% when compared to concurrent controls) were observed in HD females. These changes were not considered to be of biological significance by the study author. Slight depressions in levels of calcium (4-6%) were observed in HD males and females. There were no changes in the serum chemistry parameters of LD or MD animals which were considered to be a result of dosing with taxotere.

Urinalysis

There were no drug-related changes in the urinalyses of dosed animals.

Necropsy

Macroscopic observations. HD males and females exhibited edema and alopecia of the external ears and alopecia and discoloration of the skin; these findings correlated with histological changes observed in these animals. Other incidental changes were not considered to be related to dosing. The testes were not examined macroscopically.

Organ weights. Changes in organ weights following 6 months of taxotere treatment consisted of significantly increased liver weights in HD males and females when compared to concurrent contols. Absolute liver weights were increased 36 and 22% in males and females, respectively and liver-to-body weight ratics were increased 40 and 38% in these animals. These increased weights were considered to be associated with the increased clear cells in the cytoplasm of hepatocytes. Increased liver weights were not exhibited following the reversibility period. Absolute testicular weights of HD males were depressed 12% following dosing and 23% following recovery; these testicular changes were not reviewed by the study author.

Microscopic observations. HD males and females exhibited multiple pathologies associated with the anti-mitotic properties of taxotere treatment; findings were most pronounced in the epididymides, gastrointestinal tract, exocrine pancreas, skin, and bone marrow. Following dosing, cellular necrosis was exhibited in the epididymides of 2/3HD males and pancreas of 2/3 HD females. In addition, necrosis was observed in the colon (2/3 HD♂, 1/3HD♀), cecum (2/3HD♂,2/3HD♀), rectum (2/3HD♂,1/3HD♀), stomach (3/3HD♂, 3/3HD♀), and tongue (3/3HD♂,2/3HD♀) of these animals. Necrosis was not observed following the recovery period. Tubular degeneration of the testes was observed in 1/3 LD males and 2/3 MD and HD males; following recovery, this finding was exhibited in 1/2 MD males. Edema, inflammation, and epidermal degeneration of the external ears were observed in 3/3HD males and females and 1/3 LD females; edema was seen following the recovery period. Similarly, epidermal degeneration and increased mitotic figures were observed in the skin of the limbs and trunk of 3/3HD males and females following dosing; a decrease in the number of anagen follicles of the skin was observed following dosing and recovery. Increased clear cells of the hepatocellular cytoplasm (representing increased glycogen content) of control and dosed animals were observed following dosing and recovery. All animals exhibited hemorrhage of the injection sites as a result of the infusions. All histopathological changes with the exception of the hepatocellular findings and injection site hemorrhage were considered to be a result of the antimitotic properties of taxotere.

The major target organs of taxotere following 6 months of dosing were the lympho-hematopoietic system, the gastrointestinal tract, and the skin.

Long Term effects

Carcinogenicity

There were no carcinogenicity studies conducted.

Special Toxicity Studies

Compatability and Hemolytic Potential Studies. Previously reviewed studies indicated that 0.3mg/ml taxotere and the corresponding vehicle solution (polysorbate 80:ethanol, 50:50) diluted with 5% glucose solution did not cause precipitation or coagulation of human serum or plasma. The

hemolytic potential of 0.075mg/ml taxotere corresponding to a 0.5% vehicle solution, diluted with 5% glucose did not cause hemolysis after 45 mins of incubation. More concentrated taxotere (0.15 and 0.3mg/ml) corresponding to 1 and 2% vehicle solutions did cause hemolysis after 45 mins; there was no hemolysis after 15 mins with 0.3mg/ml taxotere or the 2% vehicle solution.The compatibility and hemolytic potential of formulation N° 2 was similar to that of the original formulation.

Summary of Toxicology

Single dose toxicity studies are summarized in the table below. All dosing was administered iv. The predominant observations included non-extension and/or paresis of hindlimbs resulting from axonal and myelin degeneration of sciatic nerves of mice, and body weight loss, and testicular and lymphohematopoietic changes in mice and rats. Lethality in mice may have been due to drug precipitation during dosing; target tissues were the testes, neuromotor system, and possibly the heart (myocardial mineralization/degeneration, myocarditis, pericarditis). Death occurred immediately following dosing. A taxotere dose of 64mg/kg administered to female mice induced an absence of hindlimb extension reflex. Rats exhibited bone marrow hyperplasia, tissue atrophy of multiple organs (including testes), and pulmonary changes; tissue atrophy was a result of vehicle administration. Testicular atrophy and pulmonary toxicity were not reversible. Dogs exhibited abnormal respiration, tremors and head shaking, myelosuppression, atrophy of the lymphoid organs, and impaired kidney function; recovery was exhibited following dosing. Death was due to gastrointestinal toxicity. All single dose toxicity studies included 4-week recovery periods with the exception of the dog study with extended recovery to 65 days. During dosing in dogs, all animals including controls administered the polysorbate 80 vehicle, exhibited clinical signs (peripheral vasodilatation, swelling of muzzle, ears and limbs, tremors, dyspnea) which were attributable to histamine release by the polysorbate 80.

Single dose toxicity studies with taxotere

Species	Formulation	Observations	LD_{10} (mg/m^2)	LD_{50} (mg/m^2)
mouse	PS 80 + ethanol in 0.5% glucose	Non-extension/ paresis of hindlimbs	285-468	N/A
mouse	PS 80 in 0.5% glucose	Non-extension/ paresis of hindlimbs	345♂ N/A♀	414(378-450) 192-285♀

mouse	PS 80 +ethanol in 0.5%glucose	Non-extension of hindlimbs/ myelin degeneration of sciatic nerve - not reversible	N/A	N/A
rat	PS 80 in 0.5% glucose	Bone marrow hyperplasia; tissue atrophy; pulmonary changes; vacuolation of the sciatic nerve	N/A	N/A
dog	PS 80 +ethanol in 0.5% glucose	Myelosuppression; atrophy/lymphoid organs; impaired kidney function	N/A	50

Previously reviewed studies indicated that neurotoxicity was exhibited in mice administered iv taxotere at single doses of 64-156mg/kg (192-468mg/m2) and 5 daily doses of 15-17.5mg/kg (45-112.5mg/m2); clinical signs included non-extension and paresis of the hindlimbs which resulted histologically from myelin and axonal degeneration of the sciatic nerve of these animals. Neurotoxic changes were dose-related and culmulative. Recovery was observed at the lowest doses within the 4-week recovery period. Vacuolation of the sciatic nerve was observed to a lesser extent in 7/10 male and 6/10 female rats administered 10mg/kg (60mg/m2) taxotere one time each 21 days for 3 cycles and in 4/5 male and female rats following 4 weeks of recovery. Since 3/10 male and female vehicle control (PS80) rats exhibited this same finding following dosing and recovery (2/5♂, 1/5♀), the study author considered this finding to be of no toxicological significance in this species. However, since the PS 80 vehicle is used clinically, the reviewer considers this finding to be significant. In addition, the vacuolation of the sciatic nerve appears to be enhanced with PS 80 and taxotere administration. Even though the study did not test untreated control animals, it seems unlikely that this finding would be observed in these animals. There were no clinical signs of neurotoxicity or histopathological changes found in rat studies of longer duration and lower dose concentrations (10 cycles at doses up to 5mg/kg [30mg/m2]). Heart weights of male rats administered 0.1 and 0.2mg/kg taxotere daily for 4 weeks were depressed by 10-11%; study authors did not consider this to be a drug-induced effect.

Acute studies with the two major degredation impurities indicated similar toxicities; clinical signs following administration of RP 70617 and RP 73077 included dyspnea, decreased motor activity, and prostration. Both impurities were found to be less toxic than taxotere. Similarly, toxicity studies found metabolites to be less toxic than the parent compound.

Multiple dose toxicity studies were conducted in mice, rats and dogs with consecutive daily dosing for 5 days to 4 weeks or single doses every 3 weeks for 6 weeks to 6 months; doses were administered iv and the recovery period extended from 4 to 8 weeks. Reversible lymphohematopoietic changes, consisting of depressed erythrocytic, thrombocytic and leukocytic parameters,

hypocellularity of the bone marrow, and thymic and lymphoid atrophy were observed in rat and dog multiple dose studies. Other major toxicities in study animals included necrosis of epididymides and seminal vesicles, atrophy of seminiferous tubules, and spermatocyte degeneration; necrosis of epididymides and testicular atrophy persisted following the recovery period. There were no reproductive tract toxicities exhibited in females; pharmacokinetic studies indicated that taxotere was not distributed in the female reproductive system. Elevations in liver enzymes and increased liver weights were exhibited following dosing. Body weights and food consumption were depressed in rats and dogs administered 30 mg/m^2; body weights recovered in dogs following recovery.
When dogs were administered a single dose of 50mg/kg (2.5mg/m^2) taxotere in PS80+ethanol, tremors were observed on study days 1 (30m following dosing) and 2 in 1/2 animals; the sciatic nerve was not examined. When dogs were dosed with taxotere in PS80/etoh for five days, tremors and collapse were exhibited in 1/2 males administered 0.3mg/kg on days 4 and 5; 1/2 females exhibited tremors at 2, 3, 4, and 5 days following dosing at 0.15mg/kg. Tremors were also exhibited in 1/2 females at 0.3mg/kg on day 1 and 1/2 females administered 0.3mg/kg on days 4, 5, and 6. There was no histopathology of the sciatic nerve.

The data from the iv multiple dose toxicity studies is summarized in the following table. The taxotere formulation used for rat studies and the 10-cycle dog study was composed of polysorbate 80 and taxotere in 0.5% glucose. Following repeat dosing, the rat appeared to exhibit greater sensitivity to taxotere at a dose of 6mg/m^2 and a plasma level of 0.2ug/ml when compared to the dog. The initial dose of the Phase I clinical trial was 5mg/m^2; one-third the TDL 5-cycle study in the dog. Dosing consisted of a 6-hour infusion every 21 days. According to preclinical data in mice and rats, neurotoxic effects may be avoided clinically by maintaining doses below 192mg/m^2. Dosing for breast cancer and non-small cell lung cancer is a 1-hour infusion every 21 days at a level of 100mg/m^2.

Species	Schedule, Duration of Study	HDNL (mg/m^2)	Plasma level (ug/ml)	Major toxicities
Rat	Daily x 4 wks/ 4wks recovery (Doses: 0.3, 0.6, 1.2mg/m^2)	1.2	N/A	Mild hematologic and testicular effects
	3-cycle Single dose/3wks x 6wks 4 wks recovery (Doses:15, 30, 60mg/m^2)	30	1.6-2.5	Hematologic effects ↓BW, FC, testicular changes, thymic atrophy @30 and 60mg/m^2; BM hypoplasia all doses

Rat	10-cycle Single dose/3wks x 6 months / 4 wks recovery (Doses: 1.2, 6, 30mg/m^2)	1.2	N/A	Severe hematologic effects, ↓BW, FC necrosis/atrophy testes @ 30 mg/m^2
Dog	5-cycle Single dose/3wks x 12wks 4 wks recovery (Doses: 7.5, 15, 30mg/m^2)	15	0.33-0.65	Leucopenia, alopecia @15 and 30mg/m^2
Dog	10-cycle Single dose/3wks x 6 months 4 wks recovery (Doses: 2, 7.5, 30mg/m^2)	7.5	0.2	Severe hematologic effects, skin lesions@30mg/m^2 (plasma level 2ug/ml@30mg/m^2); tubular degeneration of testes @ 0.375, and 1.5mg/kg

Histopathology Inventory for NDA # 20-449

Study	0026	0239	Histopathology of other toxicology studies was not tabulated.
Species	rat	dog	
Adrenals	x	x	
Aorta	x	x	
Bladder			
Bone Marrow smear	x	x	
Bone (femur)	x	x	
Brain	x	x	
Cecum	x	x	
Cervix			
Colon	x	x	
Duodenum	x	x	
Epididymis	x	x	
Esophagus	x	x	
Eye	x		
Fallopian tube			

Gall bladder		x
Harderian gland	x	
Heart	x	x
Hyphophysis		
Ileum	x	x
Injection site	x	x
Jejunum	x	x
Kidneys	x	x
Lachrymal gland	x	
Larynx		
Liver	x	x
Lymph nodes, cervical submandibular	x	x
Lymph nodes, mesenteric	x	x
Lungs	x	x
Mammary Gland	x	x
Nasal cavity		
Optic nerves	x	
Ovaries	x	x
Pancreas	x	x
Parathyroid	x	x
Peripheral nerve		
Pharynx		
Pituitary	x	x
Prostate	x	x
Rectum	x	x
Salivary gland	x	x
Sciatic nerve	x	x
Seminal vesicles	x	
Skeletal muscle	x	x
Skin	x	x
Spinal cord	x	x

Spleen	x	x
Sternum	x	x
Stomach	x	x
Testes	x	
Thymus	x	x
Thyroid	x	x
Tongue	x	x
Trachea	x	x
Uterus	x	x
Vagina	x	x
Zymbal gland		x
other-urinary bladder	x	x
other-bronchi	x	x
other-tonsils		x
other-ear		X

Reproductive Toxicity

Fertility and general reproduction study of RP 56976 administered intravenously to CRL:CD BR VAF/+rats (segment 1 evaluation) Study No.DS 92-090 Vols. 1.47- 1.48.

The study was conducted according to GLP(signed) at

Taxotere (batch # FCH 162) in polysorbate 80 was administered iv to Sprague-Dawley Crl:CD BR VAF/Plus rats (25 animals/sex/dose) at levels of 0, 0.05, 0.15, and 0.30mg/kg/day. Additional satellite groups of 18 control and 12 HD females were included for hematological determinations.

At study initiation, HD males were dosed with 0.45mg/kg/day; as a result of severe weight loss, the dose was reduced to 0.30mg/kg on study day 10. Dosing of 0.30mg/kg/day was initiated on study day 10 to an additional group of 25 males. In addition, due to severe weight loss, the dosage of HD females was reduced from 0.30 to 0.225mg/kg/day on study day 11. Males were administered taxotere for 61 days prior to mating and until scheduled sacrifice (additional 31-40 days). Males which received 0.45mg/kg were sacrificed on day 53 without mating. Females were dosed for 15 days prior to mating and until day 7 of gestation; animals were sacrificed and caesarean-sectioned on gestation day 20.

Measurements and observations

Daily: clinical signs and mortality, body weight of males and females during dosing and females following dosing, food consumption of females during gestation

Weekly: body weight of females prior to dosing, food consumption of males during dosing and females prior to mating

Week prior to necropsy: hematology (♂)

Gestation days 5-8: hematology (mated ♀- satellite group)

During breeding/pregnancy: breeding period, fertility index

Termination (♀, F0 on gestation day 20): gross necropsy, corpora lutea, implantation sites, # of live/dead fetuses, fetal examination (external, soft tissue, skeletal, body weight, sex ratio)

Termination (♂, F0 following confirmation of gestation): gross necropsy, absolute and relative testicular and epididymides weights

Mortality and clinical observations

There were no drug-related deaths in male rats; deaths in 1/25 control males , 2/25 LD males, and 1/25 MD male during dosing were not considered to be a result of taxotere administration. One of 25 HD females and 1/12 satellite females were found dead on study day 28 (following 10 days of dosing at 0.30mg/kg/day and 18 days of dosing at 0.225mg/kg/day); one female exhibited body weight loss and convulsions prior to death.

Body weight and food consumption

Body weights of MD and HD males were reduced 19 and 33%, respectively, when compared to controls.Body weights of males administered 0.45/0.30mg/kg were not reported. Body weights of HD females were reduced 7-13% from study days 8-15 prior to mating; weights progressively decreased 13-22% from gestation days 0-20. Food consumption was significantly reduced in MD and HD males and females throughout the study when compared to concurrent controls. Consumption was depressed up to 15, 40, and 42% in males administered 0.15, 0.30, and 0.45/0.30mg/kg and up to 6 and 36% in MD and HD females prior to mating and 12 and 27% in MD and HD females during gestation compared to concurrent controls. Food consumption of dosed females recovered following gestation day 12.

Hematology

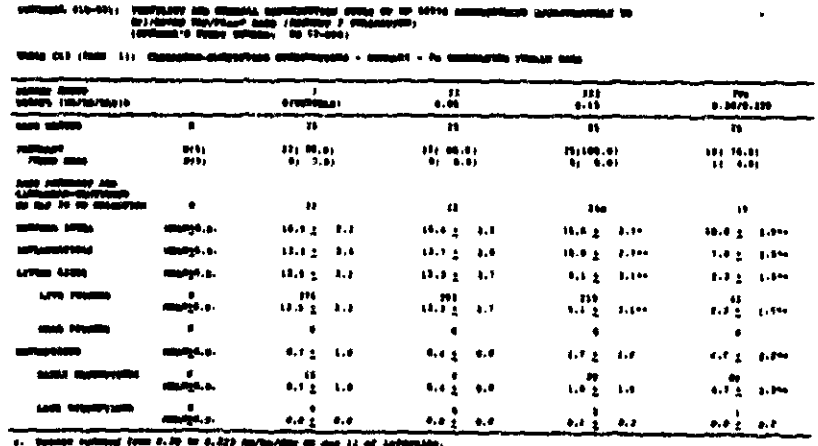
Red cell indices, white cell counts, and platelets were depressed in MD and HD males and females. RBC counts were depressed 9 and 33% in MD and HD males, respectively, and 5% in HD females; hct was depressed 26 and 8% in HD males and females, respectively. WBC counts were increased 24% in HD males and depressed 12% in MD females; platelets were depressed 27 and 15% in MD males and females, respectively.

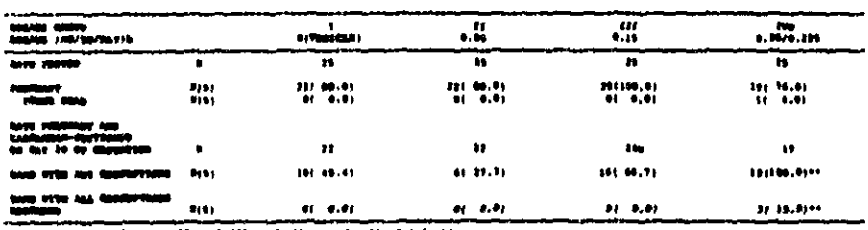
Mating parameters

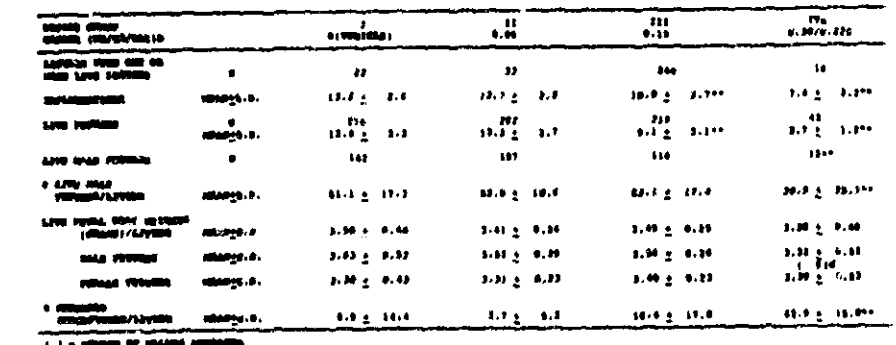
The mean time to mating of HD animals was twice the time to mating of controls and other dosed animals. The mating index was 100% in all animals with the exception of HD females with a mating index of 92%. The fertility index was 87-88% in control, LD, and HD males and females, and 100% at the MD.

Litter parameters

The number of implantations was 13.2, 13.7, 10.8, and 7.0 in control, 0.05, 0.15, and 0.30/0.225mg/kg females, respectively. The number of early resorptions was increased by 6-fold in HD females and 2-fold in MD females when compared to concurrent controls. The number of viable male fetuses at 0.30/0.225mg/kg was 8% the number of male fetuses in the control group. The litter size was 28% lower in the HD group as compared to controls. Live male fetal body weights were depressed by 9% in HD offspring; live female fetal body weights in offspring of this group were similar to offspring of the control group. The number of dams with all fetuses resorbed was increased (3/25) in the HD group.







Fetal anomalies

There were no drug-related gross fetal alterations.

Organ weights/Gross findings/F_0 generation

Absolute testicular and epididymis weights of HD males were depressed 24-27 and 12-13%, respectively; there were no drug-related microscopic changes. There were no abnormal macroscopic observations in dosed males or females.

RP 56976 Intravenous teratology study in rats with postnatal development phase.
Study No.RPR/RD/CRVA/SM 710, Vol 1.49.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Departement Securite du Medicament, Alfortville, France in 1993.

Doses for the study were based on a rangefinding teratology study (Study No. RPR/RD/CRVA/SM 685) conducted at Rhone-Poulenc Rorer in 1992 in which 8 mated female Sprague-Dawley rats were administered 0.1, 0.2, 0.5, or 1mg/kg taxotere iv (batch # FCH 160) from gestation days 6-17. Seven of eight HD females were sacrificed moribund; significant reductions were observed in food consumption and body weight gain of MD(0.5) and HD animals. Maternal observations of LD and MD(0.2) females were similar to controls. Taxotere induced intrauterine mortality at 0.5mg/kg and reduced fetal weights at all doses administered. Based on these results, dose levels of taxotere administered in the primary study appear to be appropriate.

Thirty pregnant Sprague-Dawley CD Crl:CD (SD)BR rats were administered iv taxotere (batch # FCH 162) at 0.03, 0.1, or 0.3mg/kg/day on gestation days 6-17. Twenty females were sacrificed on gestation day 20, and external, visceral, and skeletal anomalies of the fetuses were examined. Ten pregnant rats/group were observed to time of birth of pups and weaning on post partum day 21. An initial cull was performed on post partum day 4 (4 pups/sex/litter); physical and functional development of the pups was examined. A second cull was performed at weaning on post partum day 21 (2 pups/sex/litter); behavior of remaining pups was observed. The final cull was performed on post partum day 49 (1pup/sex/litter); the reproductive performance of the pups was investigated. F1 males were sacrificed following mating; reproductive organs were examined. Mated F1 females were sacrificed on gestation day 20; external anomalies of the F2 fetuses were examined. Parameters reported included maternal weight (days 1, 6, 9, 12, 17 and 20) and food consumption; maternal clinical signs; length of gestation; number of implantation sites, corpora lutea, early and late uterine deaths, and viable fetuses; and weight, sex, and variations/malformations of fetuses. Functional development, behavioral tests and reproductive performance were conducted on F1 pups.

Body weights of dams administered 0.3mg/kg were reduced 4-15% from gestation days 12 to 20; food consumption was reduced from 15-32% during this time. Embryo-feto toxicity at this dose was characterized by increased intrauterine mortality (50% post-implantation loss as compared to 15% in controls), reduced fetal weight (25% depression in weight as compared to controls), increased numbers of small fetuses (weighing <2g, 7/22 litters), and delay in skeletal ossification (increased incidence of incomplete ossification of thoracic vertebrae, nasal, interparietal, occipital and pubis bones). This effect was also characterized by small litter size (52% less than control size), and increased numbers of dead pups at birth (7 pups in3 litters as compared to 0 dead pups in control group); mean pup weight at birth was 9-10% lower than control pup weights. Body weight gain, physical and functional development, and behavioral and reproductive performance of viable pups

were not affected by maternal administration of 0.3mg/kg taxotere. Administration of 0.1 and 0.03mg/kg taxotere did not induce change in maternal, fetal, or postnatal parameters.There were no teratogenic effects observed.

Teratology study of RP 56976 in the rabbit by the intravenous route.
Study No. RPR/RD/CRVA/SM 707. Vol.1.50.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Departement Securite du Medicament, Alfortville, France in 1992.

Doses for the study were based on a rangefinding teratology study (Range-finding teratology study of RP 56976 in the rabbit by intravenous route, Study No. RPR/RD/CRVA/SM 689) in which 8 pregnant New Zealand White rabbits were administered taxotere (batch FCH 160) at levels of 0.01, 0.025, 0.05, 0.1 or 0.5mg/kg/day from gestation days 6 to 18. Rabbits administered 0.5mg/kg taxotere were found dead or sacrificed moribund following 7-9 days of treatment; food consumption and body weight gain were significantly depressed in these animals. In addition, food consumption was slightly reduced in dams administered 0.1mg/kg from gestation days 16-21; body weights were not affected.Taxotere did not induce changes in litter parameters at doses up to 0.1 mg/kg. Based on these results, dose levels administered in the primary study appear to be appropriate. Study authors indicated that the concentration of polysorbate 80 vehicle in dams administered 0.5mg/kg taxotere was 80% higher than the corresponding polysorbate 80 concentration in control dams but 100X inferior to toxic levels of the polymer.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1992. Twenty pregnant New Zealand White rabbits were administered taxotere iv at levels of 0.03, 0.1, or 0.2mg/kg (batch #FCH 162) from gestation days 6-18; four pregnant rabbits were administered 0.3mg/kg. The concentration of the polysorbate 80 vehicle was similar in control and HD animals. Animals were observed to sacrifice on gestation day 29. Observations and measurements included maternal body weight (gestation days 1, 6, 9, 12, 18, 23 and 28), daily food consumption and clinical observations, maternal hematological determinations, and litter data (number of corpora lutea, implantation sites, early and late uterine deaths, viable fetuses, and external, skeletal, and soft tissue examination of fetuses).

Initial dosing with 0.3mg/kg was suspended due to severe toxicity; 4/4 females were found dead or sacrificed moribund on gestation days 16-20. Fifteen of 20 rabbits administered 0.2mg/kg were found dead on gestation days 16-22; an additional rabbit was sacrificed moribund on gestation day 10. Surviving dams of this group (4/20) aborted on gestation days 19-25. Three of 20 rabbits administered 0.1mg/kg taxotere aborted on gestation days 26-28. Abortions were observed only at maternally toxic doses. There were no unscheduled deaths or abortions in control or LD groups.

Observations of dams administered 0.03, 0.1, or 0.2 mg/kg taxotere included a dose dependent incidence of decreased food consumption, body weight loss, and reduced feces output. In addition, body weights were reduced up to 25% in LD dams during the dosing period when compared with concurrent controls (33% loss in MD dams). Surviving dams administered 0.2mg/kg taxotere exhibited depressed red cell indices (9.9% depression in red cell counts, 13% depression in hct, 11% depression in hgb when compared to controls), and depressed platelet (61% depression when compared to controls) and white cell counts (64% depression primarily as a result of depressed neutrophil counts). Platelet counts were depressed up to 30% in dams administered 0.1mg/kg when

compared to concurrent controls. There were no changes in the hematological parameters of LD dams.

There was a slight increase in post-implantation loss in dams and decrease in viable young in groups administered 0.03 and 0.1mg/kg when compared to concurrent controls but not when compared to historical controls; increases were not significant. Fetal body weight in the 0.1mg/kg group was depressed by 8% when compared to concurrent and historical controls. Skeletal anomalies primarily involved delays in ossification in the 0.1mg/kg group (enlarged fontanel, unossified metacarpals, incomplete ossification of sternebral and pubis bones) and slight delay in skeletal ossification of the 0.03mg/kg group (enlarged fontanel or unossified metacarpals); these changes were considered to be consistent with maternal effects (decreased body weights and food consumption, reduced feces output at MD and LD) and lower fetal weights observed in these groups. No evidence of a teratogenic effect was observed following dosing with taxotere. Litter data of 0.2 and 0.3mg/kg groups was not provided due to unscheduled deaths.

Intravenous peri and post-natality (segment III) study in rats with reproductive performance of the F1 generation. Study No. RPR/RD/CRVA/SM 92-0117. Vol 1.50.

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Departement Securite du Medicament, Alfortville, France in 1992. Taxotere (batches OP3-PROC 92174 and OP4-PROC 92178; purity 100%; in a 40mg/ml stock solution of polysorbate 80) was administered iv to pregnant Sprague-Dawley Crl:CD(SD)BR rats (19-24 animals/group) at levels of 0.04, 0.10, or 0.25mg/kg/day from gestation day 15 to post-partum day 21. The pregnancy rate of HD females (19/30) was decreased when compared to control, LD, or MD females; the study author considered the rate to be within the historical range of the laboratory. Culling was performed on post-partum days 4 (litters culled to 8 pups/litter), 21(litters culled to 4 pups/litter), and 49 (litters culled to 2 pups/litter). One F1 male and female pup/litter were mated for assessment of reproductive performance. The F2 generation was observed to post-partum day 7.

Measurements and observations

Dams: Daily clinical signs, body weight (gestation days 1, 6, 9, 15, 20, and post-partum days 1, 4, 7, 14, and 21), food consumption (daily from gestation day 1 to post-partum day 13), gestation length and gross necropsy, including implantation sites and corpora lutea.

Fetuses: # live/dead, sex, visceral and skeletal anomalies.

Live offspring: Mortality, sex, external abnormalities, survival rates, weaning rates, body weight (pre-weaning days 1, 4, 7, 14 and 21 and weekly thereafter to day 77), food consumption (weekly), developmental parameters (external ears, incisors, separation of eyelids, descent of testes, opening of vagina, visual and auditory function, surface righting and negative geotaxis assessment, forelimb support and swimming development, water maze, and locomotor and exploratory activities), and reproductive assessment (mating and conception rates, # live/dead fetuses, sex, macroscopic examination).

Maternal and fetal observations

There were no significant differences in clinical signs, food consumption, or gestation length of control or dosed dams. Body weights were depressed from 5-8% in dosed females when compared to contols during gestation; changes in body weights were not dose related. Weights during the

lactation period were slightly depressed only at the HD (3-4%); this was a result of reduced food consumption in this group (4-10%). Post-implantation loss was slightly increased in LD and MD dams (14.2 and 16.6%, respectively) when compared to contols (10.2%); the number of dams with litter resorption varied slightly in dosed animals (2 at LD, 1 at MD, 2 at HD) but were considered within the historical range of the laboratory.

Neonatal parameters (F1 generation)

There were no significant differences in the number of stillborn and viable pups, malformed pups, or body weights of pups in control and dosed groups. There was a slight delay in the onset and completion of eye opening in males and females and vaginal opening in females from the HD group when compared to controls. A slight delay in functional development was also exhibited in this group as assessed by forelimb support; no other differences were seen in the physical or functional development of these animals. There were no differences in the behavioral development or macroscopic examination of pups culled at weaning or at post- partum day 49. When the F1 rats were mated, the mating and fertility performances did not differ between dosed and control groups. In addition, there were no differences in mortality, body weights, gestation length, pregnancy rates, or implantation loss. There were no differences in survival indices, body weights, or macroscopic observations of F2 pups. Nine stillborn pups were born to one LD F1 female; the finding was considered to be incidental. There were no drug-related changes in the postnatal development or reproductive performance of F1 pups or the postnatal development of F2 pups from LD or MD groups.

Summary and Evaluation of Reproductive Toxicology

The 2-generational rat fertility study demonstrated that a daily iv dose of up to 0.30 mg/kg (1.8mg/m2) taxotere for 61-70 days prior to mating in males and 15 days prior to mating until gestation day 7 in females resulted in increased number of early resorptions at 0.15 and 0.225/0.3 mg/kg, and decreased litter size, decreased numbers of viable male fetuses, and depressed fetal body weights in male offspring at 0.225/0.30 mg/kg. Complete spermatogenesis and oogenesis cycles were exhibited; however, weights of testes and epididymides were reduced. This correlates with findings of 6-month rat and dog studies. Initial dosing of 0.45mg/kg in males and 0.30mg/kg in females was reduced due to severe weight loss in these animals.

The teratology studies performed by the sponsor demonstated the maternal and embryo/feto toxicity of taxotere. A 0.3mg/kg dose of taxotere administered on gestation days 6-17 resulted in increased intrauterine mortality (50% post-implantation loss as compared to 15% in controls), reduced fetal weights, increased numbers of small fetuses, small litter size, increased numbers of dead pups at birth, and delay in skeletal ossification. Administration of 0.1 and 0.03 mg/kg did not induce change in maternal, fetal, or postnatal parameters. In the rabbit, dosing with 0.30mg/kg resulted in maternal death; doses of 0.20mg/kg resulted in maternal death and abortion of fetuses. Doses of 0.10mg/kg resulted in 20% abortion, reduced fetal body weights, and delay in skeletal ossification; skeletal ossification was delayed in fetuses with dosing as low as 0.03mg/kg. In a separate study in rats, post-implantation loss was slightly increased following dosing with 0.04 and 0.10mg/kg (14-17%) and there was a slight delay in eye opening, vaginal opening, and functional development in pups from the 0.25mg/kg group. There were no changes in the development of the F2 generation.

There was no significant demonstration of teratogenicity following taxotere administration.

Genetic Toxicity

In vitro gene mutation test of RP 56976 on Escherichia coli strain WP2 uvr A
Study No. RPR/RD/CRVA/SM 637 Vol.1.51

The study was conducted according to GLP (signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1992. *Escherichia coli* strain WP2 with/without metabolic activation was assayed with up to 1000ug taxotere (batch #FCH 160) /plate dissolved in DMSO. Positive controls included N-ethyl-N'-nitro-N-nitrosoguanidine and 2 anthramine.

The preliminary cytotoxicity assay produced slight toxicity (65% cell survival without S9, 62% survival with S9 activation, precipitate visible) at 1025ug taxotere/plate. Mutagenicity assays conducted with concentrations/plate ranging from ug taxotere did not produce an increase in the number of revertants with or without metabolic activation when compared to negative controls. A precipitate of taxotere was observed at 1000ug/plate. Positive control drugs increased the number of revertants by fold as compared to controls.

Chromosome aberration test in Chinese Hamster Ovary cells (CHO-K1)
Study No. ST/CVRA/IRSM 508 Vol. 1.51

The study was conducted according to GLP(signed)at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1990. Taxotere (batch #PHI 2512) was tested for in vitro clastogenicity on the CHO-K1 cell line at concentrations of 0.2-1 and 2ug/ml without metabolic activation and at 0.05-0.2 and 1ug/ml with metabolic activation. Cyclophosphamide and methylmethanesulfonate w used as the positive contols with and without metabolic activation, respectively.

Slight but not significant increases were observed in the percentage of cells with aberrations when compared to negative controls. At the 18-hour observation period, aberrations increased up to 1.7-fold without metabolic activation at 2ug/ml, and 2.5-fold with metabolic activation. At the 42-hour observation, aberrations increased up to 2-fold with metabolic activation when compared to negative controls. Positive control drugs increased the percentage of cells with aberrations (up to 5.9-fold without metabolic activation, up to 9.2-fold with metabolic activation), as well as the mean number of aberrations/cell, and the number of cells with more than one aberration.

The percentage of hyperploid cells was increased both with and without metabolic activation at all taxotere concentrations and at both observation periods when compared with controls. Increases ranged from at h, fold at h without metabolic activation, and fold at h, fold at h with metabolic acivation.

Effect of RP 56976 on the distribution of CHO-K1 cells in the cell cycle phases
Study No. ST/CRVA/TOX 407 Vol. 1.51

The study was conducted according to GLP(signed)at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1990. CHO-K1 cell cultures were exposed to taxotere concentrations of 0.05, 0.1, 0.5, or 1ug/ml for 16 and 30 hours; accumulation of cells in mitosis, and appearance of aneuploid cells was observed at 16 and 30 hours, respectively. Vincristine served as the positive control at a concentration of 1.25ug/ml.

Taxotere produced a concentration-dependent increase in the number of cells in the mitotic (M) phase following 16 hours of exposure to taxotere; a concentration of 0.5ug/ml taxotere produced an arrest in the M phase comparable to vincristine. The appearance of aneuploid cells was observed following 30 hours exposure to taxotere, with a concentration-dependent shift in DNA content from 2n-4n to 4n-8n. The effects of 1ug/ml taxotere were similar to those observed with vincristine; taxotere appears to exert a comparable spindle poison effect to that of the positive control.

Hypoxanthine-guanine phosphoribosyl transferase gene mutation test in Chinese Hamster Ovary cells (CHO-K1) Study No.RPR/RD/CRVA/SM 550 Vol. 1.51

The study was conducted according to GLP(signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1991. CHO-K1 cells were exposed to taxotere (batch # PHI 2512) at concentrations of 0.025, 0.05, 0.25, 0.5, 2.5, 5, and 25ug/ml with and without metabolic activation; cytotoxicity was observed at all concentrations in a dose dependent manner. Cell survival was 9, 31, 60, 67, and 85% at 25, 5, 2.5-0.25, 0.05, and 0.025ug/ml taxotere, respectively, 24h following exposure. The cloning efficiencies of the cells were disrupted at all concentrations, especially at 25 and 5ug/ml. Taxotere was less cytotoxic with metabolic activation; cell survival was 18, 63, and 76-88% at 25, 5, and 2.5-.025ug/ml. The cloning efficiencies of the cells were disrupted at all concentrations.

When CHO-K1 cells were exposed to taxotere at concentrations of 0.005, 0.025, 0.05, 0.5, and 5ug/ml without metabolic activation, cell survival was 55%, and 81-104% at 5 and 0.5-0.005ug/ml, respectively, 24 hours following exposure. Cloning efficiencies were disrupted from 21-76% of negative control at all concentrations. A significant mutant clone induction was observed at 0.025ug/ml (15 mutant cells/1million live cells). When the assay was repeated, survivability and cloning efficiencies were similar; a significant mutant clone induction was observed at 5ug/ml (13 mutant cell/1million live cells). The third repeat assay indicated 78% cell survival at 5ug/ml and no cytotoxicity at lower concentrations. Cloning efficiencies were disrupted at concentrations up to but not including 0.005ug/ml; a similar significant clone induction was observed at 0.025ug/ml. Cell survivability was not dose related; mutant clone induction was slightly above mean historical control data (10.7 mutants/1 million live cells) but not above maximum historical data (26-27mutants).

When taxotere was tested at the same concentrations with metabolic activation, cell survivability was 58% at 5ug/ml; no cytotoxicity was observed at lower concentrations in assay 1 or at any concentration in assay 2. Cloning efficiencies were disrupted at 5ug/ml (44% of negative control) in assay 1, and at 0.05-5ug/ml (57-81% of negative control) in assay 2. There was no significant mutant clone induction in either assay. Taxotere did not demonstrate any in vitro mutagenic activity.

Bone-marrow micronucleus test in the mouse by intravenous route
Study No. RPR/RD/CRVA/SM 544 Vol.1.51

The study was conducted according to GLP(signed) at Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Alfortville, France in 1991. CD-1 mice (5/sex/dose) were administered iv 0.195, 0.39, 0.78, 1.56, 3.125, or 7.2mg/kg taxotere (batch #PHI 2388) 2X at an interval of 24hrs, absolute control (5% glucose), vehicle control (polysorbate 80/ethanol) or 1mg/kg ip mitomycin C as the positive control. Bone marrow smears were obtained at 24 hours following the second treatment and analyzed for polychromatic micronuclei (PMNs).

As a result of the high cytotoxicity exhibited at 3.125 and 7.2mg/kg taxotere, results of bone marrow smears were reported for four lower dose groups. Cytotoxicity was also observed at 0.195mg/kg (cell survival depressed 7.5% as compared to absolute control). PMNs were inceased 1.7-fold, 2-fold and 9-fold in 0.39, 0.78, and 1.56mg/kg taxotere-treated mice at 24 hours as compared to vehicle controls. Mitomycin C produced cytotoxic and clastogenic (10.6-fold increase in PMNs) effects.

Summary of Genetic Toxicity

Taxotere was not found to be mutagenic in bacterial strains or the CHO/HGPRT assay, with or without metabolic activation; however, it was highly cytotoxic in multiple assays. Taxotere was found to produce pronounced polyploidy in the *in vitro* chromosomal aberration test in CHO-K1 cells. A dose-dependent increase was exhibited in the number of micronucleated cells with or without metabolic activation in the CHO-K1 micronucleus test. In the *in vivo* mouse micronucleus test, taxotere induced dose-dependent cytotoxicity and increased polychromatic erythrocytes. The results are consistent with the mechanism of action of taxotere.

Overall Summary and Evaluation

Taxotere is stucturally related to taxol; both drugs act as spindle poisons which block cells in mitosis. When compared to taxol, taxotere was more active as a promoter of the assembly of microtubule polymerization and approximately twice as potent as an inhibitor of microtubule depolymerization. Taxotere was initially formulated in a solution of polysorbate 80 and ethanol at a maximum concentration of 50mg/ml. The formulation was changed in order to remove the ethanol and lower the polysorbate concentration, whereby taxotere was solubilized in polysorbate 80 at a concentration of 80mg/ml for preclinical studies.

Taxotere was active *in vitro* against a series of human and murine tumor cell lines. *In vivo* activity was exhibited in the mouse at doses 3% the LD_{50}; cytotoxicity studies indicated sensitivity of breast, lung, ovarian, colorectal and melanoma tumor colony forming units. A high cytotoxic potency may be explained by the combination of the high affinity of the drug for microtubules, high achievable intracellular concentration, and slow cellular efflux. Taxotere demonstrated cross-resistance with other compounds in the MDR phenotype as well as resistance in cells previously exposed to the drug which do not express the MDR gene.

Tumor half-life of taxotere (21.7h) in the mouse was extended compared to the half-life of

mouse (0.78h); taxotere persists 6.6h in the plasma of the dog. The mouse exhibited the highest mg/m^2-corrected AUC among the three species. Concentrations of taxotere were exhibited in the liver, bile, intestine, spleen, myocardium, bone marrow, pancreas, genital organs, and salivary glands of the mouse and lungs, prostate, epididymis, thymus, and pituitary of the rat. Protein binding *in vivo* accounted for 84-89% of the drug in the plasma of rats and mice. Binding to plasma proteins *in vitro* was 89-95% in the mouse, 70-76% in the rat, 83-89% in the dog, and 79-83% in man. Elimination of the drug was primarily via the feces (<10% in the urine). Metabolism was primarily a hepatic function; oxidation of the tert-butyl group of taxotere represented the major biotransformation in the mouse, rat, rabbit, and dog. Cytochrome P-450 isoenzymes of the CYP3A subfamily are primarily responsible for taxotere biotransformation in the human and the rat; therefore, metabolic drug-drug interactions are possible with potent CYP3A inhibitors (e.g. ketoconazole).

The toxicity of taxotere was primarily to the lympho-hematopoietic system and the testes. The only exception was in single, and five-daily high dose studies of mice which exhibited primarily neurotoxicity, including non-extension and paresis of the hindlimbs resulting from axonal and myelin degeneration of sciatic nerves. Other toxicities in rats and dogs included weight loss, depressed food consumption, hypocellularity of bone marrow, thymic and lymphoid atrophy, necrosis of epididymides, and testicular atrophy. Necrosis of epididymides and testicular atrophy persisted following a 4-6 week recovery period. Following repeat dosing, the dog appeared to exhibit greater testicular sensitivity to taxotere at a dose of 2 mg/m^2 when compared to the rat (30mg/m^2). Toxicity increased with extended duration of dosing.

Taxotere is maternally toxic, fetotoxic and embryotoxic in rats at a dose of 1.8mg/m^2; dosing resulted in intrauterine mortality, reduced fetal weight and fetal ossification delays. Rabbits were more sensitive to taxotere at the same dose. No teratogenicity was noted. Reduced testicular and epididymidal weights were noted which correlated with findings of 6-month rat and dog studies.

Taxotere was found to be positive in the *in vitro* and *in vivo* micronucleus test and has the potential to increase the number of chromosomes. Taxotere did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay.

Labelling

Labelling conforms to the format specified under CFR21.Part 201.Subpart B dated April 1, 1994. The proposed labelling generally reflects the preclinical data with the exception of the following:

(1) Pregnancy category section: Pregnancy category D is appropriate. Relative doses used in the teratology studies to the recommended human dose should be specified as shown: " No evidence of teratogenic effects were found at doses of 1.8 or 1.1 mg/m^2/day (approx.1/50 or 1/100 the recommended human dose) in rats or rabbits, respectively." However, these studies have shown that taxotere produced embryotoxicity and fetotoxicity at 1.8 and 0.33mg/m^2 in rats and rabbits, respectively, without maternal toxicity; embryo and fetotoxicity were characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay.

(2) Carcinogenicity, mutagenicity and impairment of fertility: Taxotere has been shown to be positive in the *in vitro* micronucleus test in CHO-K1 cells and in the *in vivo* micronucleus test in

the mouse. It did not produce chromosome aberrations in CHO-K1 cells, but caused polypoidy in this cell line.Taxotere produced negative results in the Ames test and CHO/HGPRT gene mutation assay.

Labeling did not mention impairment of fertility. Taxotere at iv doses up to 1.8 mg/m^2 (approx.1/50 the recommended human dose) produced no impairment of fertility in rats. However, decreased testicular weights were reported. This correlates with findings of a 4-week toxicity study in rats and a 10 cycle (6-month) toxicity study in rats and dogs in which testicular atrophy or degeneration was observed at iv doses of 0.6, 30, and 7.5 mg/m^2, respectively (or 1/150, 1/3, and 1/15 the recommended human dose, respectively). Preclinical findings of testicular atrophy may indicate potential effects in humans.

Recommendation

The pharmacology/toxicology section of the NDA is approvable with labelling revisions as previously stated pending responses to the following issues. Preclinical mechanistic studies of edema and factors controlling this phenomenon should be conducted over the course of the further development of the drug, possibly using non-human primates. The company should provide information on animal models attempted to date (Appendix 2). In addition, the company needs to provide clinical or nonclinical data to address instability and degradation issues with taxotere.

Draft Letter to the Sponsor:

Labelling conforms to the format specified under CFR21.Part 201.Subpart B dated April 1, 1994. The proposed labelling generally reflects the preclinical data with the exception of the following:

(1) Pregnancy category section: Pregnancy category D is appropriate. Relative doses used in the teratology studies to the recommended human dose should be specified as shown: " No evidence of teratogenic effects were found at doses of 1.8 or 1.1 mg/m^2/day (approx.1/50 or 1/100 the recommended human dose) in rats or rabbits, respectively." However, these studies have shown that taxotere produced embryotoxicity and fetotoxicity at 1.8 and 0.33mg/m^2 in rats and rabbits, respectively, without maternal toxicity; embryo and fetotoxicity were characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay.

(2) Carcinogenicity, mutagenicity and impairment of fertility: Taxotere has been shown to be positive in the *in vitro* micronucleus test in CHO-K1 cells and in the *in vivo* micronucleus test in the mouse. It did not produce chromosome aberrations in CHO-K1 cells, but caused polypoidy in this cell line.Taxotere produced negative results in the Ames test and CHO/HGPRT gene mutation assay.

Labeling did not mention impairment of fertility. Taxotere at iv doses up to 1.8 mg/m^2

(approx. 1/50 the recommended human dose) produced no impairment of fertility in rats. However, decreased testicular weights were reported. This correlates with findings of a 4-week toxicity study in rats and a 10 cycle (6-month) toxicity study in rats and dogs in which testicular atrophy or degeneration was observed at iv doses of 0.6, 30, and 7.5 mg/m^2, respectively (or 1/150, 1/3, and 1/15 the recommended human dose, respectively).

1/25/95

3) The incidence of edema experienced in 6 clinical trials with taxotere ranged from 42- 74% in women treated for locally advanced or metastatic breast cancer and 37-70% in patients treated for non-small cell lung cancer; the incidence of severe edema ranged from 5-23% in this population. Preclinical mechanistic studies of edema and factors controlling this phenomenon should be conducted over the course of the further development of the drug; what animal models have been studied?

4) The requested limit of two degradation products (RPR 110928, requested limit of 1%; and RPR 112248, requested limit of 0.5%) cannot be approved without clinical or preclinical safety data on these products.

Margaret Brower

Margaret E. Brower, Ph.D.
C. Joseph Sun, Ph.D.
Pharmacologist/Toxicologist
November 22, 1994

cc:
Original ~~IND~~ (with appendix)
/Division File HFD-150 (with appendix)
/MBrower
/JSun
/JDeGeorge
/JBeitz
/DPease
/ATaylor HFD-500

1/25/95

Stat

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STATISTICAL REVIEW AND EVALUATION

NDA#: 20-449

APR 10 1996

Applicant: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Name of Drug: Taxotere (Docetaxel) for Injection Concentrate

Indication: Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

Documents Reviewed: Document Vols. 1.3 and 1.10 from original NDA submission, Vols. 7.1 and 7.2 dated Jan. 20, 1995, Vol. 3 dated Sep. 22, 1995, Document submitted Nov. 30, 1995, and Vol. 1 dated Feb. 22, 1996

I. Introduction

In the original NDA submission Rhone-Poulenc Rorer (RPR) Pharmaceuticals, Inc. requested (July 1994 registration dossier) for a shelf-life of 24 months for either upright vials or inverted vials packaged in 15ml clear type 1 glass vials with chlorobutyl rubber stoppers coated with a fluorinated polymer. The amendment submitted April, 1995 indicated that 'based on this updated stability data, the request is being modified to 12 months for 20mg and 15 months for 80mg Taxotere (see p.53, Vol. 13.1 submitted May 24, 1995). The reviewing chemist Dr. Yung-Ao Hsieh, HFD-150 requested the Division of Biometrics to perform statistical review and evaluation of the sponsor's stability data.

RPR intends to manufacture Taxotere Injection 20mg and 80mg at Dagenham from bulk solution supplied from RPR Vitry (Paris). Bulk solution were supplied initially as 6 and 10 Litre of solution in a 25 Litre (approx.) vessel and metered aseptically into 7 and 15mL clear type 1 glass vials to ensure a 0.5 and 2mL fill for 20mg and 80mg drug product, respectively. Samples were stored upright and inverted. Taxotere, as the commercial drug product, is composed of one vial of Taxotere injection concentrate and one vial of corresponding Solvent for Taxotere. The contents of the Solvent vial has to be aseptically transferred into the vial of Taxotere injection concentrate in order to prepare the "premix". This "premix" is then further diluted in order to prepare the Taxotere infusion solution which is then administered to the patient.

II. Design

For stability test, two pilot batches and three industrial batches stored at 4°C and 25°C were tested for drug substances, three industrial batches stored at 4-8°C was tested for both 20mg and 80mg drug products, and three pilot batches stored at 4°C were tested for 80mg drug products.

Storage Conditions

Drug Substances: Industrial batches
- Upright or Inverted
- Normal conditions: 4°C, 25°C
- Accelerated tests: 35°C, 35°C/90% relative humidity

Drug Substances: Pilot batches
- Upright or Inverted
- Normal conditions: same as industrial batches
- Accelerated tests: 35°C, 50°C, 35°C/90% relative humidity

Drug product: Industrial batches
- Upright or Inverted
- Normal conditions: 4-8°C, 25°C

Drug product: Pilot batches
- Upright or Inverted
- Normal conditions: 4°C, 25°C

Variable observed (unit) and Specification (RPR proposed and agreed by FDA Dec. 1, 1995):

Drug Substance:

i) Docetaxel assay content (%):	between 97.0 and 101.0

Drug Product:

i) Appearance:	yellow to brownish-yellow, clear, oily solution
ii) Assay, mg/0.5mL (mg/2mL):	18.0 to 21.0 (72.0 to 84.0)
iii) Degradation products:	
RP 70617 content (%)	not more than 4.0
RP 73077 content (%)	not more than 2.5
RPR 110928 (%)	not more than 1.0
RPR 112248 plus X (%)	not more than 0.5
Unidentified impurities >0.2%	record number
Total impurities (%)	not more than 8.0
iv) Sterility	complies with USP and Ph. Eur. requirements

The batch numbers, temperatures, and measurement times used in the study were as follows:

DRUG SUBSTANCES

Weight	Batch (Pilot, Industrial)	Temperature	Sampling time point (in months)
80mg	OP10 (P)	4°C; 25°C	0,3,6,9,12,18
80mg	FCH160 (P)	4°C; 25°C	0,1,6,12,24
80mg	19,20,21 (I)	4°C; 25°C	0,1,3,6,9,12

DRUG PRODUCTS

Weight	Batch (Pilot, Industrial)	Temperature	Sampling time point (in months)
20mg	J0594, J0595,J0596 (I)	4-8°C	0,2,4,6,8,12
20mg	JO594H,JO595H,JO596H(I)	4-8°C	0,2,4,6,8,12
80mg	JO545,JO546,JO547 (I)	4-8°C	0,1,2,4,6,8,12
80mg	cb05240,cb05364,cb05545 (P)	4°C	0,1,3,5,7,9,12,15,18,21,24,27

III. Sponsor's analysis

The RPR provided electronic datasets and data listings for the above specified stability studies and SAS output and graphs for the 80mg pilot batches in the Nov. 30, 1995 submission. There were no summary or conclusions from these documents. In the original NDA submission, however, RPR mentioned that the statistical comparison of the results of the docetaxel assay and the evaluation of related substances (sum of related substances) was conducted. The statistical methods selected were those described in the document entitled "Guideline for submitting Documentation for the Stability of Human Drugs and Biologics" of February 1987. The same statistical approach was used to determine the provisional shelf life of Taxotere 80mg/2mL from the stability data on the pilot batches. It is noted that not all statistical analyses results were presented in the NDA submission.

Drug Substance

In the original submission of drug substances (see Vol. 1.3), RPR's stability samples were stored at 5 conditions +4°C, +25°C, +35°C, +50°C, and +3[illegible]°C/90% relative humidity, and tested according to the schedule listed in the General Test Methodology (see Appendix 1). RPR concluded that "Docetaxel was stable at temperatures of +4°C and +25°C for 24 months in both packages tested. It appeared at temperatures of +35°C and +50°C the variation in the active ingredient are more likely due to the effects of temperature rather than humidity. One pilot batch did not comply with specifications after 12 months of storage. As a precautionary measure, the drug substance should be stored at +4°C, protected from light and moisture for 24 months". In the amendment of Nov. 30, 1995, RPR stated that "all the figures have been checked between the original NDA and the amendments and that no discrepancy was noticed between tables and statistical analysis".

Drug Product

The following results were from the original NDA submission.

For 20mg drug product, from the results of 3 industrial batches, RPR concluded that samples of all three batches stored upright and inverted at 4-8°C exhibit a similar stability profile

with a decrease (of ~ 4.5-5.0%) in docetaxel assay content. This is matched by a similar increase in total decomposition products. The degradation route was almost equally and exclusively to RP70617 and RP73077 with only a small amount (about 0.3% with respsect to docetaxel content) of additional RPR110928 being formed. No other unidentified impurities individually greater than 0.2% w/w (with respect to docetaxel) have been detected in these 4-8°C stored samples. Samples of all three batches stored at 25°C for 2 months upright and inverted, failed the requirements for assay, content of RP70617 and total impurities content. The stability profiles of samples of these 3 batches mirror the profiles seen for development batches. The results also confirm that contact with the rubber plug does not result in accelerated or catalyzed decomposition of the docetaxel.

For 80mg drug product, RPR stated that results from 3 pilot batches: cb05240, cb05364, and cb05545 showed that the increase of related degradation product substances was tightly correlated to the decrease of docetaxel content. A model with equal slopes and different intercepts was used. RPR stated that the real time data for the first two batches remained within specifications after 24 months storage at 4°C.

For 80mg drug product, from the results of 3 industrial batches, RPR concluded that "At 4°C, the stability results for upright vials and inverted vials show no significant differences, a shelf-life of 24 months is recommended according to real time stability data of the three pilot batches (cb05240, cb05364, and cb05545). The stability data clearly indicate that the product must not be stored at 25°C" (see Vol. 1.10).

In the amendment of Nov. 30, 1995, RPR stated that for the drug product no errors were found for industrial batches, but new tables of results had to be edited for the pilot batches. RPR emphasized that "the conclusions of this new statistical analysis remain strictly unchanged compared to the conclusion in the original statistical analysis".

IV. Reviewer's Analyses

Methods

The reviewer applied the statistical procedures described in the FDA "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" (February, 1987) to the stability data provided by the sponsor. The procedures consist of the following steps.

Acceptance criteria

In order to have an acceptable level of a variable under test, with 95% confidence coverage, the lower confidence bound should be above the lower specification limit and the upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the lower confidence bound should be above the lower specification limit or the upper confidence bound should be below the upper specification limit with 95% confidence coverage.

Data analyses and results

Following the advice of the reviewing Chemist Dr. Hsieh, the stability data submitted by the sponsor were analyzed. The results are presented for each variable.

1. Drug Substance

Docetaxel assay content in %
(agreed specifications: , specifications used by the sponsor:)

Storage condition: 4°C

The p-values of statistical tests for the selection of degradation model are presented in Table 1. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines, lower and upper 95% confidence bounds were calculated. The estimated degradation lines along with the lower and the upper 95% confidence bounds are presented in Figures 1a, 1b, 1c, 1d, and 1e.

The results of the analysis support an expiration dating period of 24 months at 4°C. However, the data were collected only up to 12 months for the 3 industrial batches. The extropolation can be granted at most 6 months. Thus, the expiration dating period of 18 months would be reasonable.

Storage condition: 25°C

The p-values of statistical tests for the selection of degradation model are presented in Table 2. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines, lower and upper 95% confidence bounds were calculated. The estimated degradation lines along with the lower and the upper 95% confidence bounds are presented in Figures 2a, 2b, 2c, 2d, and 2e.

The estimated expiration dates shown in Appendix 1 are 19, 28, 33, and 38 months for batches 19, 20, 21, and OP10. From Figure 2e, the 95% lower bound indicated that pilot batch FCH160 failed to be within the specification limits at time 0. Excluding this batch, the minimum expiration dating period was estimated to be 19 months. Since data were collected up to 12 month, extrapolation of 6 month, viz., the expiration dating period of 18 months would be reasonable.

The statistical summary of the estimated expiration dates and model parameter estimates can be found in Appendix 1.

2. Drug Product

2.1 Taxotere Injection 20mg

The following results were obtained from 3 industrial batches stored at 4-8°C.

Docetaxel assay content in % of the theoretical value (90-105)

The p-values of statistical tests for the selection of degradation model are presented in Table 3.

Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines, lower and upper 95% confidence bounds were calculated. The estimated degradation lines along with the lower and the upper 95% confidence bounds are presented in Figures 3a, 3b, and 3c.

The results of the analysis support an expiration dating period of 12 months at 4-8°C.

Total impurities content in % (≤ 8.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 4. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figures 4a, 4b, and 4c.

The results of the analysis support an expiration dating period of 12 months at 4-8°C.

RP 70617 content in % (≤ 4.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 5. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figures 5a, 5b, and 5c.

The results of the analysis support an expiration dating period of 12 months at 4-8°C.

The statistical summary of the estimated expiration dates and model parameter estimates can be found in Appendix 2.

2.2 Taxotere Injection 80mg - industrial batches

The following results were obtained from 3 industrial batches at 4-8°C temperature.

Docetaxel assay content in % of the theoretical value (90-105)

The p-values of statistical tests for the selection of degradation model are presented in Table 6. Based on these p-values a model with common intercept and common slope was selected. The degradation line, lower and upper 95% confidence bounds were calculated. The estimated degradation line along with the lower and the upper 95% confidence bounds is presented in Figures 6.

The results of the analysis support an expiration dating period of 15 months at 4-8°C.

Total impurities content in % (≤ 8.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 7. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figures 7a, 7b, and 7c.

RP 70617 content in % (≤ 4.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 8. Based on these p-values a model with different intercept and common slope was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figures 8a, 8b, and 8c.

The results of the analysis support an expiration dating period of 15 months at 4-8°C.

The statistical summary of the estimated expiration dates and model parameter estimates can be found in Appendix 3.

2.3 Taxotere Injection 80mg - pilot batches
The following results were obtained from 3 pilot batches at 4°C temperature.

Docetaxel assay content in % (90-105)

The p-values of statistical tests for the selection of degradation model are presented in Table 9. Based on these p-values a model with separate intercepts and common slope was selected.

The results of the analysis support an expiration dating period of 15 months at 4°C.

Total impurity content in % (≤ 8.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 10. Based on these p-values a model with separate intercepts and common slope was selected.

The results of the analysis support an expiration dating period of 15 months at 4°C.

RP 70617 content in % (≤ 4.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 11. Based on these p-values a model with separate intercepts and common slope was selected.

The results of the analysis support an expiration dating period of 15 months at 4°C.

RP 110928 content in % (≤ 4.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 12. Based on these p-values a model with separate intercepts and separate slopes was selected.

The results of the analysis support an expiration dating period of 15 months at 4°C.

RP 112248 Plus X content in % (≤ 4.0)

The p-values of statistical tests for the selection of degradation model are presented in Table 13. Based on these p-values a model with common intercept and common slope was selected.

The results of the analysis support an expiration dating period of 15 months at 4°C.

The statistical summary of the estimated expiration dates and model parameter estimates can be found in Appendix 4.

V. Summary

The sponsor submitted data of up to 27 months from 7mL and 15mL package size vials of Taxotere concentrate for injection 20mg and 80mg, respectively. The requested expiration dating period was 12 months for 20mg and 15 months for 80mg package size. The stability for the drug substance was tested under two temperatures (4°C and 25°C). The stability for the drug product was tested under 4°C for the pilot batches and under 4-8°C for the industrial batches.

RPR tested the stability data on both pilot and industrial batches. They concluded that the results of their stability analyses supported that the drug substance should be stored at +4°C, protected from light and moisture for 24 months. However, for the drug product, the amendment submitted April, 1995 indicated that the expiration date was modified to 12 months for 20mg and 15 months for 80mg Taxotere (see p.53, Vol. 13.1 submitted May 24, 1995). With the new electronic data submitted for this claim, there was no conclusion from RPR.

On the request of the reviewing chemist Dr. Hsieh, this reviewer analyzed the stability data of assay, potential degradation products: RP70617, RP110928, and RP112248 Plus X, and total impurity for drug products and assay at 4°C and 25°C for drug substances.

For drug substances, the results of this reviewer's analysis support an expiration date of 24 months at 4°C but not at 25°C. It should be noted that the estimated expiration dating periods were based on the data extrapolation for industrial batches and for one pilot (OP10) batch.

For drug products, it is not clear from the sponsor's report submitted whether batches JO594 and JO594H, and similarly batches JO595 and JO595H, batches JO596 and JO596H, are

15 months for 80mg Taxotere (see p.53, Vol. 13.1 submitted May 24, 1995). With the new electronic data submitted for this claim, there was no conclusion from RPR.

On the request of the reviewing chemist Dr. Hsieh, this reviewer analyzed the stability data of assay, potential degradation products: RP70617, RP110928, and RP112248 Plus X, and total impurity for drug products and assay at 4°C and 25°C for drug substances.

For drug substances, the results of this reviewer's analysis along with extrapolation rule support an expiration date of 18 months at 4°C and 25°C. It should be noted that the estimated expiration dating periods were based on the data extrapolation for industrial batches.

For drug products, it is not clear from the sponsor's report submitted whether batches JO594 and JO594H, and similarly batches JO595 and JO595H, batches JO596 and JO596H, are the same. If they are not the same batches, it is a concern why for the same Taxotere concentrate for injection 20mg, the stability test for the assay content and RP70617 degradation product used one set of batches but that for the total impurity content used another set of batches.

Except for the stability tests of total impurity content in % from the set JO594H, JO595H, and JO596H for Taxotere concentrate 20mg injection, the results of stability tests for assay content and RP70617 for either 20mg or 80mg supported an expiration dating period of 15 months. It is noted that the pilot batches submitted had the storage time actually observed up to 27 months. However, the industrial batches submitted had the storage time actually observed up to 12 months only. The sponsor should be requested to submit the stability data up to the granted expiration time to verify these expiration dating periods as soon as the data become available.

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco C Gnecco 3/29/96

Dr. Chi Chi 4/10/96

cc:

Archival NDA 20-449/DIV File
HFD-710 Dr. Anello
HFD-150/ Dr. Wood
HFD-150/ Dr. Hsieh
HFD-150/ Ms. Pease
HFD-344/ Dr. Lisook
HFD-710/ Dr. Chi
HFD-710/ Mr. Orticke
HFD-710/ Dr. Gnecco
HFD-710/ Dr. Wang
HFD-710/ Chron

SWANG/594-5764/3-14-1996/WP61/TAXOTERE.*

This review consists of 11 pages of text, 4 appendices, 13 reviewer tables, 26 reviewer figures, and 15 sponsor figures.

Appendix 1: Drug Substance - estimated expiration dating periods and model parameters

Drug Substance	OP10	FCH160	19	20	21
25°C					
Intercept	99.03	97.54	99.87	99.43	99.13
slope	0.006	0.006	0.006	0.006	0.006
Expiration-date	38	–	19	28	33
4°C					
Intercept	99.16	98.53	99.80	99.70	99.28
Slope	-0.015	-0.015	-0.015	-0.015	-0.015
Expiration-date	55	40	69	67	57

Appendix 2: Drug Product (20mg) - estimated expiration dating periods and model parameters

Drug Product (20mg)	JO594	JO595	JO596
Docetaxel Assay (%)			
Intercept	98.6	100.04	100.04
slope	-0.49	-0.49	-0.49
Expiration-date	15	17	17
Total impurities (%)	(JO594H)	(JO595H)	(JO596H)
Intercept	2.75	2.12	2.24
Slope	0.39	0.39	0.39
Expiration-date	12	13	13
RP70617 content (%)			
Intercept	1.25	0.82	0.88
Slope	0.12	0.12	0.12
Expiration-date	19	23	22

Appendix 3: Drug Product (80mg, industrial batches) - estimated expiration dating periods and model parameters

Drug product (80mg)	JO545	JO546	JO547
Docetaxel Assay (%)			
Intercept	99.09	SAME	SAME
Slope	-0.45		
Expiration-date	17		
Total Impurities (%)			
Intercept	2.20	2.11	1.88
Slope	0.30	0.30	0.30
Expiration-date	18	18	19
RP70617 content (%)			
Intercept	0.93	0.89	0.85
Slope	0.17	0.17	0.17
Expiration-date	17	17	17

Appendix 4: Drug Product (80mg, pilot batches) - estimated expiration dating periods and model parameters

Drug Product (80mg)	cb05240	cb05364	cb05545
Docetaxel Assay (%)			
Intercept	97.79	98.42	100.81
slope	-0.23	-0.23	-0.23
Expiration-date	28	30	39
Total Impurities (%)			
Intercept	3.14	3.03	3.03
Slope	0.12	0.12	0.12
Expiration-date	36	37	50
RP70617			
Intercept	0.78	0.95	0.27
Slope	0.07	0.07	0.03
Expiration-date	80	84	84
RP110928			
Intercept	0.26	0.26	0.32
Slope	0.007	0.003	0.01
Expiration-date	84	66	84
RP112248			
Intercept	0.06	same	same
Slope	0.006		
Expiration-date	84		

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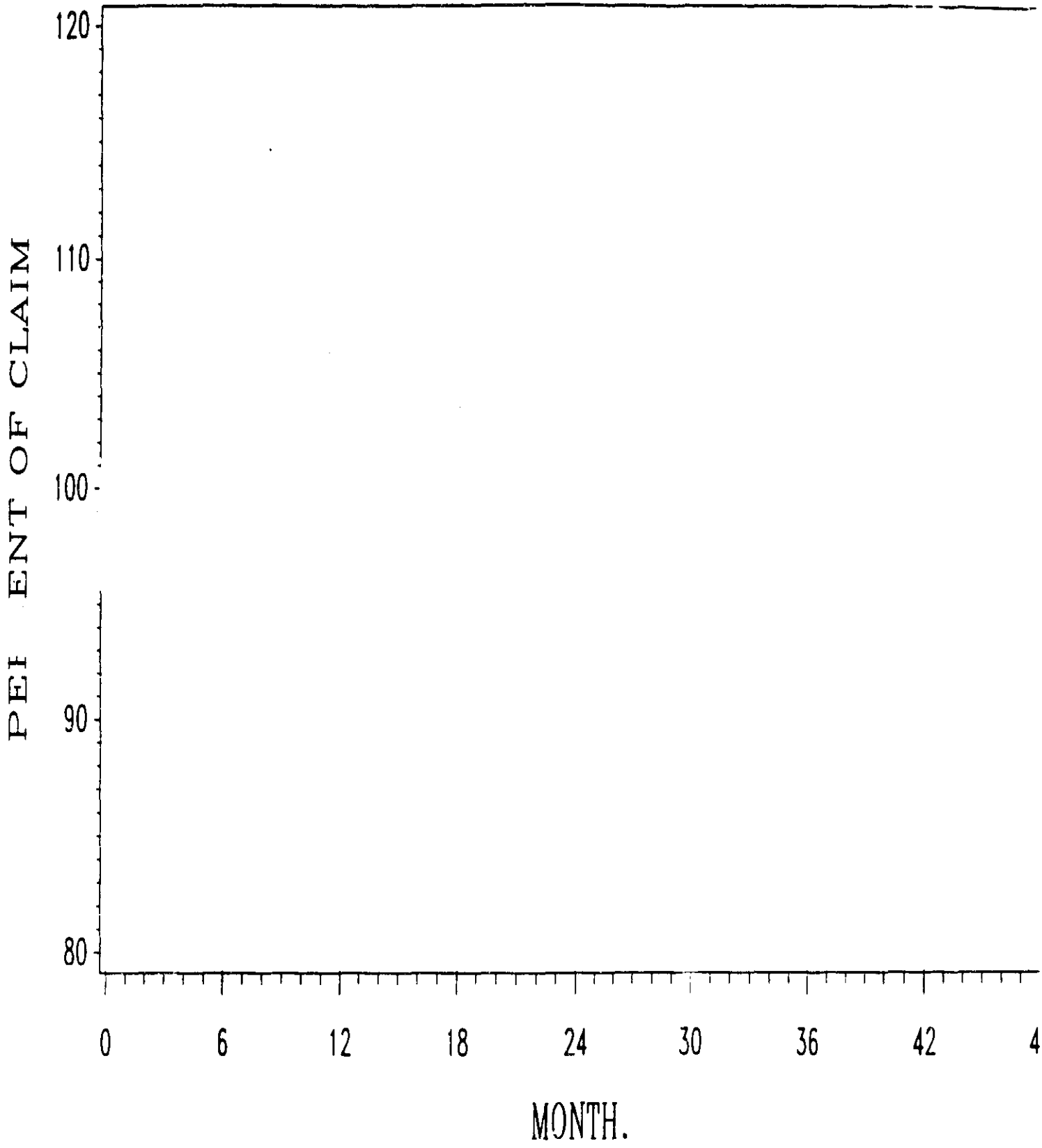
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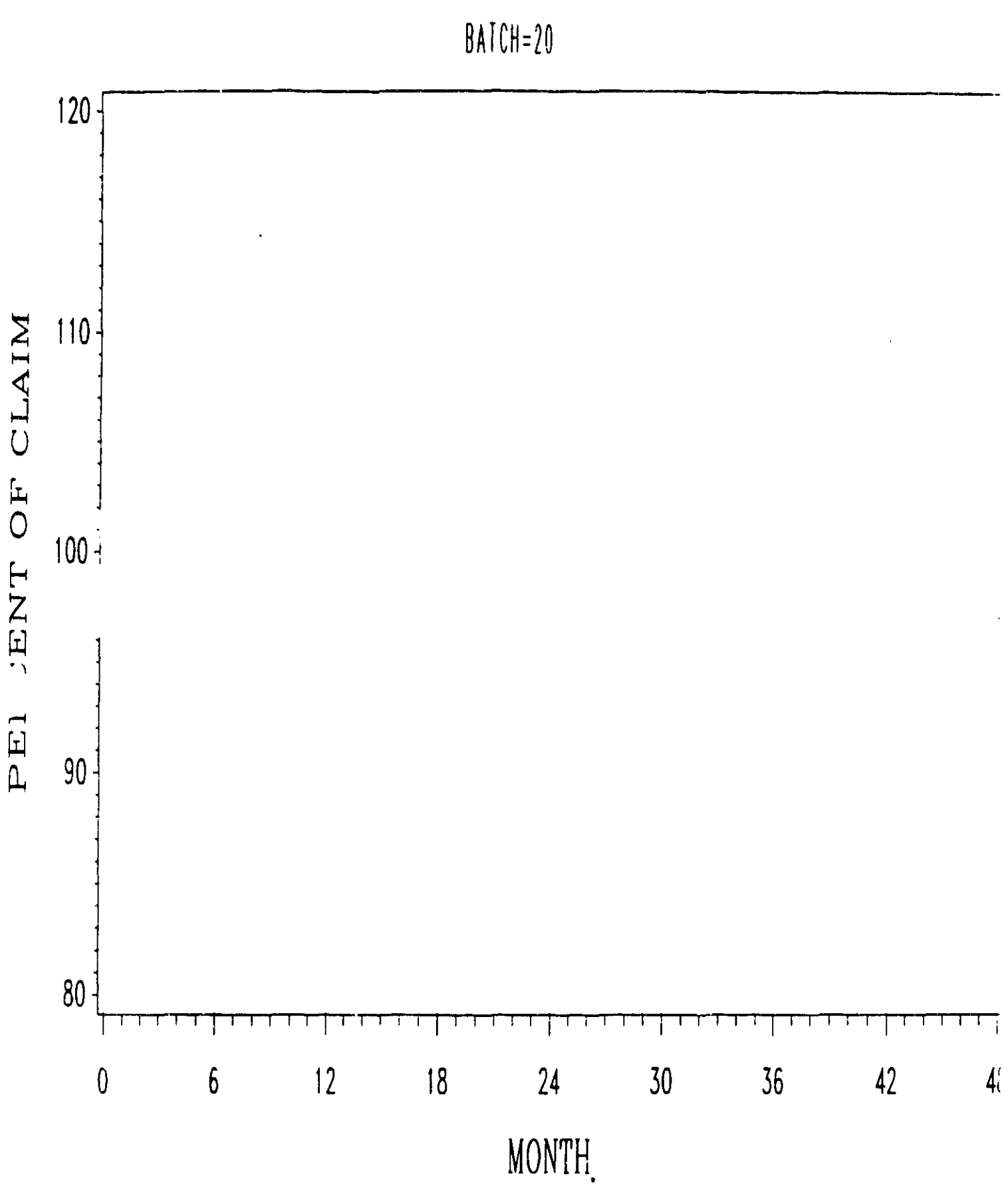
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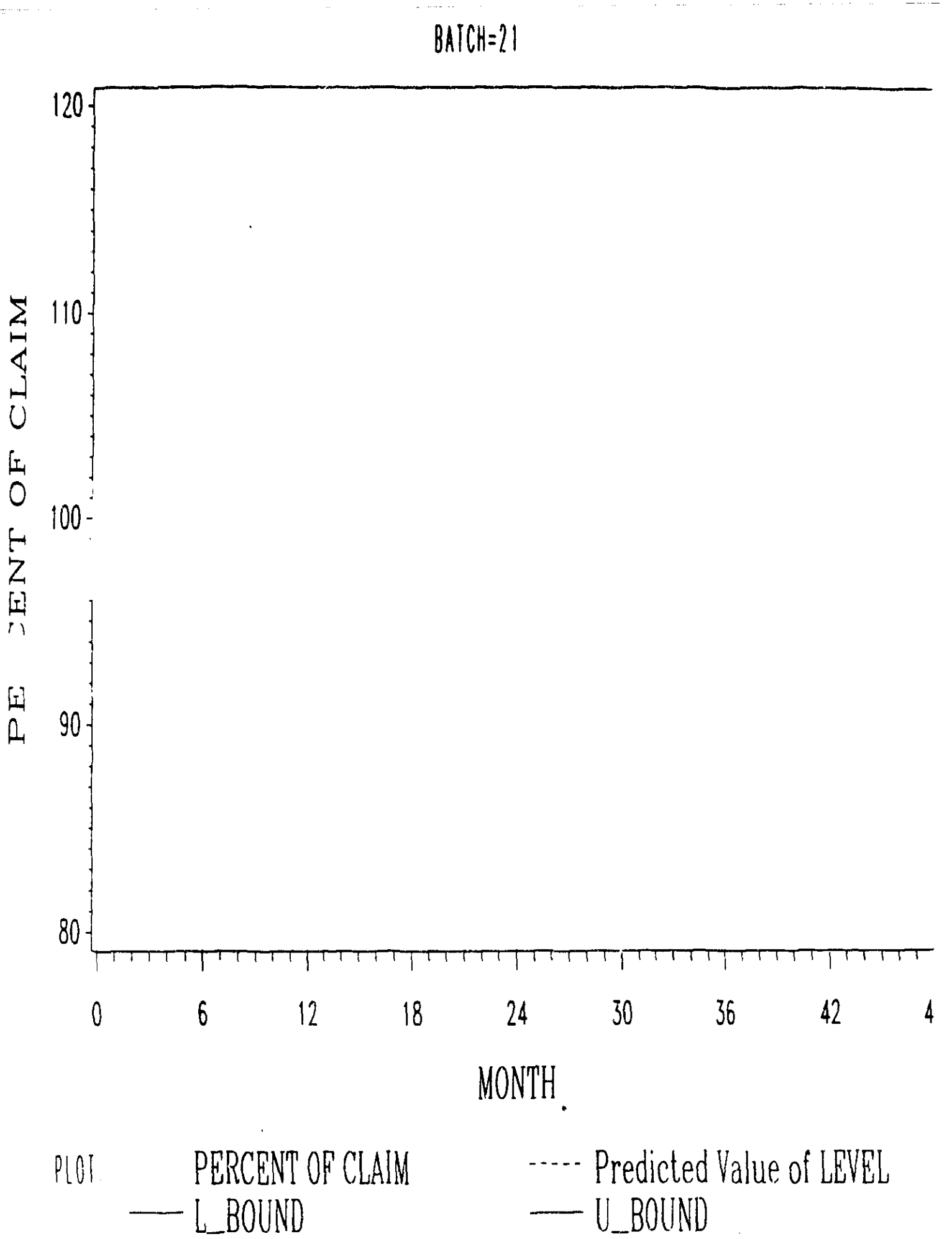
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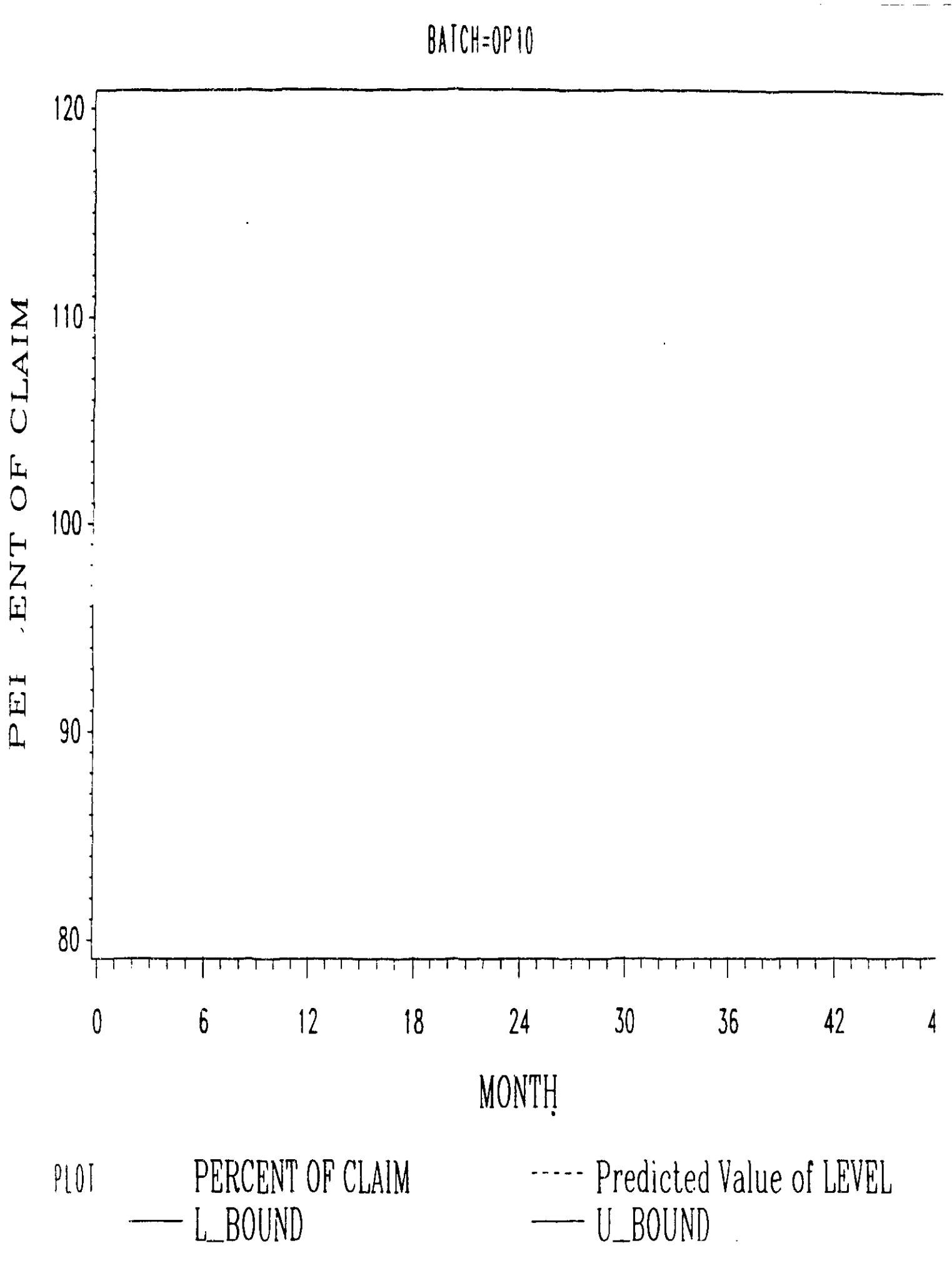
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PEI ENT OF CLAIM
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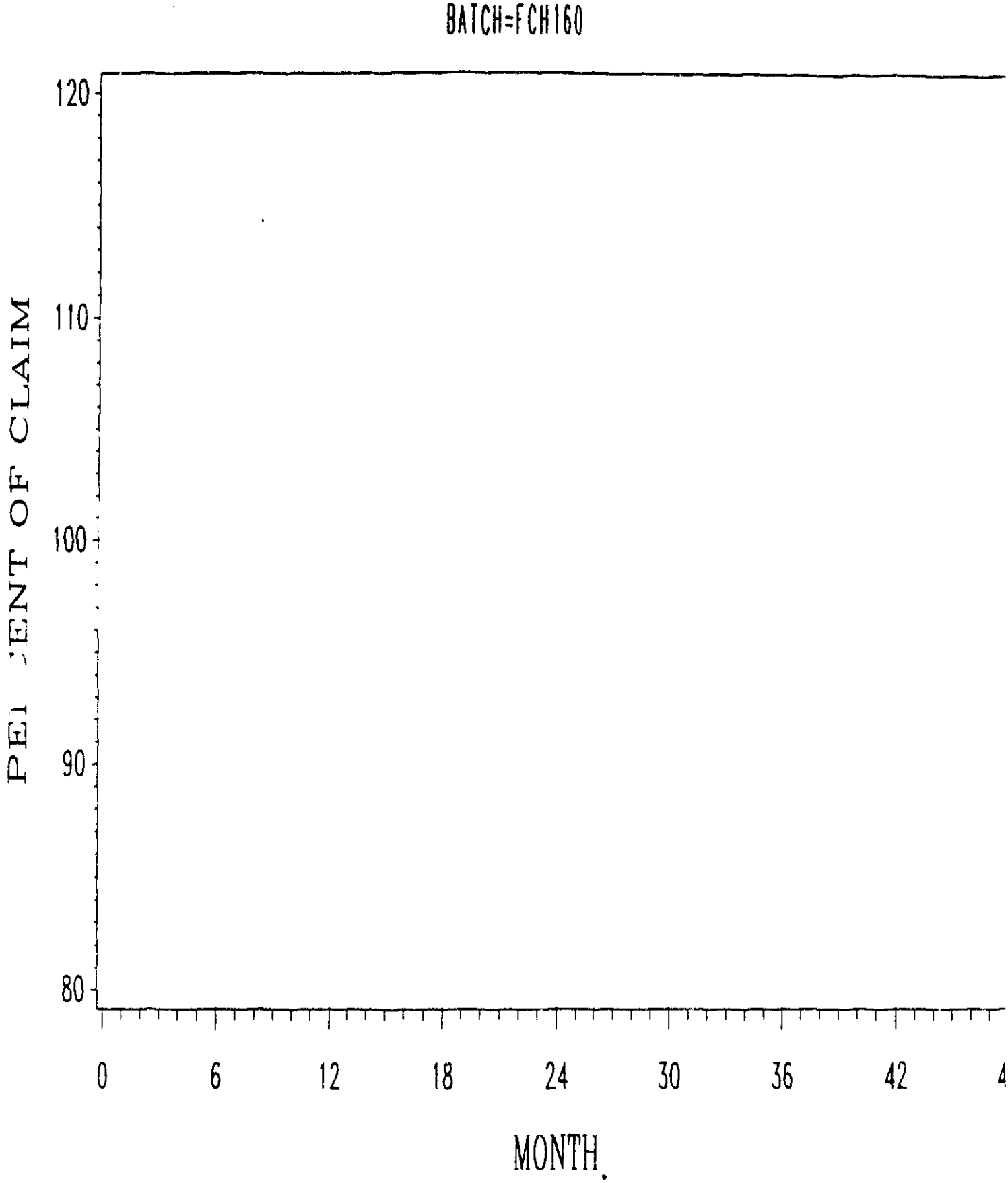
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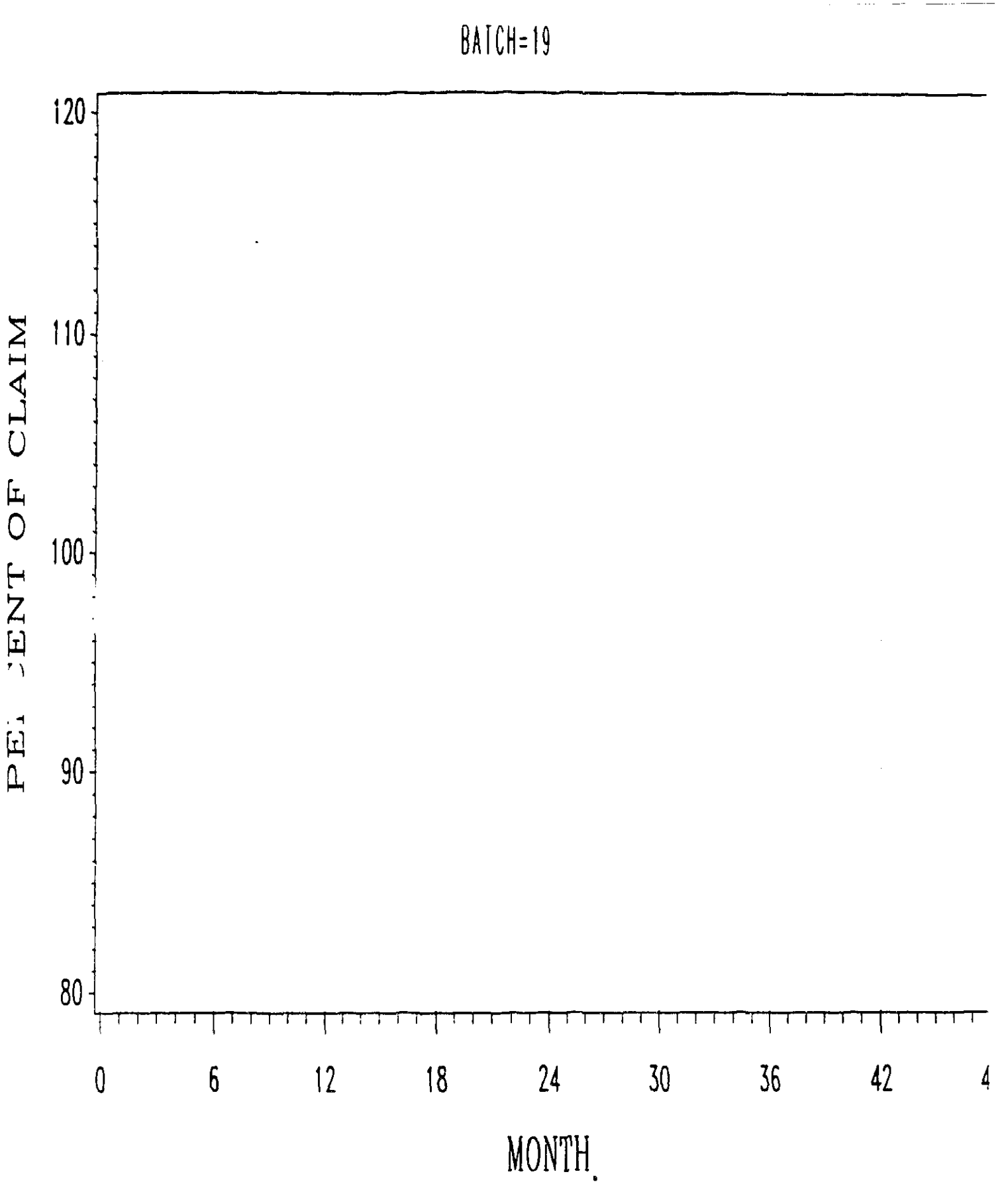
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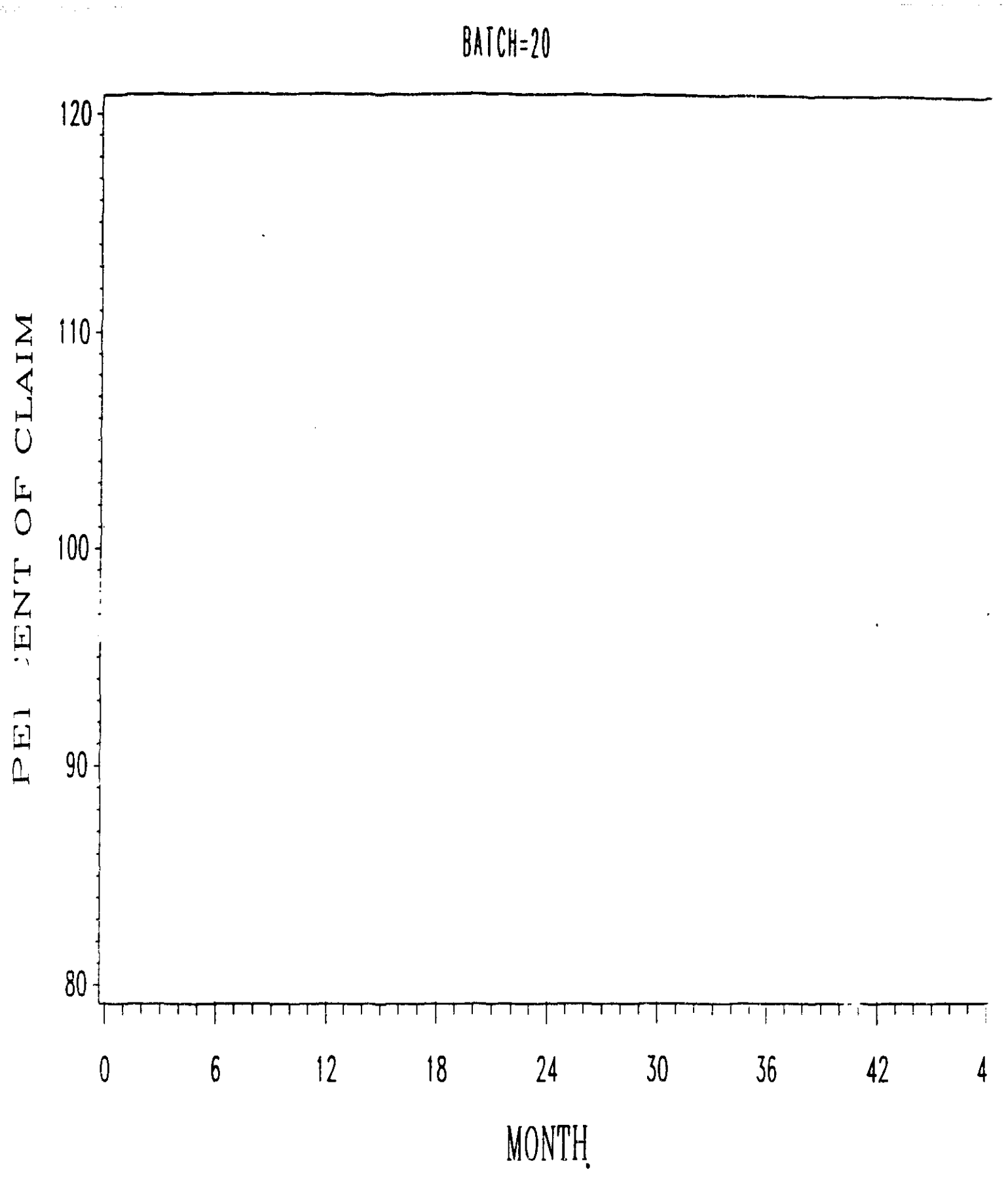
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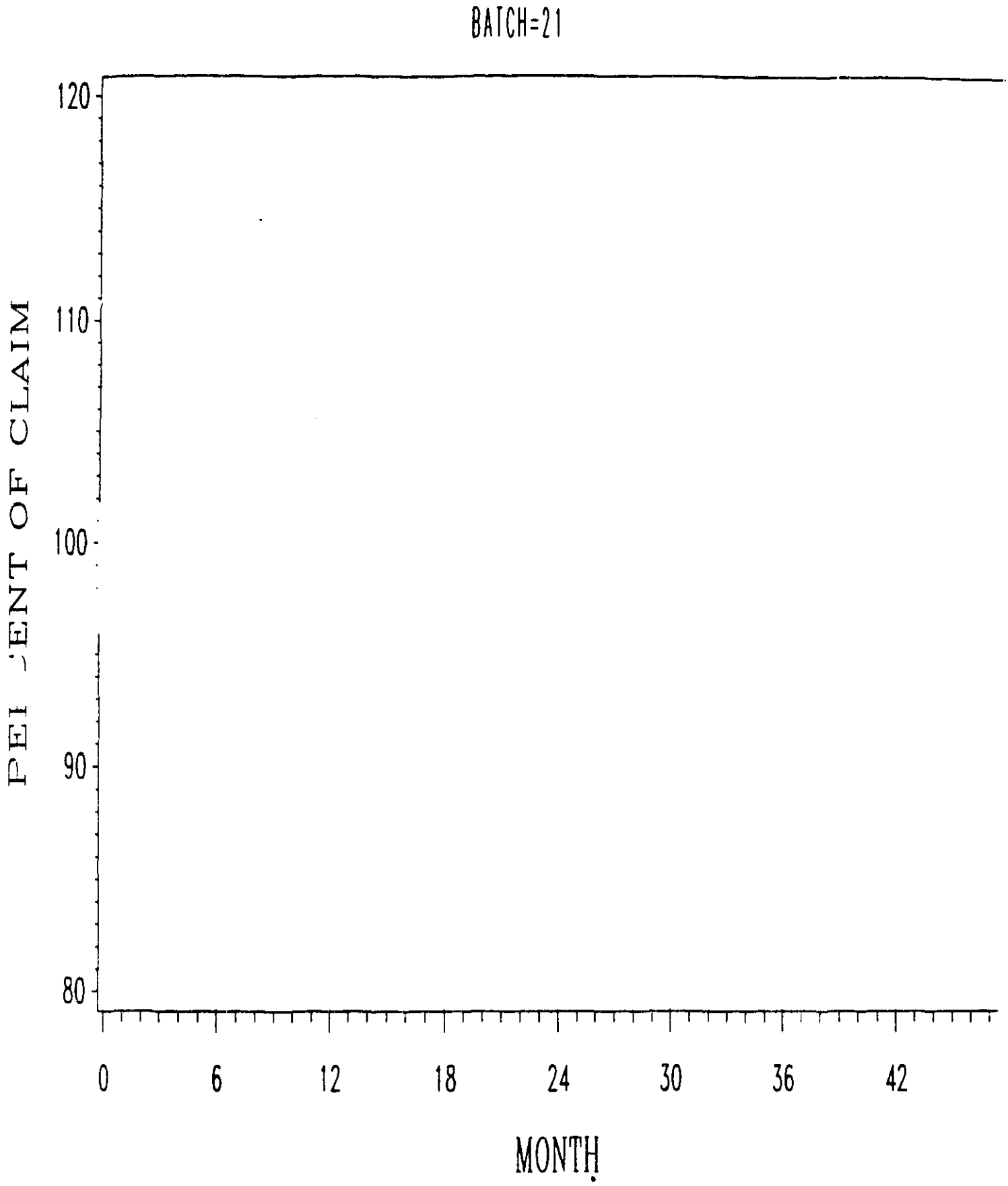
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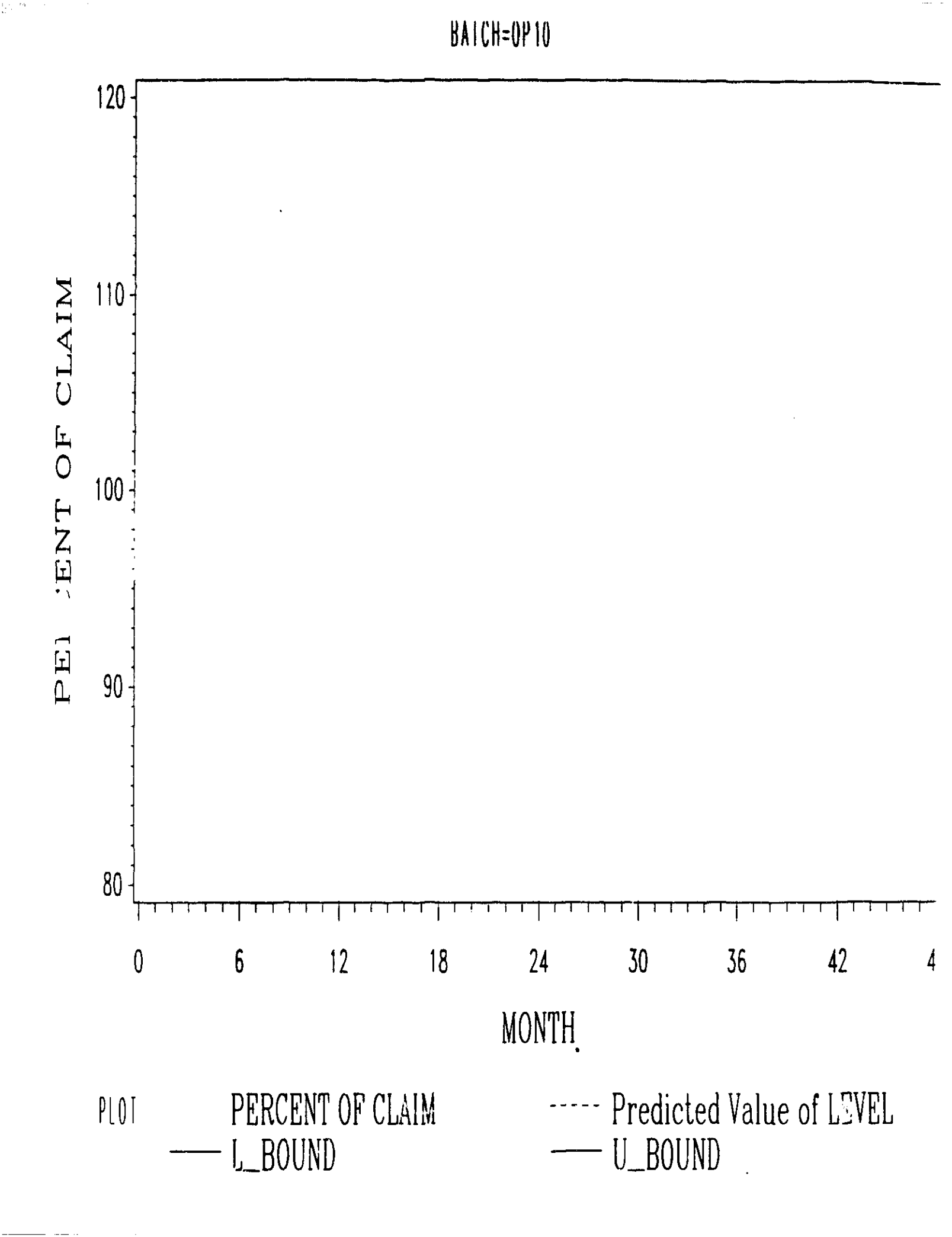
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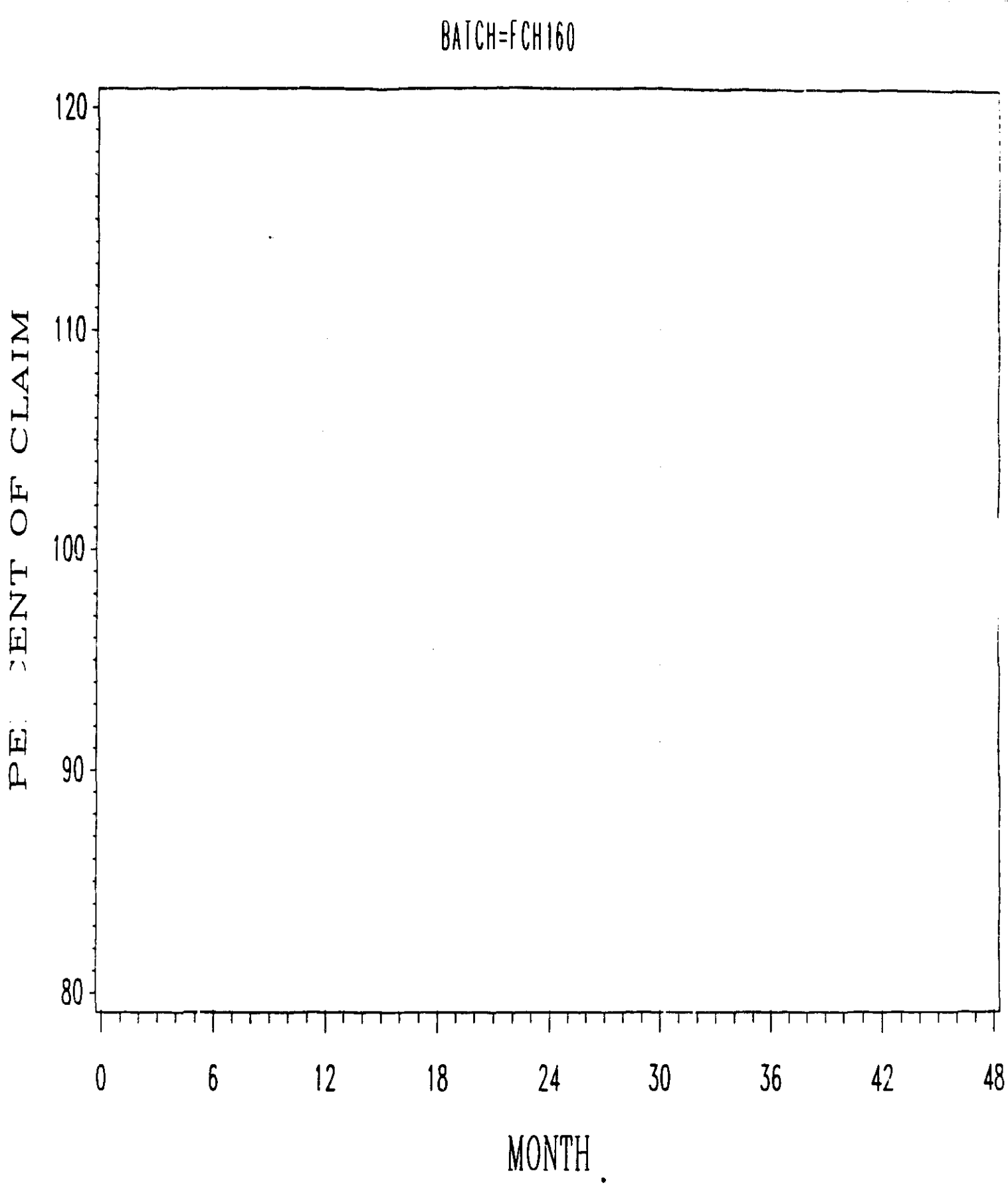
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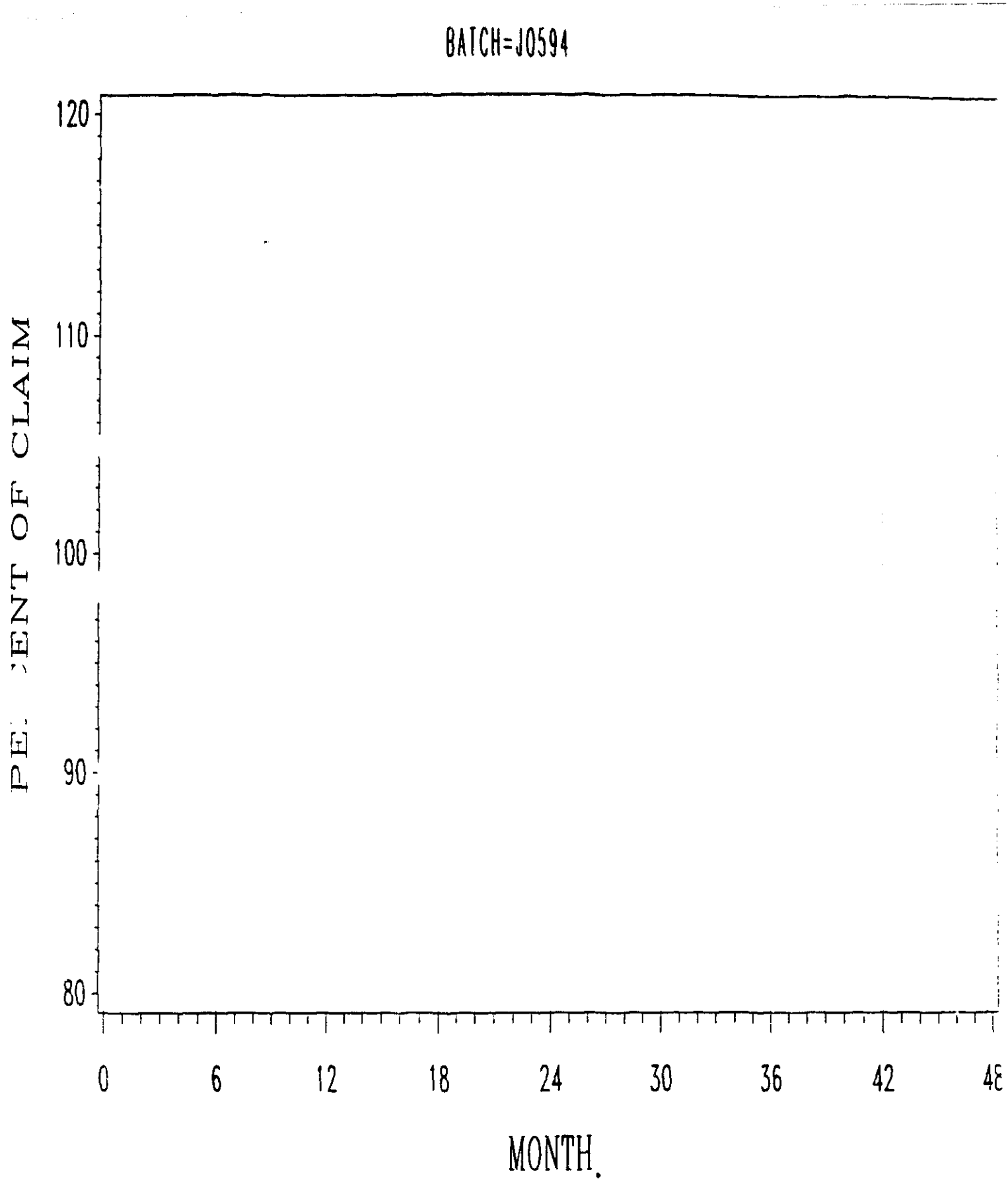
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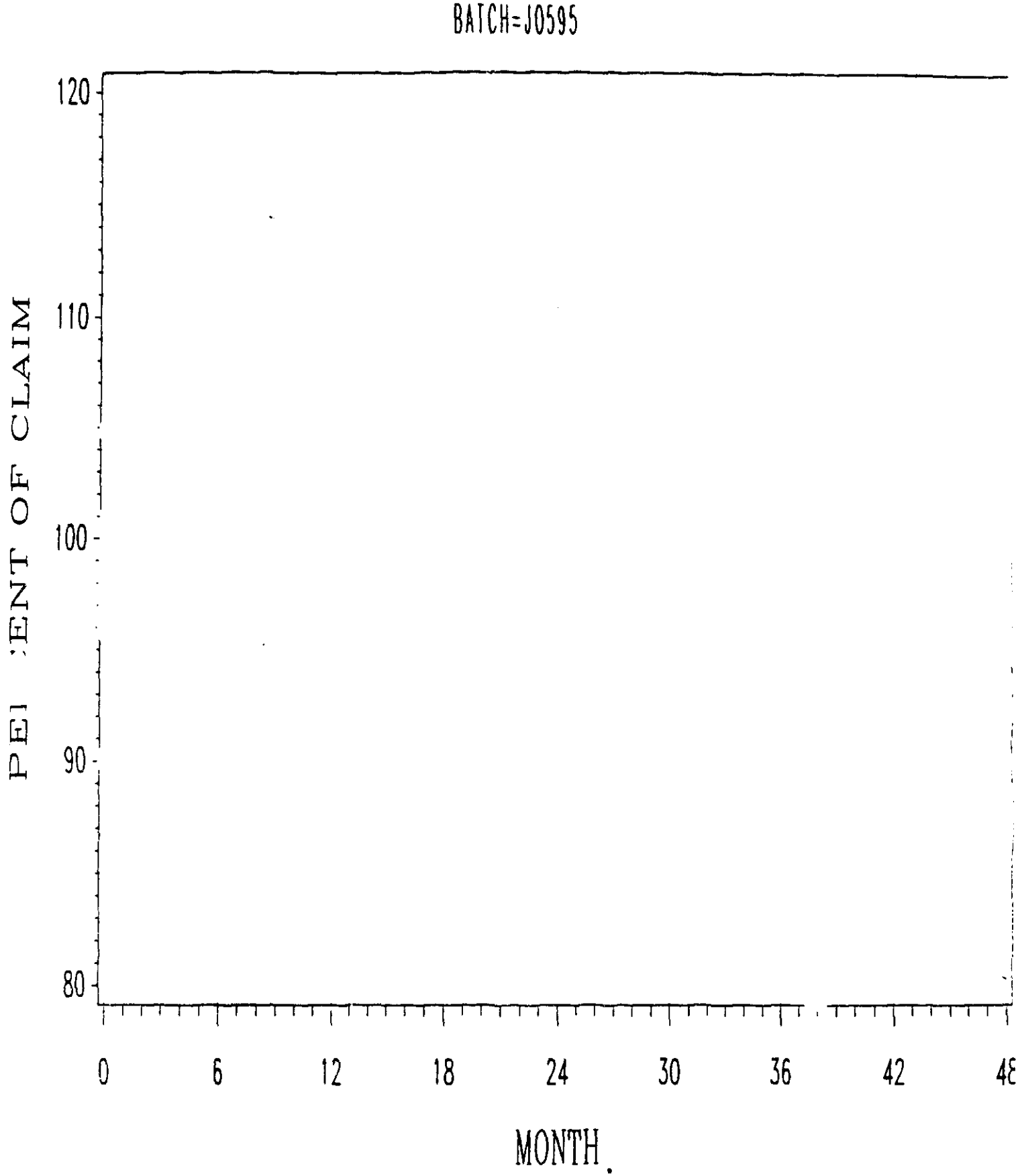
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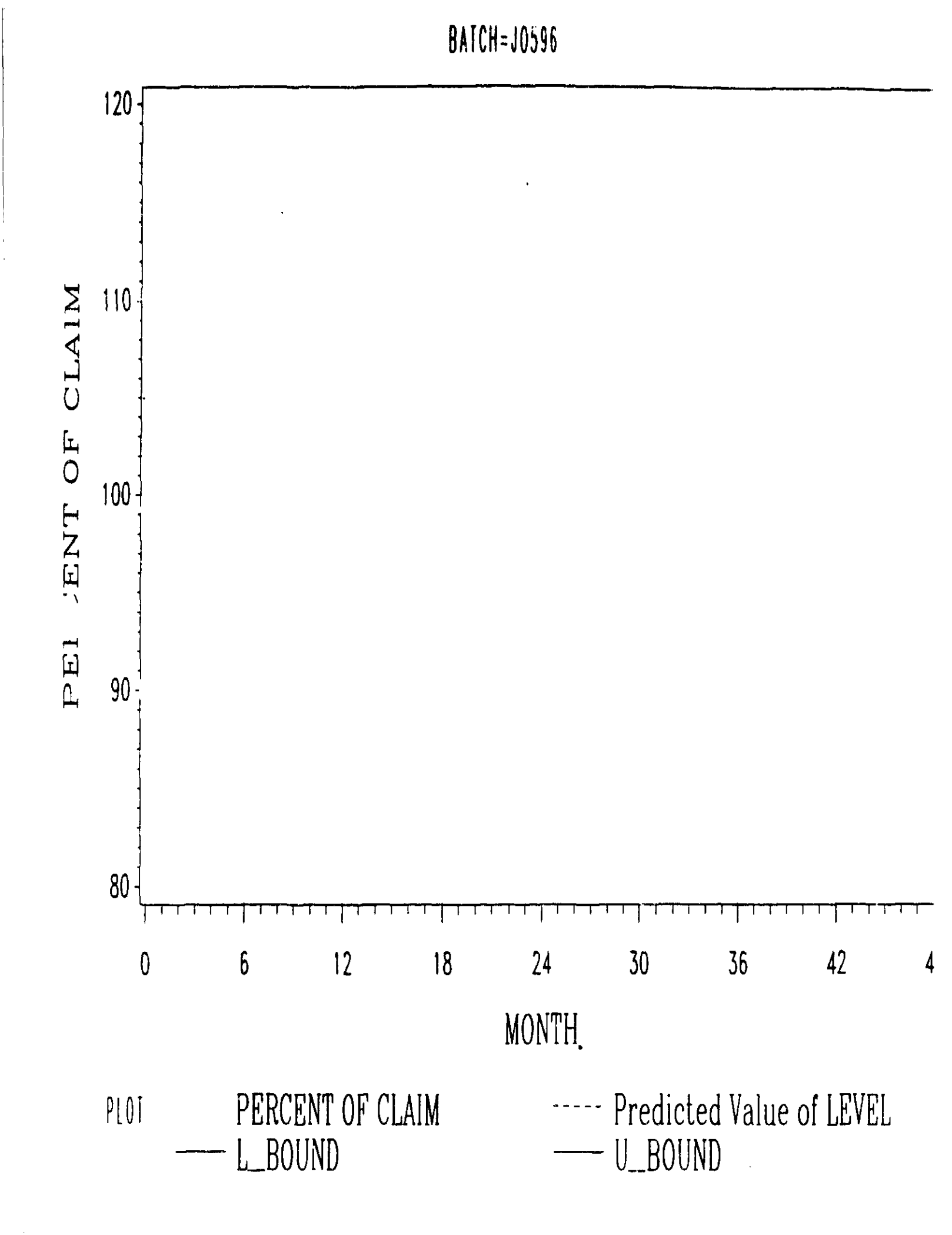
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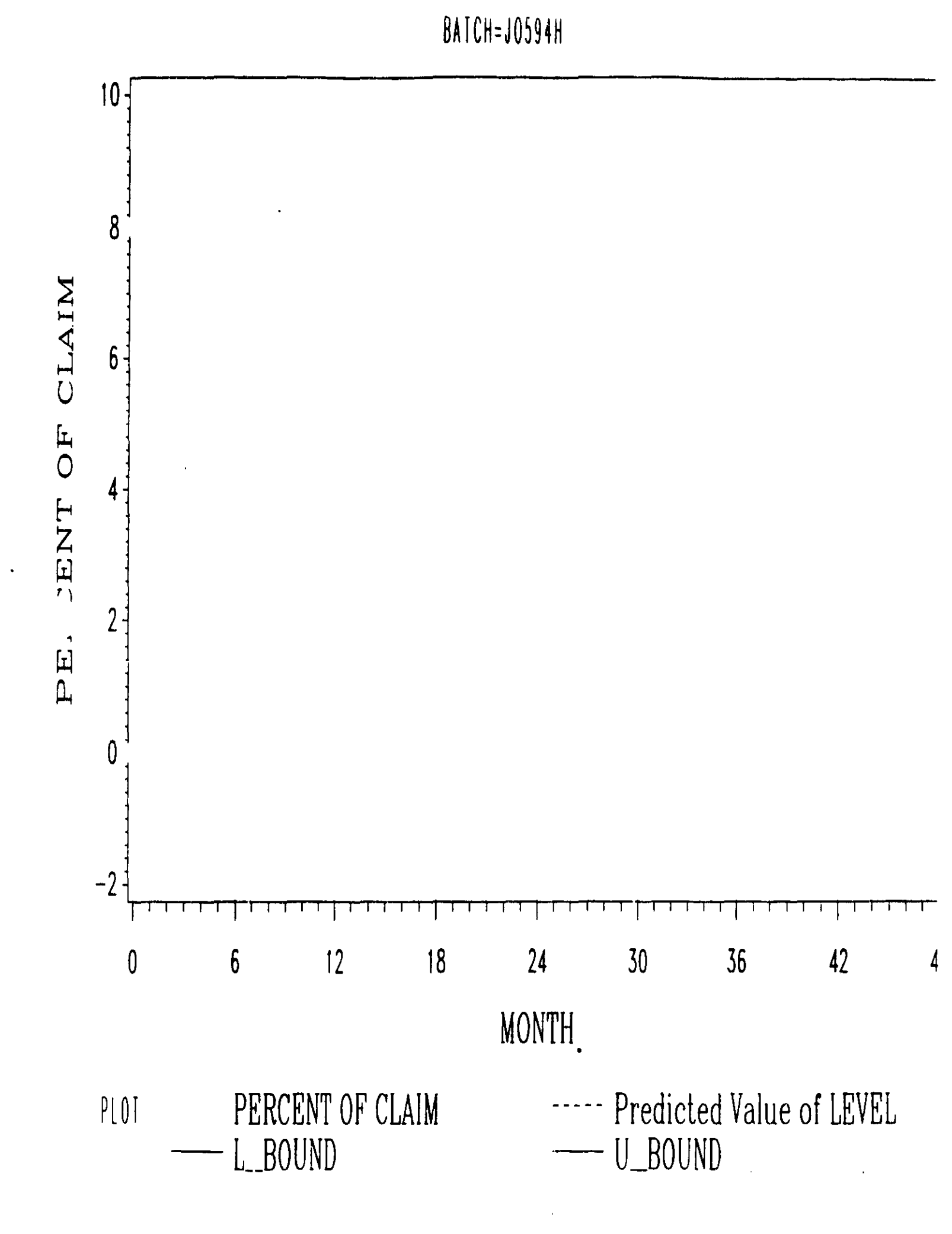
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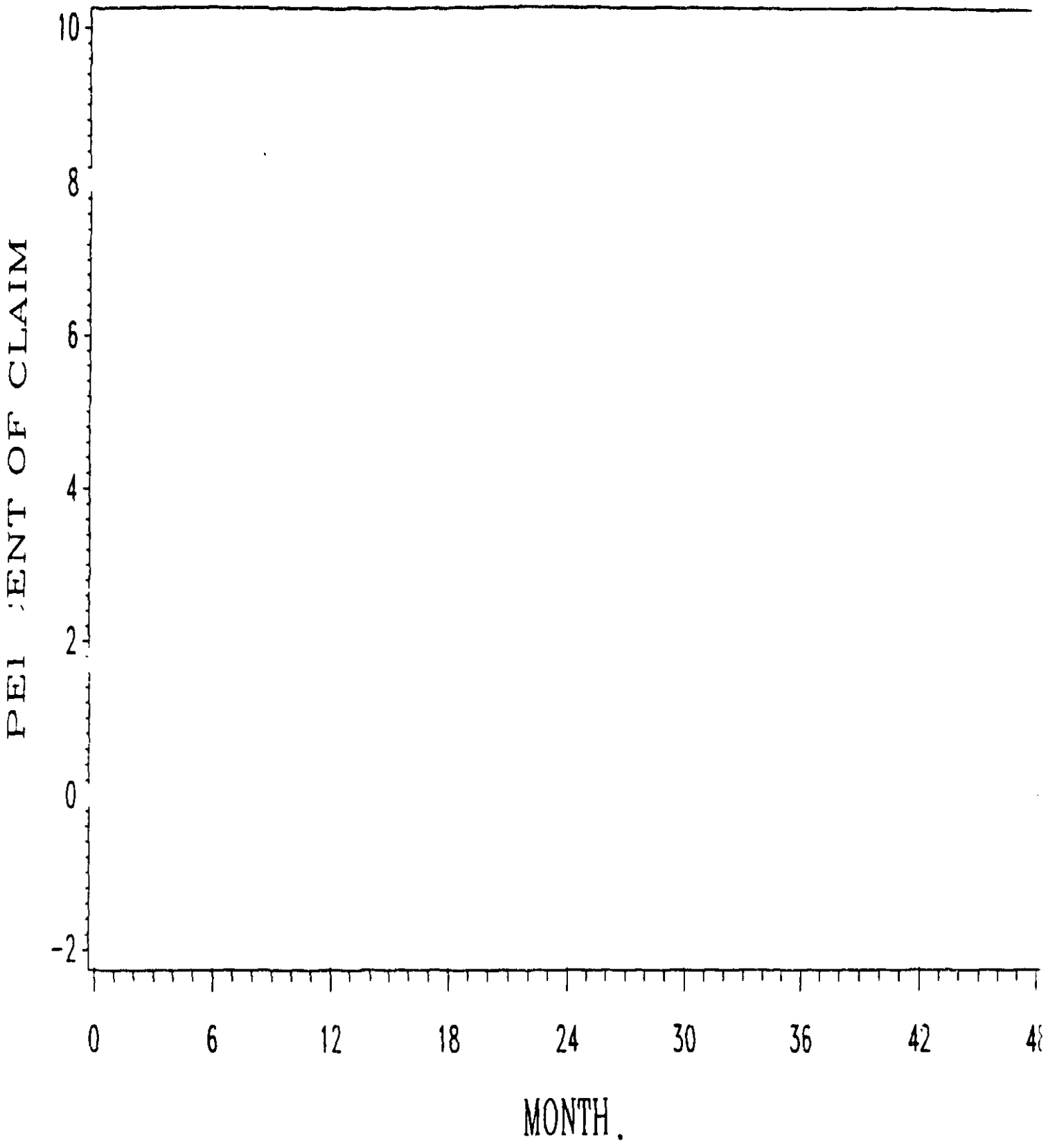

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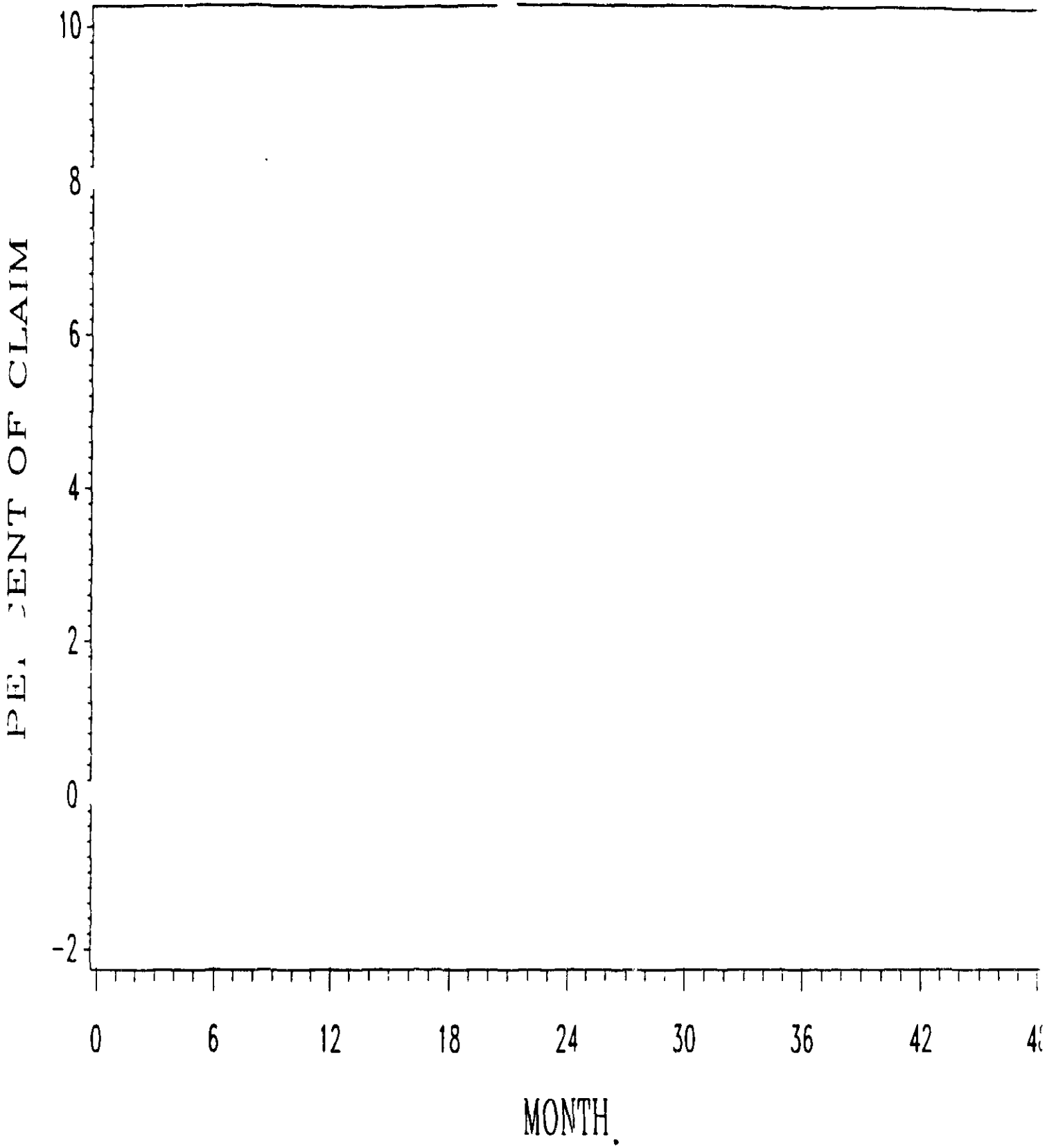

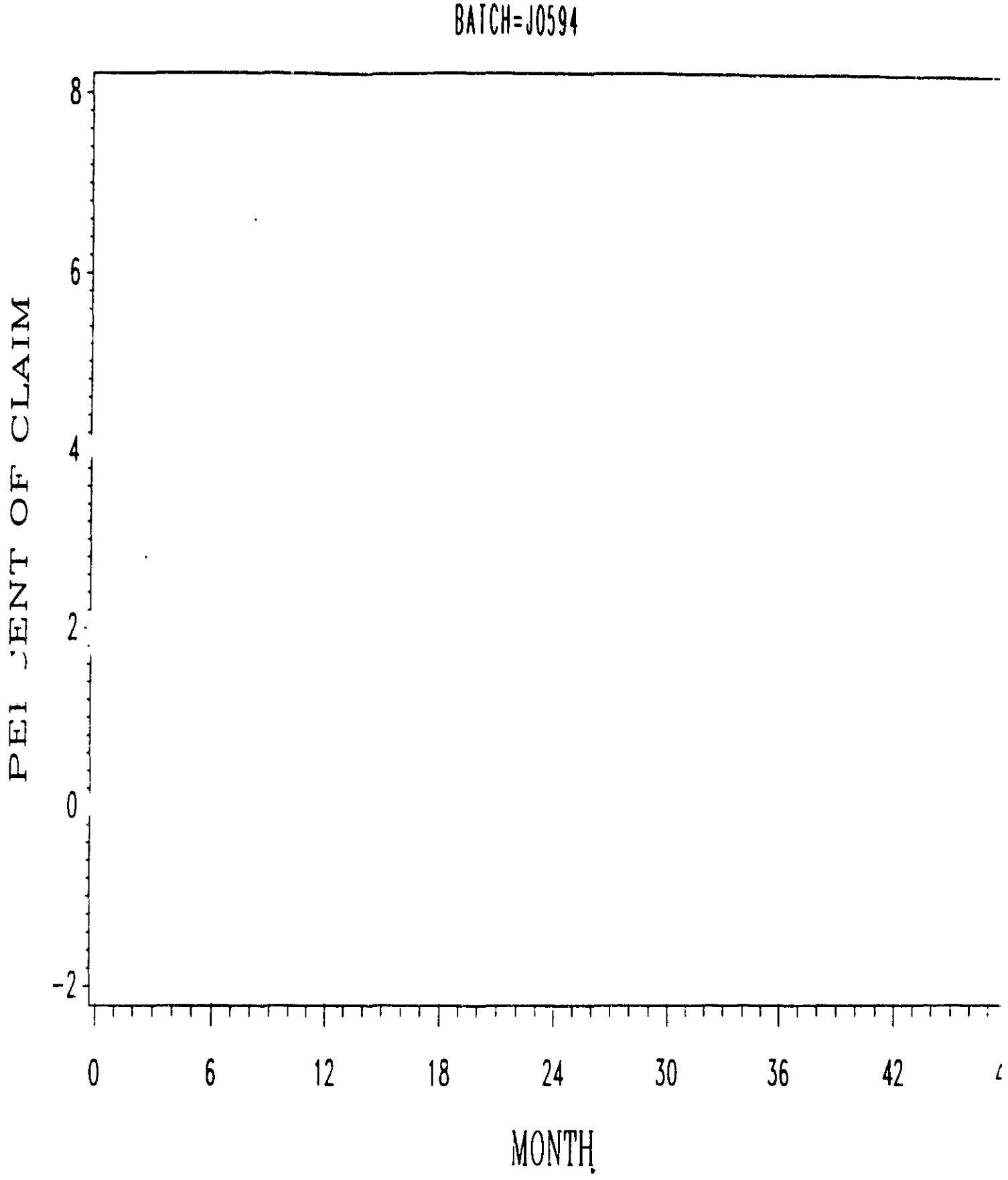
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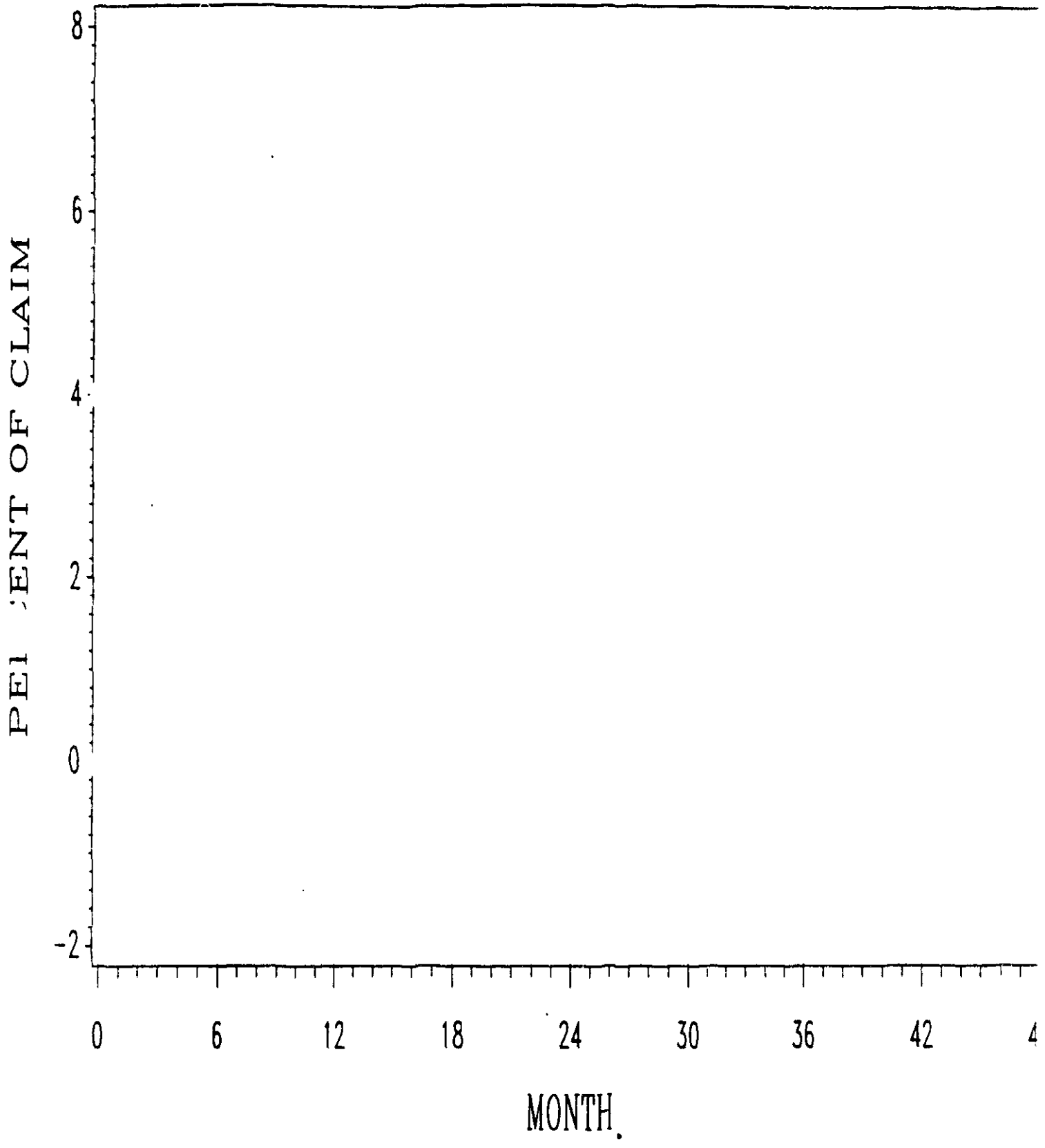
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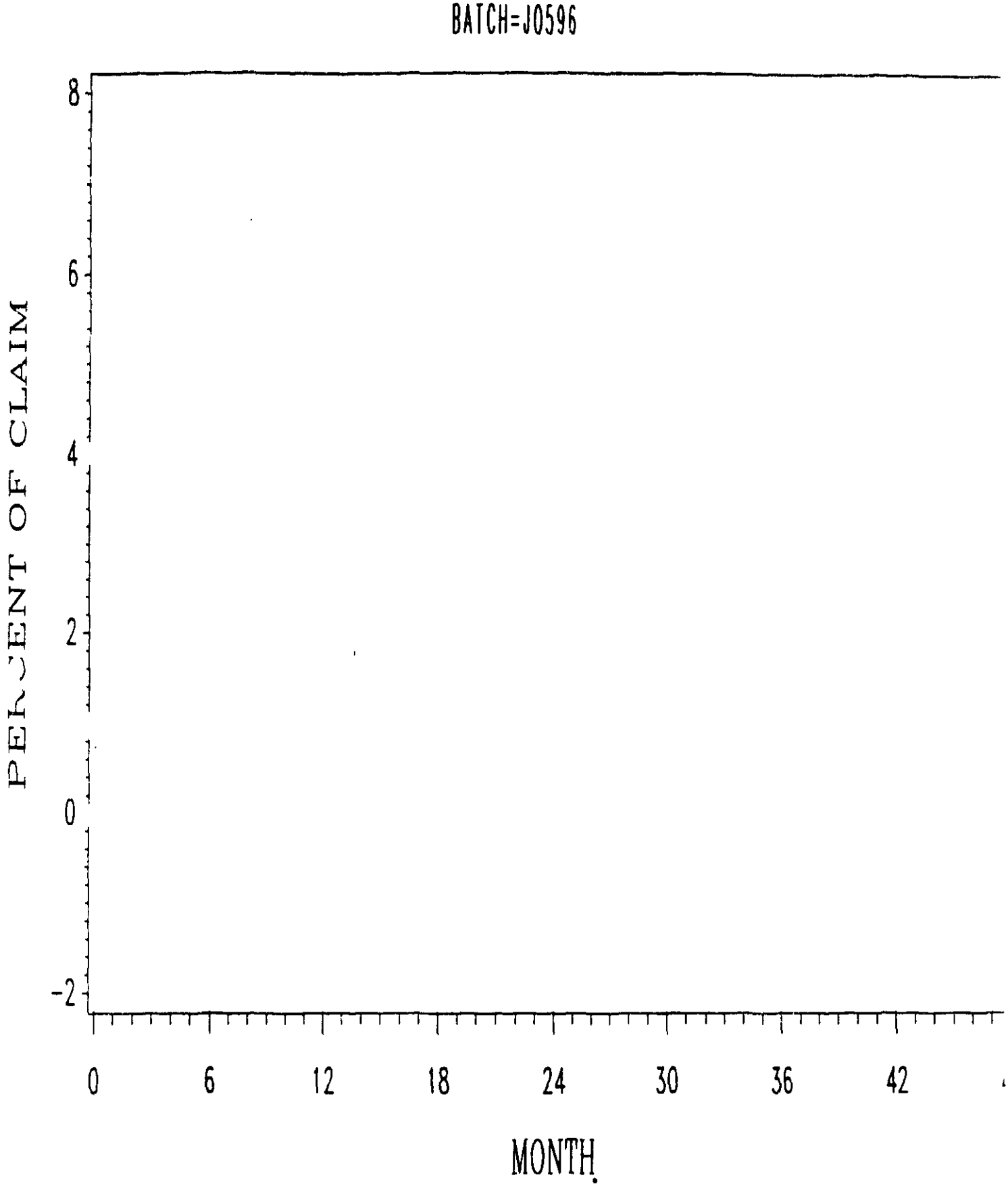
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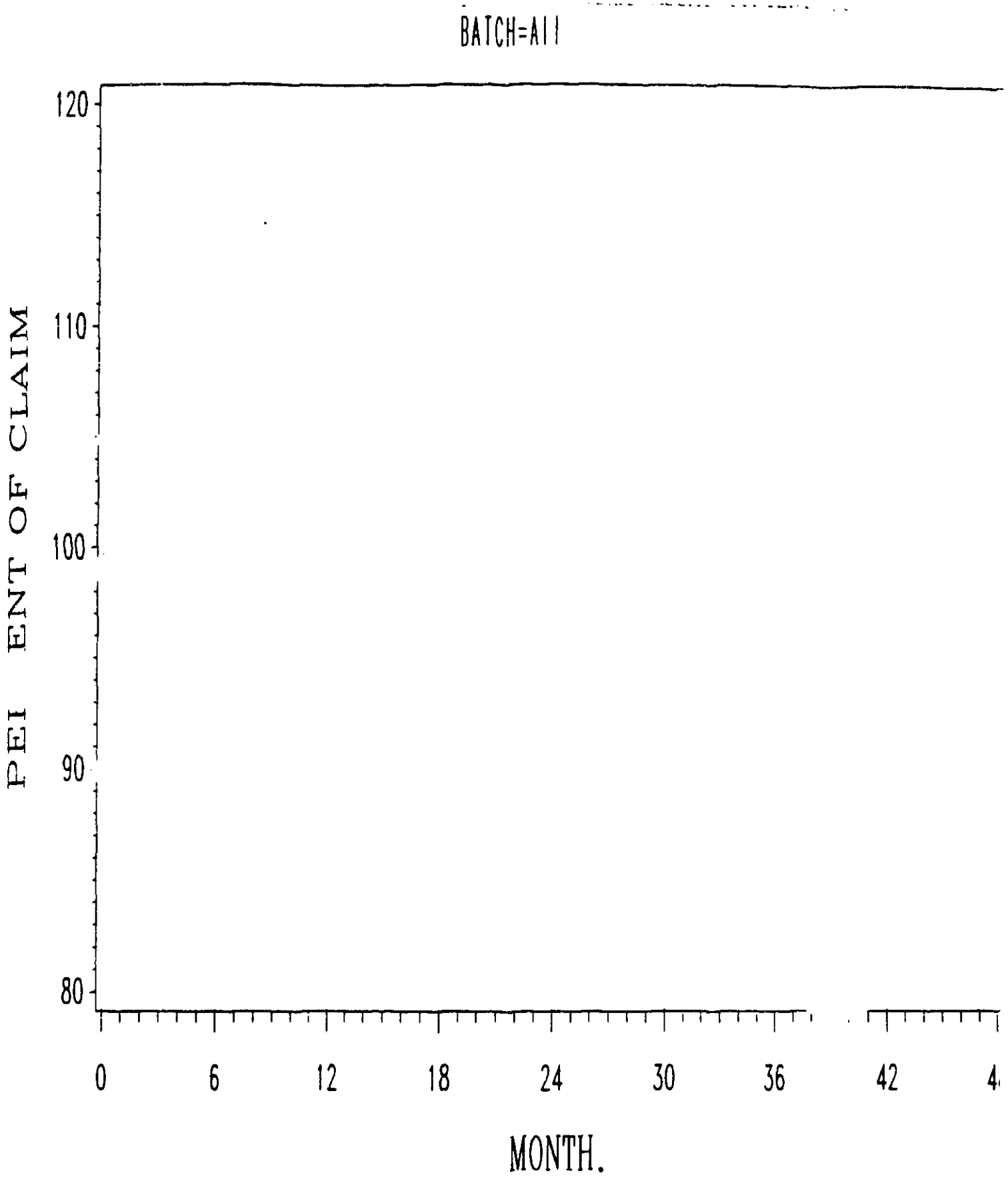
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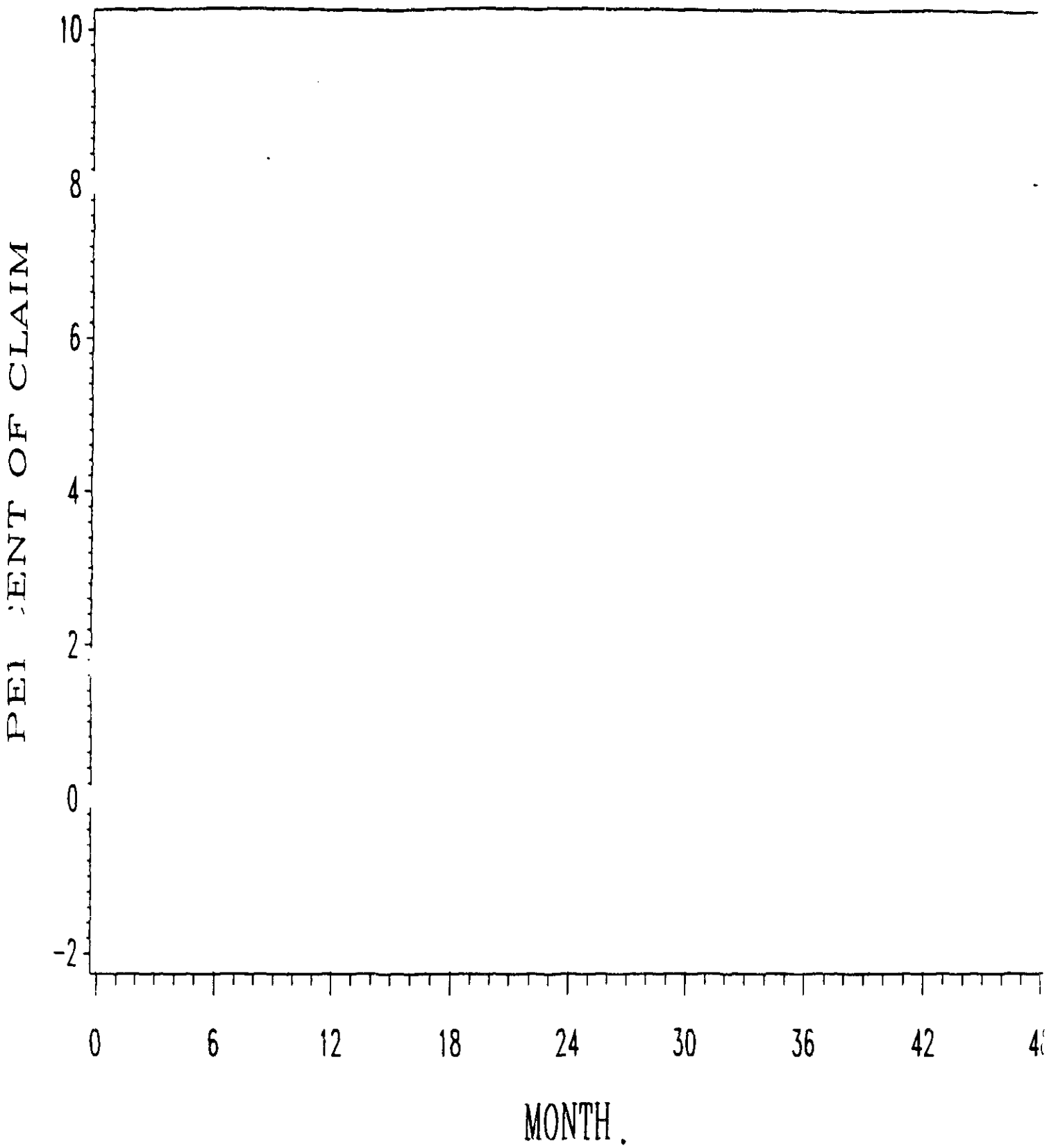
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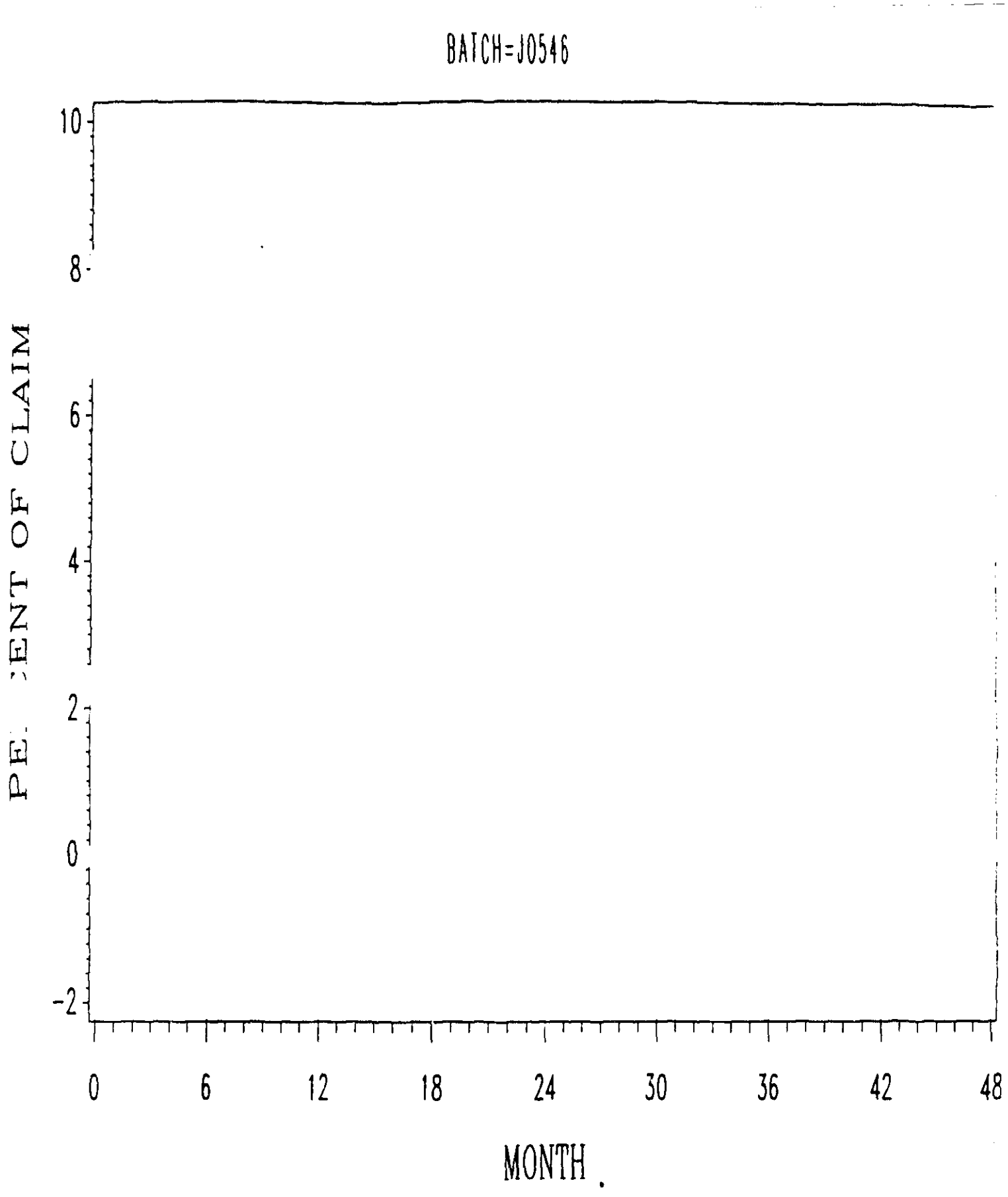
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PERCENT OF CLAIM
Predicted Value of LEVEL
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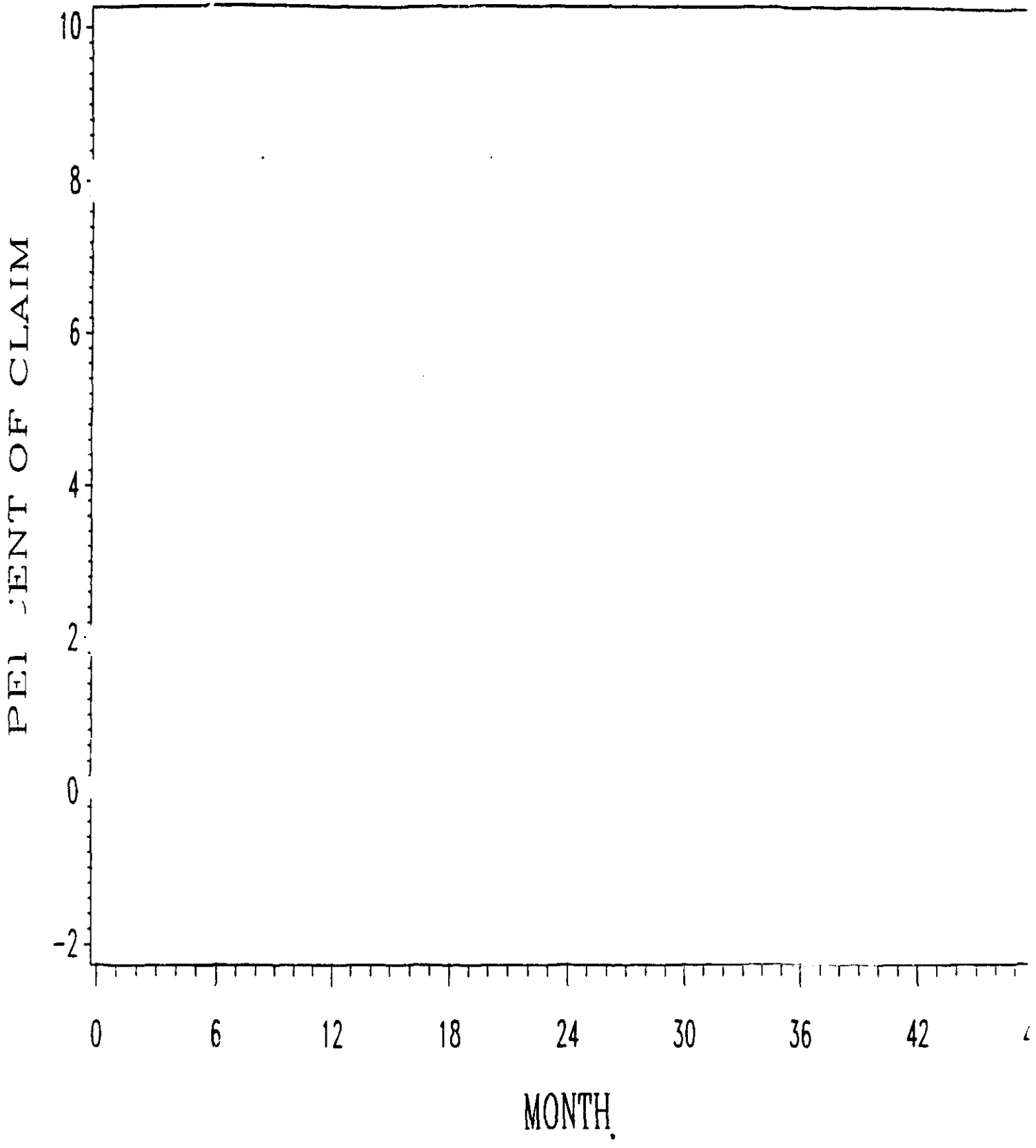
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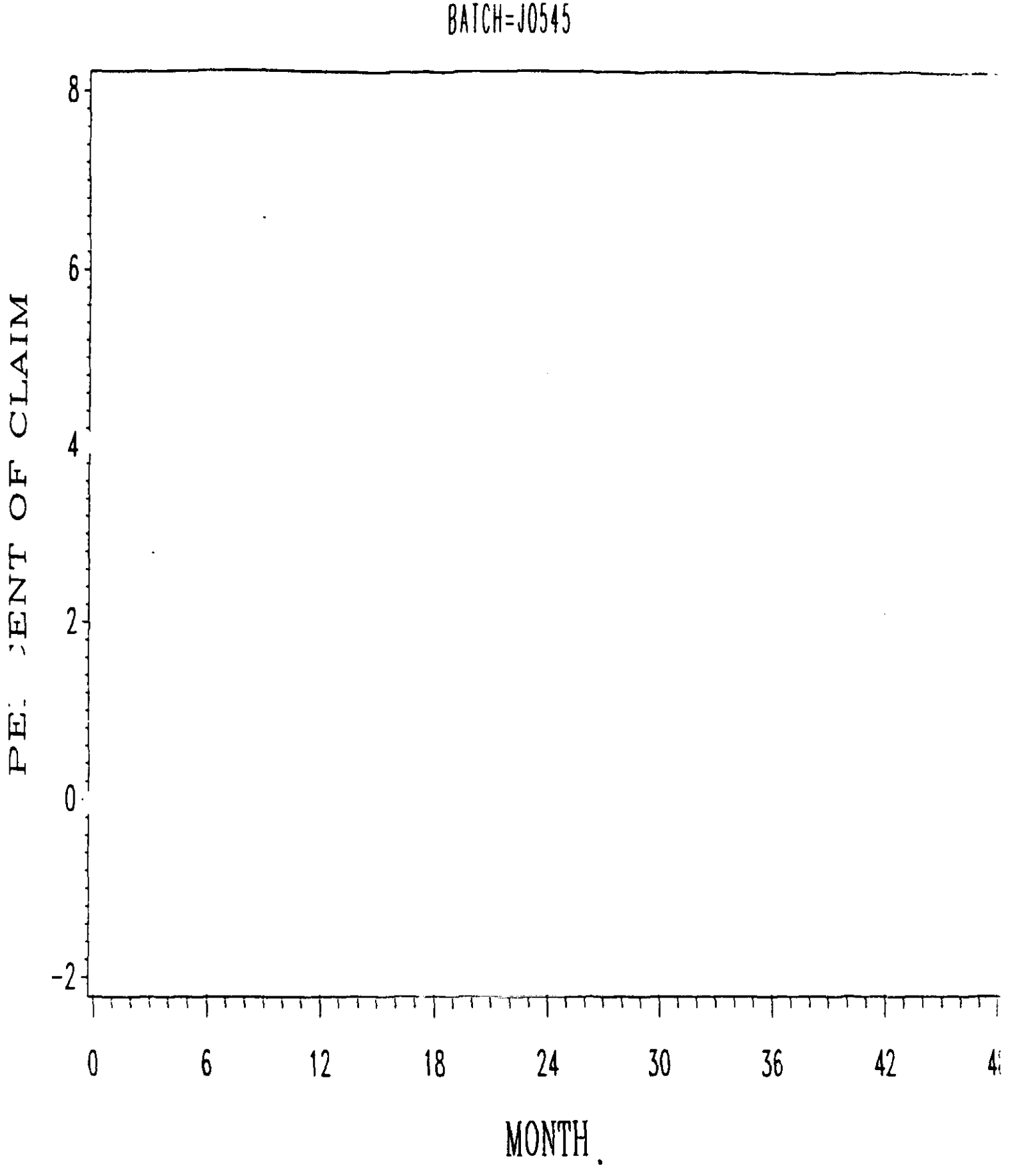
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----- Predicted Value of LEVEL
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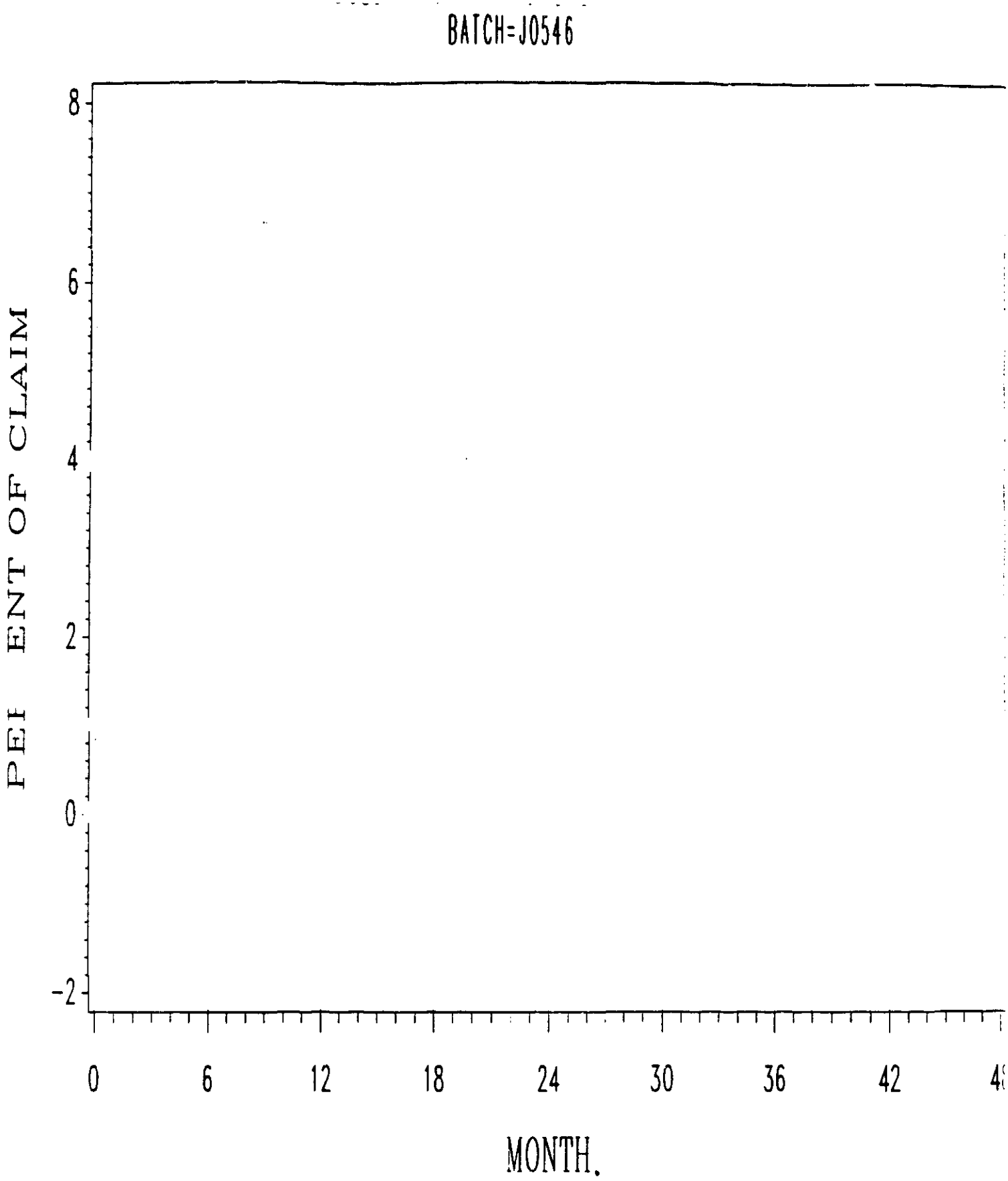
—— U_BOUND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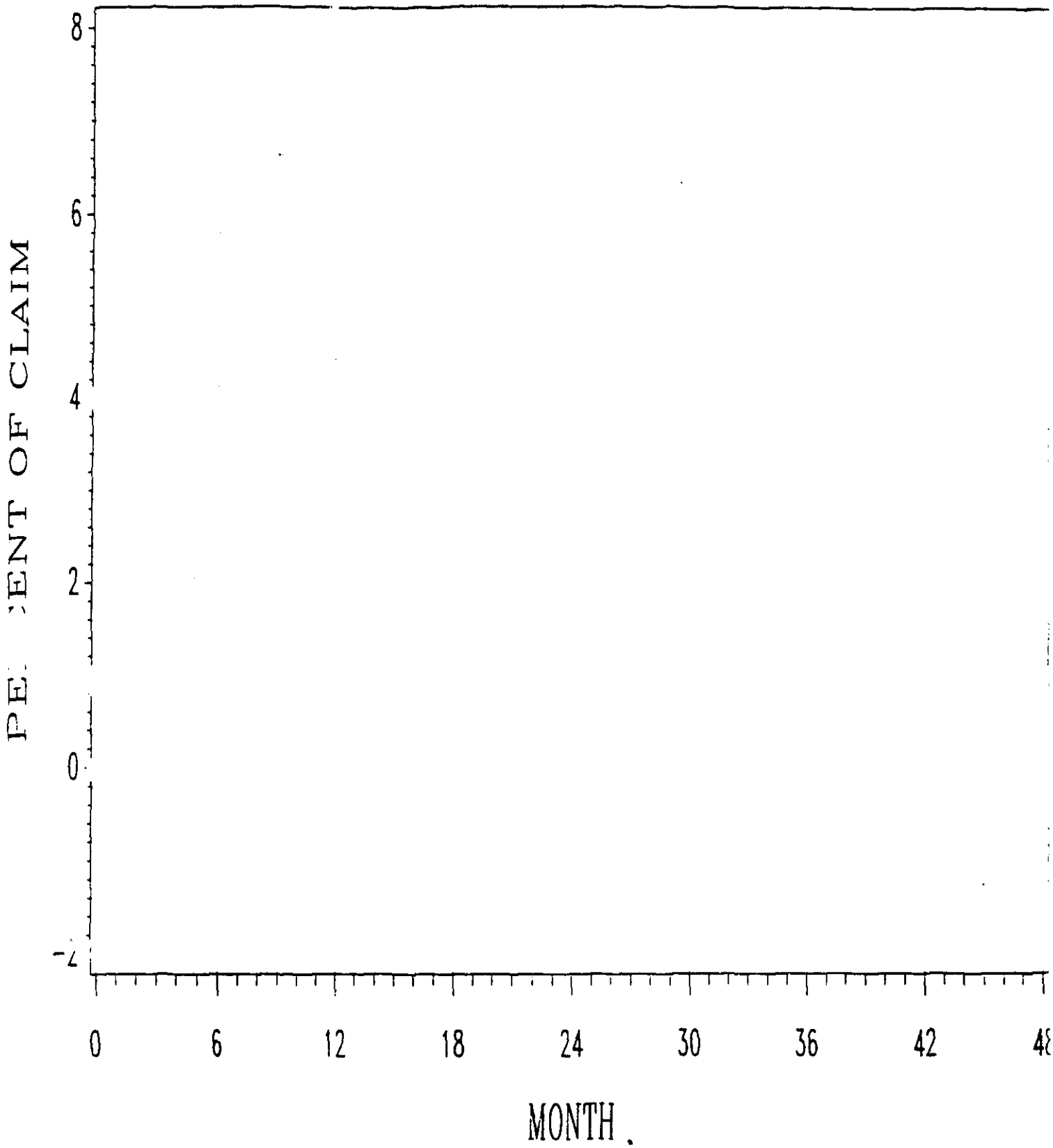

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Figure 9: Assay of DoceTaxel Content (ENRG).

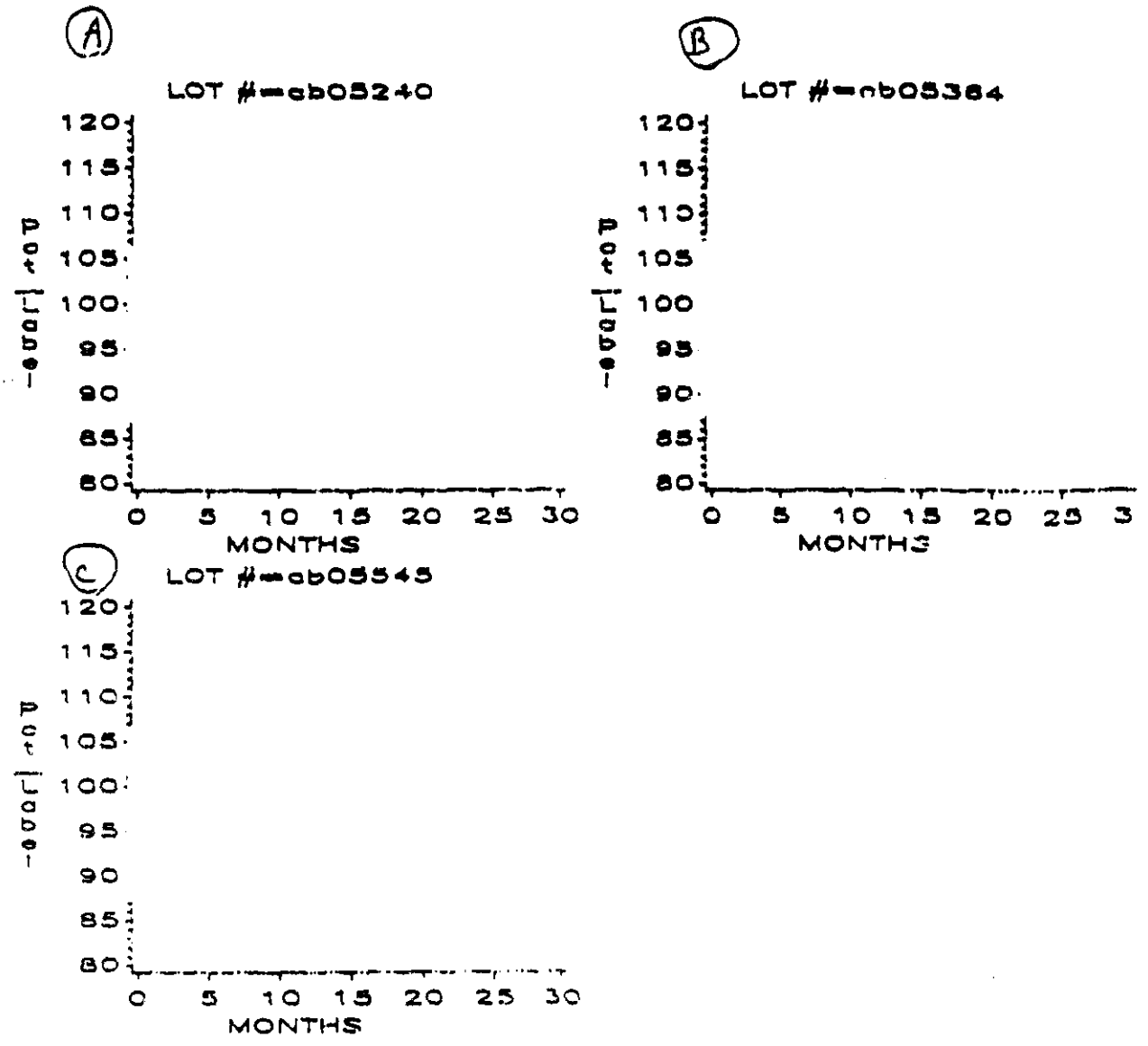
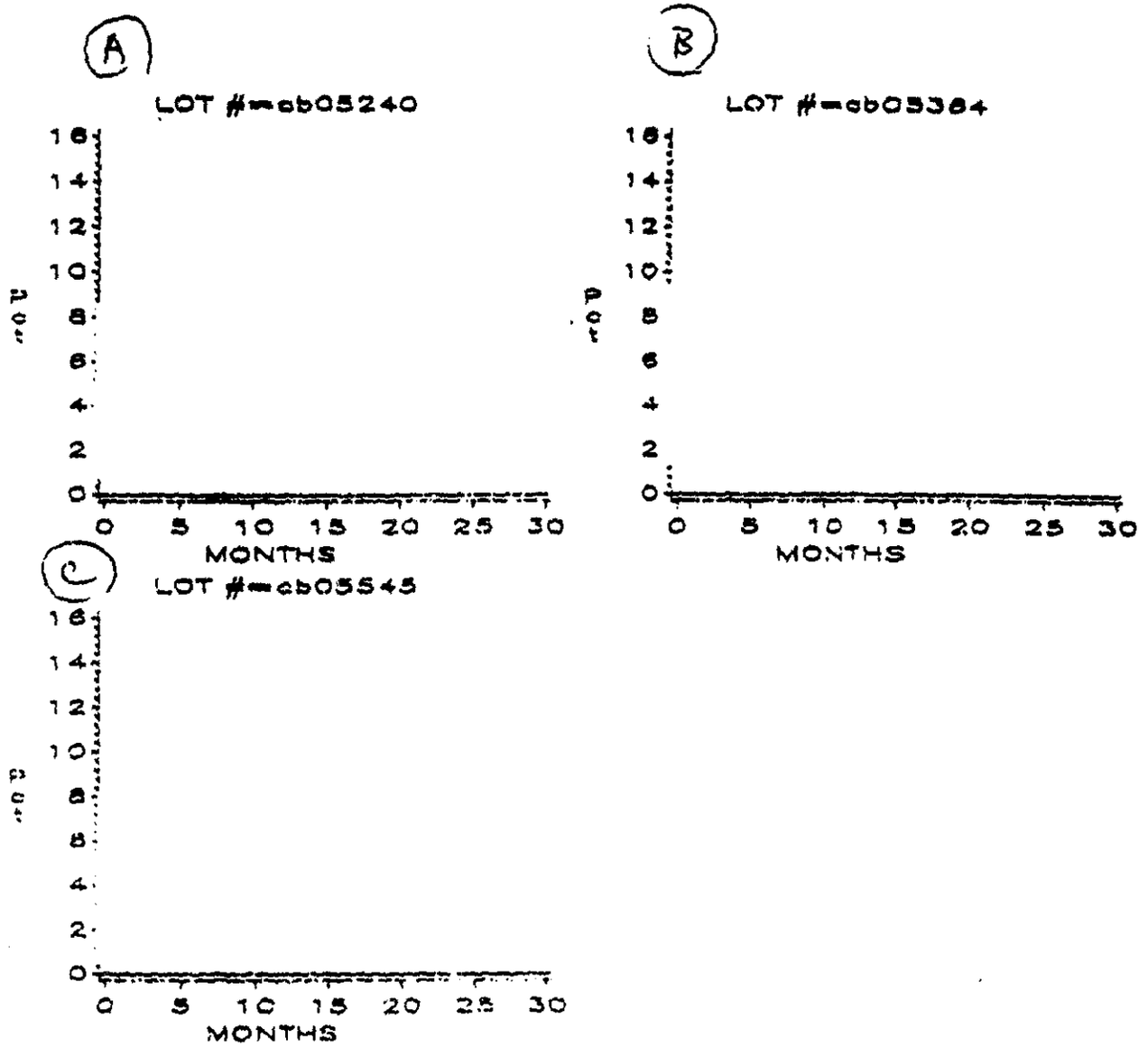


Figure 10: Sum of Related Substances (SOMSA)

TAXOENRG



Figures 11 :

RP 70617

TAXOENRG

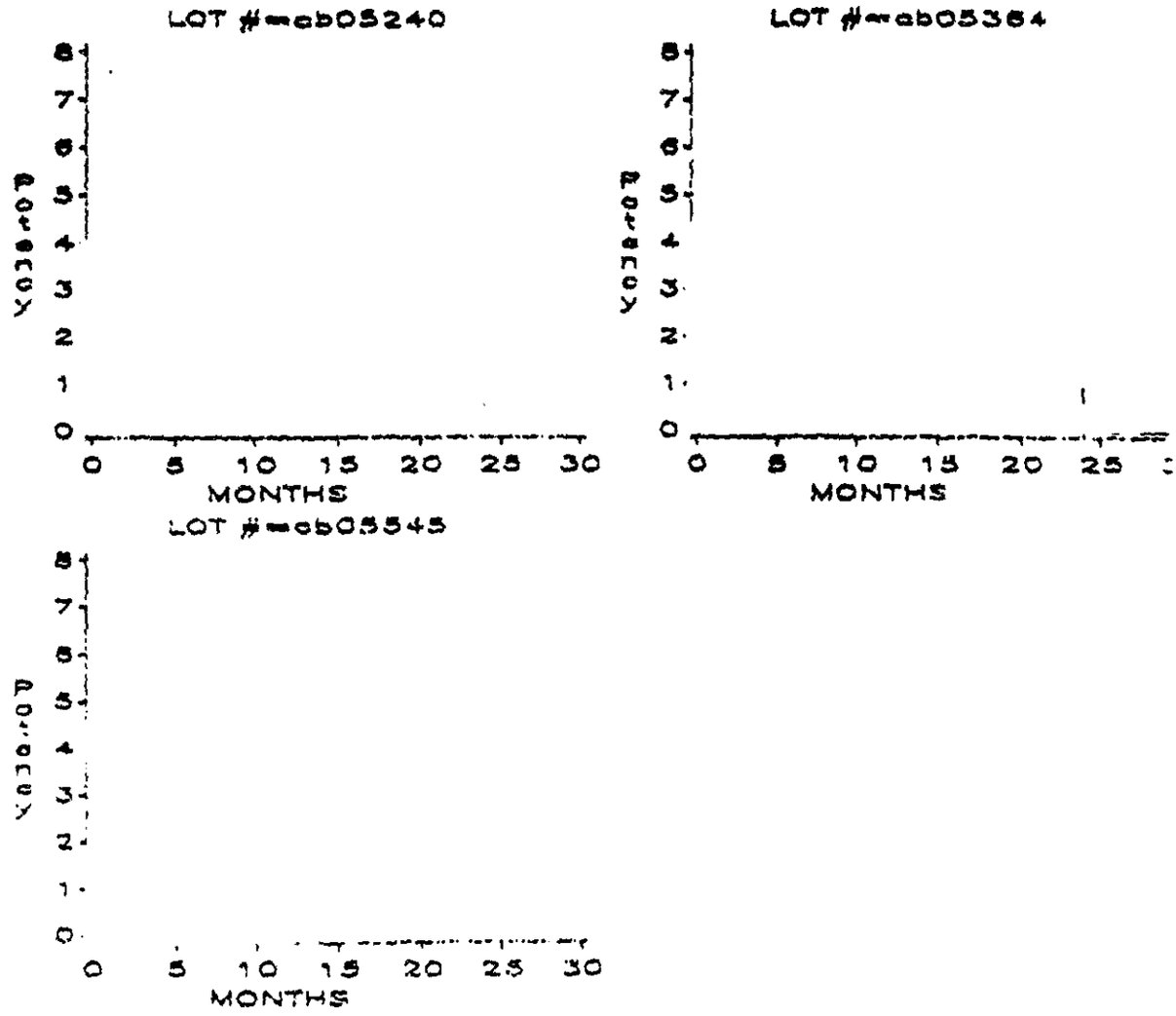


Figure 12: RPR110928

TAXOENRG

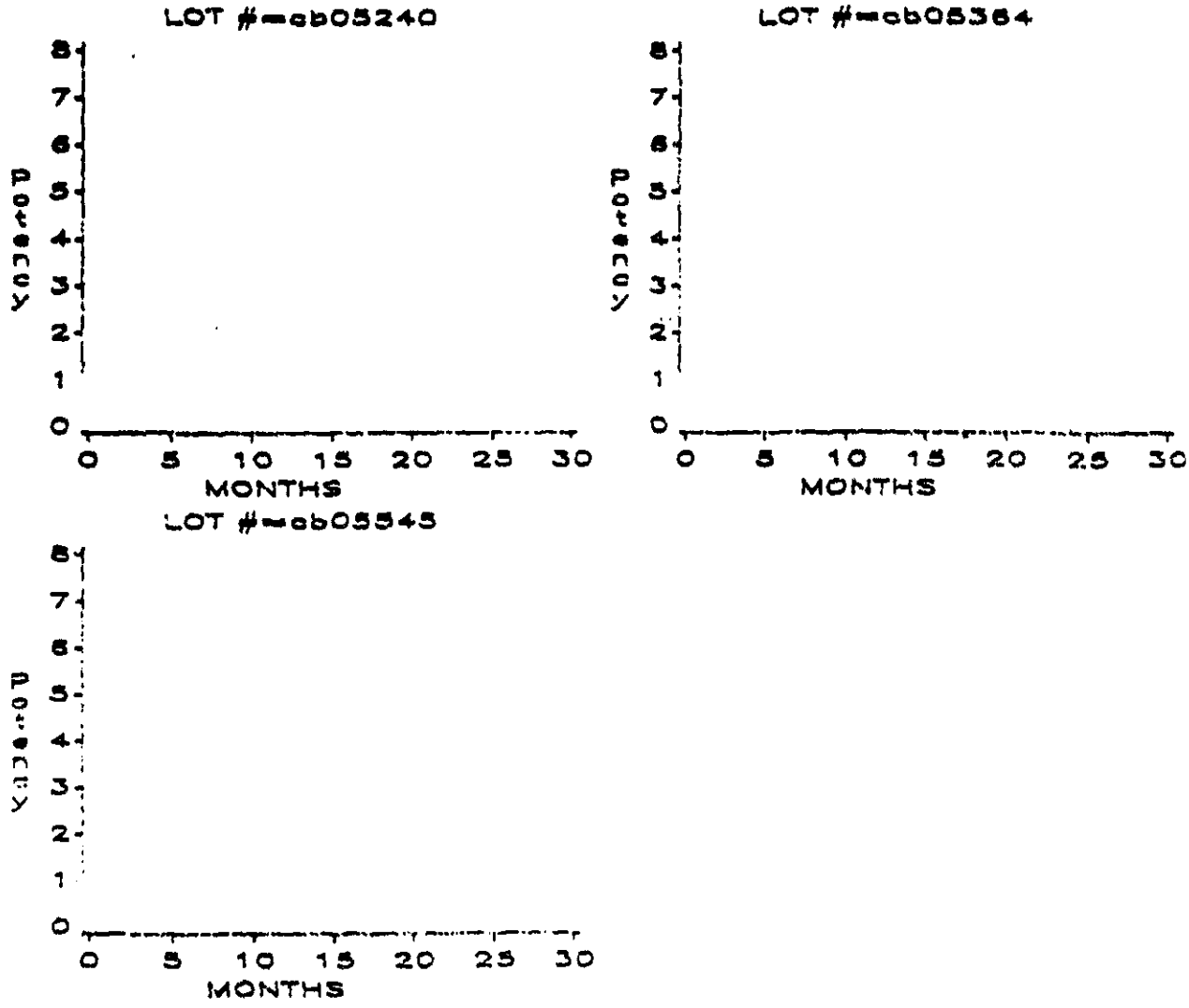
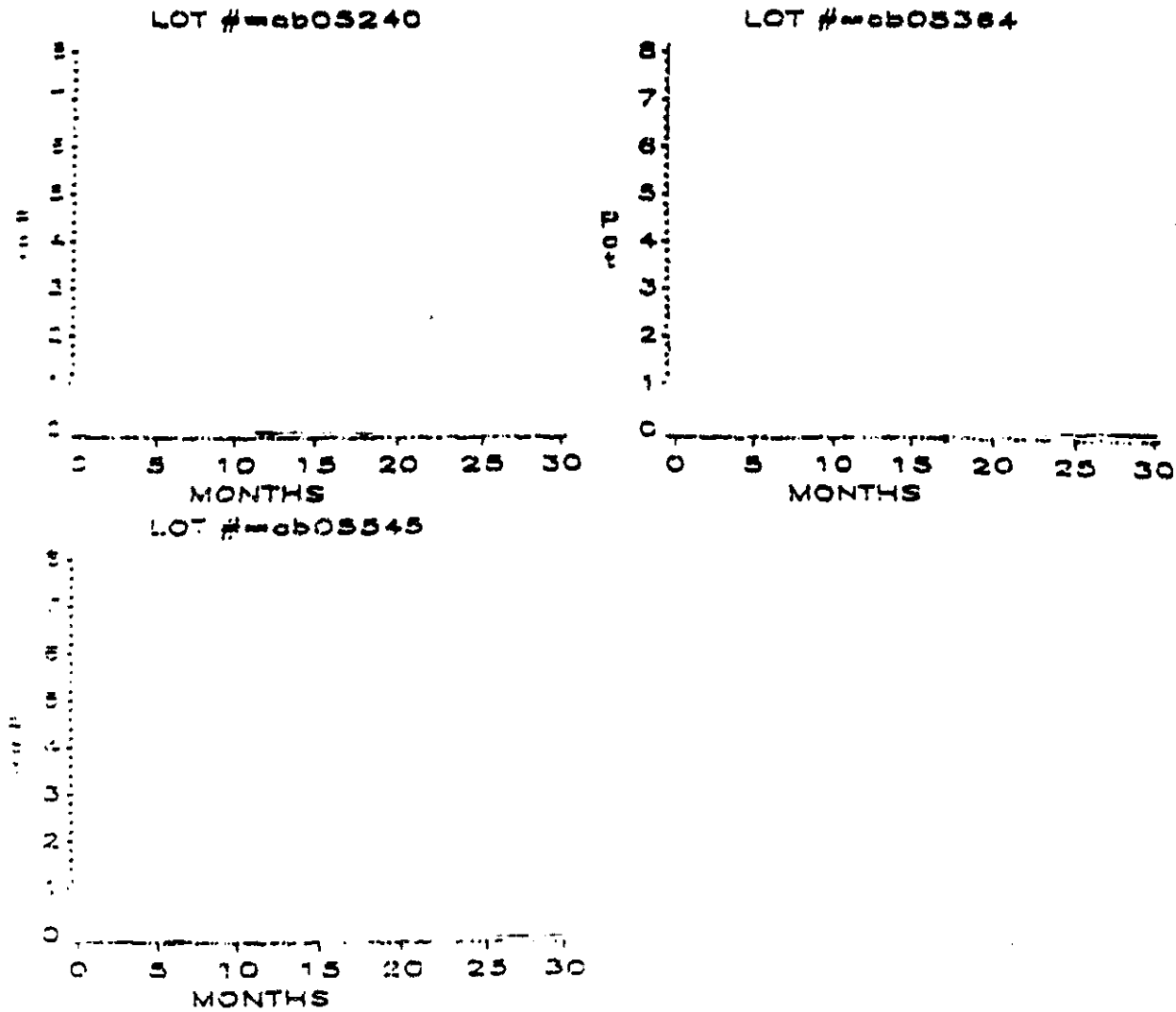


Figure 13: RPR112248

TAXOENRG



Statistical Review and Evaluation

DATE: OCT 20 1995

NDA#: 20-449

APPLICANT: Rhône-Poulenc Rorer

NAME OF DRUG: Taxotere 20 mg and 80 mg

DOCUMENTS REVIEWED: Xerox Copies of the Taxotere, C.M.C. Section - **Drug Substance**: p. 58, Answer to Question 21.b., Addendum to Answer; p. 60, Answer to Question 21.c., Addendum to Answer. Xerox Copies of Taxotere, C.M.C. Section - **Drug Product**: p. 80, Answer to Question 32.a.; p. 81, Answer to Question 32.b., Addendum to Answer; p. 82, Answer to Question 32.c. and Addendum to Answer; Appendices 1, 2, 3, 4, 5, 6, 7, 35 and 38;

SUMMARY FOR INCOMPLETION OF STATISTICAL REVIEW.

Dr. Hsieh (HFD-150) requested the Division of Biometrics to review the sponsor's stability submission. The sponsor used the method of General Linear Models to analyze the stability data and to compute estimated expiration dating periods. The use of a General Linear Model is in general a proper statistical procedure when analyzing stability data. When verifying a sponsor's analysis this reviewer found that the input data used by the sponsor are not identical to those given in Appendices 1, 2, and 6. I therefore called to sponsor 10/13/95 to request a clarification as to which data sets are the correct ones. I also requested the sponsor to provide the correct data sets on diskette to expedite our review. So far neither a hard copy of validated data nor data on diskettes have been received by this reviewer.

Roswitha E. Kelly

Concur: Karl K. Lin, Ph.D. 10/20/95

cc: HFD-150/NDA 20-449 Original
HFD-150/Dr. Hsieh
HFD-150/Ms Pease
HFD-710/Chron
HFD-715/Dr. Fairweather
HFD-715/Dr. K. Lin
HFD-715/R. Kelly
HFD-715/DRU 2.2.1 Taxotere 80mg and 20 mg, Rhône-Poulenc Rorer
HFD-715/RKELLY/10/20/95/wp-taxotere.rev

FEB 7 1996

STATISTICAL REVIEW AND EVALUATION (ADDENDUM)

NDA#:	20-449
Applicant:	Rhone-Poulenc Rorer Pharmaceuticals, INC.
Name of Drug:	Taxotere (Docetaxel) for Injection Concentrate
Indication:	Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.
Documents Reviewed:	Document Package faxed on Nov. 22, 1995, received on Nov. 28, 1995; amendment to an approvable NDA (fourth partial submission) dated Dec. 1, 1995, received Dec. 6, 1995
Medical Officer:	Julie Beitz, M.D.

I. BACKGROUND

This NDA was originally presented at the Dec. 13, 1994 ODAC meeting. The committee was concerned about toxicity, including toxic deaths, fluid retention, febrile neutropenia and infection. The NDA was brought back to the ODAC held on Oct. 17, 1995. The original indication of "Treatment for patients with locally advanced or metastatic, second line (prior therapy should have included an anthracycline unless clinically contraindicated) breast cancer" was modified to limit treatment to only patients who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

The discussion at the October ODAC meeting focused on this limited indication. As was discussed at that meeting, many of the critical subgroup analyses carried out by the sponsor and utilized by the committee in its deliberations on Taxotere have not been provided in full to the FDA.

The decision for Taxotere with this new indication was approvable. A letter was sent to the sponsor on Oct. 27, 1995 requesting they submit revised draft labeling and provide the data on medical/pharmacology-toxicology/chemistry related concerns. The submitted document dated Nov. 21, 1995 addresses the sponsor's response to the items described in the above letter. The submitted amendment to an approval NDA dated Dec. 1, 1995 contains the electronic EXCEL data spreadsheet and the corresponding graphs.

II. OVERVIEW OF THE MEDICAL/STATISTICAL CONCENRS

In the FDA letter to sponsor, the medical section includes: 1) and 2) requests of case report forms for specific patients, 3) submission of tumor lesion measurements/assessments of Japanese data (electronically for expedition), 4) summary of all hematologic and non-hematologic toxicities observed in the 134 approvable-based patients, 5) details of the assessment of performance status over time for responders and non-responders that were presented at the October 1995 ODAC meeting (Sponsor's slides 61-65 should be submitted along with supporting electronic data), 6) submission of all safety information sponsor now has regarding sponsor's new drug, and 7) detailed proposal for conducting a physician education program.

In addition, FDA needs a letter from sponsor documenting their intent to complete and submit results of the following studies as soon as possible after marketing: 1) the ongoing studies of TAX311, TAX303, and TAX304, 2) an ongoing study in second line breast cancer comparing docetaxel 100mg/m^2 with 75 mg/m^2, 3) an ongoing comparison of different corticosteroid premedications for the amelioration of fluid retention, 4) an ongoing study of the benefit of G-CSF with respect to myelotoxicity endpoints, 5) ongoing and future studies in patients with combined elevations of transaminase and alkaline phosphatase to define safe and effective doses for such patients, 6) submission of the results of a safety registration study required by the regulatory authorities in Europe to the NDA, and 7) further exploration of pharmacokinetics/pharmacodynamic relationships, specifically toxicity and response.

Further submission of labelling revision according to the revised indication and patient package insert is required.

III. THE Sponsor'S RESPONSES

The efficacy reports submitted by the sponsor for medical/statistical questions #3, #4 and #5 (see p.7-p.23 of the faxed document dated Nov. 21, 1995) were reviewed.

Q3: Japanese clinical experience with Taxotere 60 mg/m^2

In the Japanese Taxotere clinical experience, a recent analysis performed by the sponsor shows that of the 174 patients who received prior chemotherapy regimens, 32 had received adjuvant chemotherapy only, 72 patients had received chemotherapy for adjuvant and metastatic indications and 70 patients had received chemotherapy for a metastatic or locally advanced indication. The tumor response in relation to the number of prior chemotherapy regimens (sponsor table 3.2) and in relation to indication of taxotere treatment (first-line, second-line, etc., sponsor table 3.3) at 60 mg/m^2 showed an overall objective tumor response rate of 45.4% (79/174). These rates are 56.3% (18/32), 44.2% (42/95), and 40.4% (19/47) for first, second and $\geq$ third line indications, respectively. To classify whether a patient is anthracycline resistant or not, sponsor stated difficulties encountered as follows.

- In the early phase II breast cancer Taxotere trial (n=48), the response to prior chemotherapy was recorded as 'yes or no'. The definition of 'anthracycline resistance' as presented to the ODAC could not be applied.

- In the later phase II breast cancer Taxotere trial (n=126), the specific response to prior chemotherapy was captured. The definition of 'anthracycline resistance' can be applied.

- Of the 92 later phase II patients who had prior anthracycline exposure, 21 patients were reported to have PD as best response to the anthracycline containing chemotherapy regimens (14 received prior chemotherapy for both adjuvant and metastatic disease and 7 received chemotherapy for metastatic or locally advanced disease only). Of these 21 patients, 16 received prior doxorubicin, 3 received epirubicin, 1 received terarubicin and 1 received an investigational anthracycline. The dosage and schedule of the prior anthracycline therapy was not captured in the later phase II breast cancer CRFs. These 21 patients may not be comparable to the strictly defined 'anthracycline resistant' breast cancer population in the Taxotere pivotal trials.

In addition, sponsor noted that the above mentioned efficacy data provided by the Japanese investigators have not been reviewed by an independent panel as were the pivotal US and European breast cancer clinical trials. The information on indication for prior chemotherapy and number of prior chemotherapy regimens has not been confirmed by the Japanese investigators, and, therefore, should not be considered final. The early phase II studies are being re-evaluated in an attempt to elucidate if there were patients in this group whose disease could be classified as 'anthracycline resistant' as utilized at the ODAC meeting.

Q4: Summary of all hematologic and non-hematologic toxicities observed in the 134 anthracycline-resistant patients on studies TAX233, TAX267, and TAX286 grouped according to baseline liver function.

The sponsor lists all the hematologic and non-hematologic toxicities by patients (Table 4.1) and by courses (Table 4.2).

Q5: Assessment of performance status over time for responsders and non-responders that were presented at the ODAC meeting.

Sponsor presented a series of graphs on the Karnofsky performance (KP) status profile over time for the anthracycline-resistant patients at the ODAC meeting. These graphs included responders (n=55), stable disease patients with baseline PS=1 (n=23), and progressive disease patients with baseline PS=1 (n=13). The sponsor stated that "the last performance status of each cycle was used as the performance status for the cycle". From these graphs, the sponsor concluded that

- In this anthracycline resistant patient population, most symptomatic patients improved or maintained their performance status while on Taxotere; and

- In those instances where a deterioration was observed, the degree of this deterioration was rarely profound.

IV. REVIEWER'S COMMENTS

The approval decision was based on 134 anthracycline-resistant breast cancer patients. Patient characteristics reported in these patients included ECOG performance status, number of organs involved, visceral disease, liver involvement, previous chemotherapy, number of prior chemotherapy regimens, and prior radiotherapy (see sponsor's slides 57, 58). The majority (84%) of patients had ECOG baseline performance status of 0 or 1. A little less than a half of the patients (46%) had three or more organs involved. About three quarter (71%) of the patients had visceral disease, and 43% had liver involvement.

For the comparison of baseline patient characteristics on prior treatment, number of prior regimens and time since last chemotherapy in Japanese and US/EORTC trials, see the attached Table 1 of the FDA MO's review of the amendment of the original NDA. The breakdowns of prior treatment, using (1) adjuvant/neoadjuvant only, (2) adjuvant only, and (3) adjuvant/neoadjuvant + advanced are not dissimilar among the Japanese study and the three pivotal trials, TAX233, TAX267, and TAX286. The time since last chemotherapy until the initiation of Taxotere was one month longer in the Japanese trials.

Reviewer Table 1 - Objective Tumor Response Rate in anthracycline-resistant patients

Objective Tumor Response Rate	Japanese 60mg/m2 n=174	TAX233(US) 100mg/m2 n=41	TAX267(US) 100mg/m2 n=42	TAX286(EORTC) 100mg/m2 n=51
ORR	79/174(45%)	19/41(46%)[d]	21/42(50%)[d]	15/51(29%)[d]
95% CI[e]	38%-53%	31%-62%	35%-65%	17%-42%
ORR (J. vs US/EORTC) 95%CI	45% (38%-53%)	41%[f] (33%-49%)		
ORR by Prior Tx Adj/neoadj Only Advanced	18/32(56%)[g] 61/142(42%)[g]	3/4(75%)[a] 16/37(43%)[a]	½(50%)[b] 20/40(50%)[b]	0/5[c] 12/33(36%)[c]
ORR in pts w/ PD as Best Response to Prior Anthracycline	7/21(33%)[g]	4/13(31%)	5/15(33%)	9/25(36%)

[a]Sponsor Table 4.10, 8-39-188 [b]Sponsor Table 4.10, 8-45-232 [c]Sponsor Table 30, 9-12-221, n=38 evaluable patients only [d]Sponsor's ODAC slide 59 [e]95% CI calculated by the Reviewer [f]Sponsor's ODAC slide 60 [g]Table 2 of FDA MO Review

Reviewer Table 1 summarizes the sponsor's ODAC slides 59, 60 and Table 2 of the FDA MO's Review to the amendment of the original NDA. The objective tumor response rate (ORR) for the Japanese study of 60 mg/m^2 is in the range of the three pivotal studies of 100 mg/m^2 (TAX233, TAX267 and TAX286). The objective tumor response rates to Taxotere for patients with prior treatment for advanced disease or ORRs in patients with PD as best response to prior anthracycline were similar across trials. The ORRs for patients with prior adjuvant/neoadjuvant treatment only is difficult to compare across the trials due to small sample sizes in trials TAX267 and TAX286.

Q3: The FDA MO was able to classify patients into prior treatment subgroups for the Japanese study and compared it with the three pivotal studies.

Q4: The p-value reported using Fisher's Exact test for the by-course comparison may not be valid since toxicity for a given course may cumulate to future courses within a patient. In other words, toxicities for a given patient may not be independent. The p-value reported for the by-patient comparison may be used as a reference for identifying important toxicities that differentiate between patients with elevated liver test vs. patients with normal liver test.

Q5: After detailed data checking between the EXCEL data spreadsheet submitted in this amendment and the data listing in Vols.1.139, and 1.145 from the original NDA submission, and Vol. I of III from the May 23, 1995 submission, this reviewer found that "the last performance status of each cycle was used as the performance status for the cycle" may not be correct. Many patients have the initial performance status of each cycle used as the performance status for the cycle.

Reviewer Table 2 - Evolution of KPS for CR+PR, and PS=1, SD/PD patients

	PS=0 CR+PR (Fig.5)	PS=1 CR+PR (Fig.2)	PS=2 CR+PR (Fig.1)	PS=1 SD (Fig.3)	PS=1 PD (Fig.4)
KPS recorded up to EOS*	9(47%)	21(74%)	4(57%)	18(78%)	15(88%)
improved	0	1	1	0	1
stable	7	9	2	9	9
deteriorated	2	9	0	7	5
unknown	0	2	1	2	0
KPS not recorded up to EOS	10	8	3	5	2
improved	0	0	2	0	0
stable	7	7	1	5	2
deteriorated	3	0	0	0	0
unknown	0	1	0	0	0
Total pts.	19	29	7	23	17

* EOS: end of study

From the above table, 38% (21/55) of responder patients did not have their KPS measurments recorded up to end of study. This may severely distort the KPS profile over time. It depends on the missing data pattern through treatment discontinuation. This problem may be serious particularly when the dropout rate is high, e.g., high dropouts due to treatment related adverse events.

If the summary is restricted to patients who have objective tumor response and have KPS status recorded up to their individual end of the treatment, 6% (2/34) improved, 53% (18/34) stayed stable, 32% (11/34) deteriorated, and 9% (3/34) didn't have KPS recorded even though the data listing of vital signs was recorded up to EOS.

The FDA MO identified 18 out of 134 patients who were likely to have KPS deteriorated over time but were not captured in the EXCEL data spreadsheet. These 18 patients consist of (a) treatment-related morbidity (n=8), (b) death (n=3), © patients withdrawn for toxicity, likely to deteriorate (n=4), and (d) patients withdrawn for moderate to severe fluid retention (n=3). Ten of these patients were presented in the sponsor's graphs. Of the 10 patients, two (TAX267, #263; TAX286, #22) were from the KPS not recorded to EOS group. Of those who had KPS recorded to EOS (n=8), 5 were in the deteriorated category, 1 was in the not known category, and 2 were in the stable group (these two were (d)).

The sponsor's conclusions on KPS improvement or stablization need to be interpreted with caution as indicated by this summary breakdown.

OVERALL SUMMARY

Based on the original protocols, the primary endpoint for these single agent, open-label, phase II studies was objective tumor response. The number of cycles of Taxotere to maximal response and duration of response were secondary endpoints. The clinical benefit responses, measured by changes in performance status, pre-existing symptoms and analgesic use, were also secondary endpoints. Other efficacy endpoints were time to first response, time to disease progression, and survival.

The results for objective tumor response, duration of response, and time to disease progression based on the originally submitted database, including TAX211, TAX233, and TAX267, can be found in Reviewer Tables 1 and 2 of the original statistical review for breast cancer dated 9/8/95. The results for Objective Tumor Response Rate based on this new indication can be found in Reviewer Table 1.

For the clinical benefit response, the sponsor stated that "In most of the phase II studies conducted, although no specific questionnaire on Quality of Life had been addressed, 2 parameters were taken into account: analgesic requirements (AR, prospective analysis, US studies only) and Performance Status (PS, retrospective analysis) (see Sponsor vol. 1.217 p.77, Integrated Summary Metastatic Breast Cancer)". In particular, the results of change from baseline through cycles 2, 4, and 6 of PS, pain and cough, and AR submitted by the sponsor were

commented on by this reviewer (see Addendum to the Statistical Review and Evaluation I, dated 10-19-95) as follows "*These dropouts are not random in that they are likely to be treatment related, e.g., disease progression, severe toxicity, etc. Therefore, these percentages only apply to patients who stayed on the trial to at least cycle 6. The interpretation of these percentages for the subpopulations, i.e., patients who stayed on the trial by cycle 6, could be misleading*". For KPS evolution over time presented at the ODAC meeting, similar reasoning applies. The sponsor's conclusions on KPS benefit to patients need to be interpreted with caution.

Sue-Jane Wang

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco C Gnecco 2/7/96

Dr. Chi Chi 2/7/96

cc:

Archival NDA 20-449
HFD-710 Dr. Anello
HFD-150/ Dr. Justice
HFD-150/ Dr. Beitz
HFD-150/ Ms. Pease
HFD-344/ Dr. Lisook
HFD-710/ Dr. Chi
HFD-710/ Mr. Orticke
HFD-710/ Dr. Gnecco
HFD-710/ Dr. Wang
HFD-710/ Chron

SWANG/12-19-1995/WP60-TAXOTERE.AD3

This addendum consists of 7 pages of text, 4 sponsor tables, 5 sponsor figures and 2 reviewer Tables.

D-PCWC

CST

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

NDA#: 20-449

Applicant: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Name of Drug: Taxotere (Docetaxel) for Injection Concentrate

Indication: Breast cancer, locally advanced or metastatic, second line (prior therapy should have included an anthracycline unless clinically contraindicated)

Documents Reviewed: Document Package faxed on Sept. 13, 1995 and submitted on late Sept. for the 10/17/95 ODAC.

Medical Officer: Julie Beitz, M.D.

I. BACKGROUND

This NDA was originally presented at the Dec. 13, 1994 ODAC meeting. The committee was concerned about the toxicity, including toxic deaths, fluid retention, febrile neutropenia and infection. A post-ODAC meeting requested by the sponsor was held on Dec. 20, 1994. An informal presentation of additional safety analysis was performed. This safety update was intended to clarify concerns expressed by ODAC members. These additional safety analyses were subsequently submitted on Jan. 18, 1995. The sponsor further submitted a safety update (March, 1995) and a preparation package for the Oct. 17, 1995 ODAC meeting.

II. OVERVIEW OF THE PREPARATION PACKAGE AND REVIEWER'S COMMENTS

The additional efficacy reports submitted by the sponsor (see IV.2 clinical benefit in p.19-21 of the Preparation Package faxed on Sept. 14, 1995) were reviewed.

In this package, in addition to the objective tumor response, the sponsor submitted a clinical benefit summary based on 162 breast cancer patients treated with Taxotere at 100 mg/m^2

in multicenter trials, *i.e.*, TAX211 (n=28, #center=12), TAX233 (n=41, c=3), TAX267 (n=42, c=4), and TAX286 (n=51, c=13).

Based on the original protocols, the primary endpoint for these single agent, open-label, phase II studies was objective tumor response. The number of cycles of Taxotere to maximal response and duration of response were secondary endpoints. The clinical benefit responses, measured by changes in performance status, pre-existing symptoms and analgesic use, were also secondary endpoints. Other efficacy endpoints were time to first response, time to disease progression, and survival.

The results for objective tumor response, the duration of response, and the time to disease progression based on the originally submitted database, including TAX211, TAX233, AND TAX267, can be found in the REVIEWER TABLES 1 and 2 of the original Statistical Review and Evaluation (Breast Cancer).

For the clinical benefit response, the sponsor stated that "In most of the phase II studies conducted, although no specific questionnaire on Quality of Life had been addressed, 2 parameters were taken into account: analgesic requirements (AR, prospective analysis, US studies only) and Performance Status (PS, retrospective analysis) (see Sponsor vol. 1.217 p.77, Integrated Summary Metastatic Breast Cancer)". In particular, the results of change from baseline through cycles 2, 4, and 6 of (1) PS, (2) pain and cough, and (3) AR were reported in the preparation document.

(1) Performance Status (162 patients, based on 4 trials)

In sponsor Table 18, the sponsor stated that "regardless of the tumor response, most of the breast cancer patients in whom previous chemotherapy had failed improved or stabilized their PS by cycle 6 ..."

Reviewer Comments: The percentage in the last column of sponsor Table 18 (i.e., End of Cycle 6) does not represent the PS profile for the study population unless random dropouts were assumed. It is noted that 19%, 43%, and 72% of the patients dropped out at cycles 2, 4, and 6, respectively. These dropouts are not random in that they are likely to be treatment related, e.g., disease progression, severe toxicity, etc. Therefore, these percentages

only apply to patients who stayed on the trial to at least cycle 6. The interpretation of these percentages for the subpopulations, i.e., patients who stayed on the trial by cycle 6, could be misleading.

(2) Pain and Cough (based on 3 trials)

Pain (40%, 53/134 of the patients had baseline pain) and cough (13%, 18/134 of the patients had baseline cough) were the two most frequent symptoms present at baseline. These two symptoms were selected and summarized. From sponsor Table 19, the sponsor indicated that "the positive results of high percentages of patients having pain reduction or no change were observed at cycles 2, 4, and 6".

Reviewer Comments: It is not entirely clear how the pain measurements were defined, collected and categorized. The sponsor stated that "The positive results of high percentages of patients having pain reduction or no change were observed at cycles 2, 4, and 6" could be misleading. For example, if the severity of pain is non-decreasing, then the pain levels of patients who dropped out before cycle 6 are more likely to be unchanged or worsened. A reasonable estimate of the pain improvement for those patients who had baseline pain at cycle 6 would be closer to 23% (12/53) instead of 46% (12/26). If the pain improved in the first few cycles and eventually deteriorated, then a reasonable estimate would still be close to 23%.

(3) Analgesic requirements (based on 2 trials)

As shown in sponsor Table 20, the sponsor summarized that "the majority of patients did not require any increase in analgesic usage".

Reviewer Comments: At baseline, 42% of the patients required analgesics for tumor-related pain. The sponsor stated that "the majority of patients did not require any increase in analgesic usage" needs careful interpretation. ARs may fluctuate over time, the percentages are only summaries for patients who stayed on the trial to the corresponding cycle columns. The example described in (2) applies to AR.

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Wilson 10/19/95

cc:

NDA 20-~~[illegible]~~ 449
HFD-150 D.V.F.M
HFD-150/ Dr. Justice
Dr. Beitz
Ms. Pease
HFD-344/ Dr. Lisook
HFD-713/ Dr. Dubey [File: DRU 1.3.2. NDA]
Dr. Wilson
HFD-713/ Dr. Wang

SWANG/9-22-1995/WP60-TAXOTERE.ADD

MEMO OF CONSULT

TO: Julie Beitz, M.D.
Robert Justice, M.D.
Dotti Pease, CSO

FROM: Sue-Jane Wang, Ph.D.

DATE: June 14, 1995

SPONSOR: Rhone-Poulenc Rorer (RPR)

DRUG: Taxotere (Docetaxel)

INDICATION: The first and/or second line treatment for the breast cancer or Non-Small Cell Lung Cancer

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TOPIC: IND clinical study design and statistical issues in protocols

Several protocols have been submitted by Rhone-Poulenc Rorer. A summary of these protocols by cancer type are as follows:

BREAST-CANCER

TAX303 - a randomized phase III trial for first line therapy,
Docetaxel (100mg) vs Adriamycin (Doxorubicin)
(n=106 as of 6/6/95, a total 312 was planned)
Primary endpoints: Time to disease progression
Secondary endpoints: Response rate, survival, quality of life (QOL) etc.

TAX311- a randomized phase III trial for first and second line therapy (see amendment - serial# 235, 312, and 352),
Docetaxel (100mg) vs taxol (175mg)
(n=22, a total of 400 was planned)
Primary endpoint: objective tumor response rate
Secondary endpoints: Time to disease progression
Other endpoints: QOL (using FACT-B), survival, etc.

Non-Small Cell Lung Cancer

1st-line

TAX308 - a randomized phase III trial for first line therapy
(serial #334)
docetaxel (100mg) vs BSC
Primary endpoint: survival
Secondary endpoints: QOL, safety and efficacy (response rate, time to progression, response duration), etc.

Other US Phase III first line study plans (hypothetical trials) - the design will be finalized when results of ongoing combination phase II trials are available.

second-line

TAX317 - a randomized phase III trial for second line therapy
(serial #271)
Docetaxel (100 mg) vs BSC
Primary endpoint: survival
Secondary endpoints: QOL, safety and efficacy (response rate and response duration)

TAX320 - a randomized phase III trial for second line therapy
(fax 2/9/95),
Docetaxel 100mg, 75mg, vs a third arm
(possible agent for the 3rd arm: Taxol, or Navelbine, Iphosphomide)
Primary endpoint: survival
secondary endpoints: QOL, safety and efficacy (response rate, response duration)

Except the hypothetical trials, the sample size calculations based on the specified parameters and the design are reasonable.

In the statistical considerations section of the hypothetical trials, the protocol stated that "The sample size of the study is based on the assumption that the hazard ratio of the two arms are equivalent to within 30% of each other (hazard ratio $\leq$ 0.3) with an approximate median survival of 36 weeks". Dr. temple raises the concern of what the hazard ratio of 0.3 mean and stated that it would be of interest in looking at one month to 6 weeks allowable equivalence for the survival primary endpoint.

REVIEWER'S COMMENTS

The hazard ratio, less than or equaling 0.3, is questionable. It appears that if "the hazard of the treatment is no more than 30% worse of the control hazard, i.e., $1/\delta \leq 1.30$, not $\delta \leq 0.3$" was assumed, then the sample size of 200 per study arm would be reasonable (see definition of δ below).

Let δ denote the allowable equivalence hazard ratio of control to treatment. Thus, if $\delta=.80$, it means that the hazard of the control is 80% that of the treatment hazard. Conversely, $1.25=1/\delta$, the hazard of the treatment is no more than 25% worse of the control hazard.

For the control arm, a median survival of 9 months converts to an one-year survival probability of 0.397. Based on the standard assumption of 5% type I error rate and 80% power, the potential δ interested are summarized. REVIEWER TABLE 1 applies the Blackwelder method. when the time to event endpoint was considered for planning a therapeutic equivalence, two scenarios were tabulated, 18 months accrual period and 2 years accrual period (see REVIEWER TABLE 2).

REVIEWER TABLE 1: Sample size calculation based on the hazard ratio and 1-year survival

δ	median survival (in months)	1-year surv. prob. of the treatment	sample size per group
.890	8	0.354	1602
.833	7.5	0.330	660
.80	7.2	0.315	440
.75	6.8	0.292	269
.70	6.3	0.267	175
.30	2.7	0.046	24
.769(1/1.3)	6.3	0.267	321

* Blackwelder, controlled clinical trial, 1982

REVIEWER TABLE 2: Sample size calculation based on the hazard ratio and 18 months or 2 years follow-up

δ	median survival (in months)	sample size per group (18-mons)	sample size per group (2-year)
.890	8	1151	1104
.833	7.5	474	454
.80	7.2	315	303
.75	6.8	192	184
.70	6.3	124	119
.30	2.7	11	11
.769(1/1.3)	6.3	230	220

* Lin & Givens, Biopharmaceutical sequential statistical applications. Marcel Dekker Publishing, 1992.

The statistician from RPR has discussed with the reviewer during the industry meeting held on June 6, 1995, and stated that the correction will be made and submitted when these trials are finalized for the first line treatment of NSCLC.

CC: S. Wilson, Ph.D.
File
Orig NDA 20-449
Div File
J Baitz
S J Wang

SEP - 8 1995

STATISTICAL REVIEW AND EVALUATION (Breast Cancer)

NDA#: 20-449

Applicant: Rhone-Poulenc Rorer Central Research (RPR)

Name of Drug: Taxotere for Injection Concentrate (Docetaxel)

Indication:

Breast cancer, locally advanced or metastatic, second line (prior therapy should have included an anthracycline unless clinically contraindicated)

Non-small cell lung cancer, locally advanced or metastatic, first and/or second line (see STATISTICAL REVIEW AND EVALUATION - NSCLC)

Documents Reviewed: Volumes 102, 103, 108, 137, 138, 143, 144, 148, 149, 151, 173, 174, 180, 186, 187, 194, 200, 201, 202, 208, 210, 216, 217, 218. Safety update report Vol. 1.1 5.1, 5.2

SAS data base

Medical Officer: Julie Beitz, M.D.

This review was completed after discussions with the medical reviewers, Drs. Beitz and Justice.

STATISTICAL ISSUES

(1) For the response duration efficacy analysis, the definition in the protocol was different from that applied in the final medical report. The protocol-defined duration of response was, a) *CR: from the time of documentation of complete remission to disease progression*, b) *PR: the time interval from the initial dose of Docetaxel to the time of disease progression.* However, in the final medical report, the duration of response was calculated for all responding patients from the date of the first infusion of the study drug up to the first documentation of progression. Thus, the duration of tumor response determined in the final medical report may be inflated. Possible inflated DOR was found to be 1.3 to 2.3 months. Note: the calculation of duration of response adopted in the final medical report includes the time to first response and is no different from the definition of time to disease progression for responders.

(2) For the three pivotal trials in previously treated patients, viz., TAX233(n=41, US), TAX267(n=42, US), and TAX221(n=28, Europe), the study duration was 3 months longer

for the European trial than the two US trials. Specifically, for the European trial, the accrual period was one third of US trials (4.5 months in the European trial vs. 13.5 months in US trials) and the follow-up period was five times longer than US trials (15 months vs. 3 months). By pooling these three trials for previously-treated patients in the integrated efficacy analysis, the sponsor's assessment is misleading with respect to the time to event endpoints which are affected by the study duration. The longer duration of response (2.75 months) and the time to disease progression (1.5 months to 3.2 months longer) in the European trial is confounded by its longer follow-up period.

(3) Although the study duration and duration of the response were similar between the two US trials (TAX233 and TAX267), the censoring pattern 29% (2/7) of the censoring occurred before 27 weeks from initial Docetaxel treatment in TAX233 and 94% (16/17) of the censoring occurred before 27 weeks in TAX267) and censoring rate (17% vs 41%) were different. Hence, the estimated median TTP should not be combined from these two studies.

(4) In the safety udpate submitted on Nov. 7, 1994, the sponsor added in an additional pivotal study (TAX286) conducted in Europe. In this trial, there were no complete responders. The objective response rate was 29% (15/52) with a 95% confidence interval of 17% to 43%, and the median DORs were 24 weeks, with a 95% C.I. of 22 weeks to 27 weeks based on the definition in the final medical report and 16 weeks with a 95% C.I. of 12 weeks to 19 weeks when computed from the documentation of the tumor response. It is noted that the study duration of this trial is the shortest (less than one year) and the response rate was the lowest among the four pivotal trials.

(5) The objective response rates obtained from the phase II second line trials were 46.3%, 45.2%, 50.5% and 28.8% for TAX233, TAX267, TAX221 and TAX286, respectively. The sample size ranges from 28 to 52. The estimated median DOR ranges from 24 weeks to 28 weeks based on the final medical report or from 16 weeks to 23 weeks based on the documentation of the tumor response. These pivotal trials were nonrandomized, open-label, and noncomparative. The sponsor stated that there are three ongoing randomized phase III trials for second-line treatment. These comparative studies should provide statistical evidence for meaningful superior efficacy on DOR and/or TTP if it exists.

I. BACKGROUND

In this application the sponsor seeks approval for Taxotere in two indications, *i.e., the treatment of patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed, and the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) even* after failure of platinum-based chemotherapy*. For the advanced breast cancer indication, 3 phase II pivotal studies (2 US and 1 Europe), 4 phase II supportive studies (1 US, 1 Canada, 2 Europe), 3 phase II Japanese studies, 4 ongoing phase II European trials, 3 ongoing phase III trials (1 US and 2 Europe), and several studies of uses other than those claimed in the application are sponsored by the Rhone-Poulenc Rorer Central

Research. The protocols were similar for the 7 completed phase II trials conducted in Europe, the US and Canada. The differences were primarily in the patient population (previously treated vs. previously untreated patients with locally advanced or metastatic disease), the dose of Docetaxel (100 or 75 mg/m^2), and whether a routine prophylactic medication for antiemetics and antiallergics was mandated. The sponsor's rationale for pooling these 7 completed US/Canada/Europe trials resulted in five major subgroups, i.e., patients who were: (1) previously untreated starting at a planned dose of 75 mg/m^2 ; (2) previously untreated at a planned dose of 100 mg/m^2;(3) previously treated at a planned dose of 75 mg/m^2; (4) anthracycline resistant patients at a planned dose of 100 mg/m^2; (5) anthracycline refractory patients at a planned dose of 100 mg/m^2.

In the safety update submission (Nov. 7, 1994), two more European, multicentric, phase II studies with docetaxel as single agent in metastatic breast cacner were added. The TAX286 trial was conducted in anthracycline resistant patients, and the TAX281 trial was for previously untreated patients. The TAX286 trial is now included in this review.

*NOTE: The indication for NSCLC has been changed. The word has been dropped by RPR from their letter submission dated Nov. 7, 1994.

The 3 pivotal breast cancer trials, Tax233 and TAX267 include only second line patients. Trial TAX221 consisted of 28 previously treated patients and 11 previously untreated patients. The review focuses on the indication proposed in the submission, viz., second line treatment. The electronic patient data from the 3 pivotal studies were reviewed. A later submitted pivotal trial (TAX286) dated Nov. 7, 1994 was also reviewed. For the NSCLC indication, please refer to the STATISTICAL REVIEW AND EVALUATION (NSCLC).

ONGOING PHASE III TRIALS

The sponsor has three ongoing multicenter, randomized, open-labelled, comparative phase III trials. These trials are summarized in Table I. The objective of TAX303 is to determine whether Docetaxel produces a significant prolongation of median TTP (10 months) in comparison to doxorubicin (6 months) in patients with metastatic breast cancer who have failed CMF. For TAX304, the objective is to show a significant difference of 2 months in the median TTP between mitomycin C/vinblastine (4 months) and Docetaxel (6 months). The primary objective for TAX311 is to detect a 14% difference (Taxol:28% vs Taxotere:42%) in objective tumor response (ORR).

Table I. ONGOING PHASE-III TRIALS

Trial	Treatment Arms	Primary Objective	Planned sample size(per arm)
TAX303 (Europe)	(1)doxorubicin in CMF failure (2)Docetaxel	4-month increase in median TTP (from 6 months to 10 months)	185
TAX304 (Europe)	(1)mitomycin C + vinblastine (2)Docetaxel	2-month increase in median TTP (from 4 months to 6 months)	194
TAX311 (US)	(1)Taxol (2)Docetaxel	14% increase in ORR (28% vs 42%)	200

*CMF: Cyclophosphamide, methotrexate, 5-fluorouracil

II. DESCRIPTION OF THE STUDIES

i) THE PIVOTAL TRIALS

- TAX221 (Early Clinical Trials Group of the European Organization for Research and Treatment of Cancer, with studies conducted in several European countries - ECTG):

This was a multicenter (12), nonrandomized, open label, phase II European trial in patients previously treated with systemic chemotherapy for metastatic or advanced breast cancer. 39 patients (28 previously treated and 11 previously untreated) recruited between May 6, 1992 and Sep. 23, 1992 received Docetaxel in polysorbate 80 at 100mg/m^2 by IV over 1 hour every 3 weeks. Information available up to Dec. 15, 1993 was used for statistical analysis.

The study objectives were: *(1) to determine if partial (PR) or complete responses (CR) can be achieved and their duration (DOR) if they occur, (2) to assess the probability of an actual response rate warranting further evaluation of the therapeutic effectiveness in the case that CR or PR can be achieved, (3) to characterize the toxic effects, and (4) to characterize the pharmacokinetic-pharmacodynamic relationships of Taxotere.* Time to first response (TFR), time to progression (TTP), survival and quality of life in terms of Karnofsky performance status (KPS) were also evaluated.

Tumor measurements were recorded at the end of every cycle, if the tumor was measurable, or after every 2 cycles, if complex radiologic studies e.g., x-rays/scans were

required. The study protocol required that responses be confirmed on two cycles separated by a minimum of four weeks. Disappearance of all tumors is considered a CR. A 50% or greater decrease in the sum of the products of the diameters of measurable lesions with no increase in size of any lesion or appearance of any new lesions is considered a PR. Duration of response is defined as the interval from the time of documented complete remission to that of disease progression for complete remission and the interval from the initial dose of Docetaxel to the time of disease progression for partial remission.

The ORR and DOR were performed on the intent-to-treat (ITT) and evaluable patients. The ITT patients were all patients who received at least one infusion of Docetaxel. A patient must have received at least two cycles of treatment to be considered as evaluable for efficacy. Early progression will be considered evaluable for response. Responding or disease-stable patients received Docetaxel for as long as tolerated or until evidence of disease progression or of unacceptable toxicity.

Safety analyses were performed on the ITT patients from the time of their first dose of Docetaxel. Toxicities were graded on a scale of 0 to 4 using the NCI Common Toxicity Criteria and recorded for each treatment cycle. The treatment may be delayed for as long as 1 week to allow for recovery from a prior toxicity. Dose modifications were limited to no more than two 25% reductions. Other than hematologic parameters (measured twice weekly during cycles 1 and 2, then weekly for all remaining cycles) and complex radiologic studies (every two cycles), the efficacy, toxicity and QOL parameters were measured at baseline, every 3 weeks and end of therapy. Incidence rates of adverse events concerning hypersensitivity reaction (HSR), fluid retention, neurotoxicity, skin toxicity were reported. A time-to-event analysis was performed on first onset (number of courses and cumulative dose) of fluid retention and of chronic skin toxicity.

The sample size specified in the protocol was based on Gehen's two-stage procedure, viz., a minimum of 14 and a maximum of 25 patients assuming a true response rate of $>=20\%$ and the chance of rejecting the drug after the first 14 patients is .044.

- TAX233 (US):

This was a multicenter (3), nonrandomized, open label, phase II US trial in anthracycline resistant patients with histologically confirmed metastatic breast cancer. Docetaxel in polysorbate 80 at an IV dose of 100 mg/m^2 was administered over 1 hour every 3 weeks. Data from this study contain 41 patients recruited between June 23, 1992 and July 29, 1993. Analyses are based on all information available up to Oct. 31, 1993.

The study had the following objectives: *(1) to estimate the major objective response rate and duration of response; (2) to determine the qualitative and quantitative toxicity and reversibility of toxicity; and (3) to determine the pharmacokinetics.* Other efficacy endpoints assessed were: TFR; TTP; survival; clinical benefit in terms of Karnofsky performance; consumption of analgesics; and tumor-related symptoms. Changes in analgesic requirement

and tumor-related symptoms were to be monitored prospectively. Performance status was analyzed retrospectively.

The tumor measurements definition, recording, confirmation, and duration were consistently defined as in TAX221. The ORR and DOR were performed on the ITT and evaluable patients. The ITT patients were defined as all patients who received at least one infusion of Docetaxel and the evaluable patients consisted of eligible patients who have received a minimum of one cycle of treatment. All baseline lesions were reassessed with the same method of measurement as baseline.

Other than the amendment 4 to the original protocol which mandated "premedication with dexamethasone and diphenhydramine prior to infusions", guidelines on dose modification, schema, and incidence rates of adverse events, time-to-event analysis were similar to study TAX221.

The protocol specified sample size was based on a modified two-stage Fleming design, viz., a minimum of 20 and a maximum of 40 evaluable patients assuming a null true response rate of 5% or less versus an alternative true response rate of 20% or more with 92% power at a significance level of 5%.

- TAX267 (US):

The protocol for this trial is identical to that of trial TAX233. There were 41 patients accrued from 3 US centers between June 9, 1992 and Aug. 10, 1993.

- TAX286(Europe):

The result of this trial was submitted on Nov. 7, 1994 along with the safety update. The inclusion and exclusion criteria were similar to those two US phase II pivotal trials with the exception of stricter definition of anthracycline resistance excluding patients resistant to mitoxantrone. This single agent open-label trial accrued 52 patients between Aug., 1993 and Nov., 1993 (4 months). The original cutoff date for European trial was Dec. 15, 1993 (1 month follow-up from last patient's enrollment), the updated efficacy cutoff date was May 31, 1994 (6.5 months follow-up), which resulted in 10.5 months for the entire study.

It is noted that the sponsor claimed a new updated efficacy cutoff date of June 30, 1994 for North-American trials and May 31, 1994 for European trials. However, this review used the original cutoff date for the submitted studies in the the original NDA submission, and presented the later submitted trial (TAX286) using the sponsor's updated cutoff date.

ii) THE SUPPORTIVE TRIALS

Other than TAX266 (US, n=37) which was a single center study, TAX228 (Canada, n=51), TAX237 (EORTC-ETCG, n=35), TAX280 (France, n=40), TAX242 (Japan, n=51), TAX279 (Japan, n=74), and TAX289 (Japan, n=81) were multicenter, nonrandomized, open label, phase II trials with Docetaxel as single-agent chemotherapy in metastatic breast cancer patients. The four US/European studies involved first line breast cancer patients and the three Japanese studies were limited to second line patients. However, Japanese studies used a lower dose (60 mg/m^2) and are not included in this review. Table 1 of the sponsor's final medical report summarizes these 10 completed phase II studies. Study TAX281 was added as a supportive first line trial on Nov. 7, 1994 submission.

III. OVERVIEW OF STUDY RESULTS AND REVIEWER'S ASSESSMENTS

The target population in the three pivotal trials was patients with metastatic breast cancer who are resistant to anthracycline/anthracenedione treatment. The baseline characteristics of these 111 patients can be found in the previously treated column of Table 11 of the final medical report. About half of the patients were 50 or more years of age. Eighty-two percent of the patients has a 0 to 1 WHO performance score. Eighty percent of the patients had more than one organ involved. Three quarter of the patients had visceral involvement and the frequently involved organ was liver (46% of the patients).

PRIMARY ENDPOINTS: ORR and DOR

Reviewer Table 1 summarizes the ORR, and three DOR calculations, (1) using the definition provided in the final medical report in which DOR is the same as TTP, (2) using a consistent definition, viz., from the documentation of ORR until disease progression, and (3) using the definition in the protocol, i.e., for CRs, from the documentation of ORR, and for PRs, from the first infusion of Docetaxel until disease progression. The reported 95% confidence interval was computed using the protocol definition. The results in Reviewer Table 1 on the ORR and DOR based on the final medical report confirms the sponsor's analyses (Table 20 of final medical report; vol1.137, 8-38-80(TAX233), vol1.143, 8-44-79(TAX267), vol1.149, 8-50-106(TAX221)).

The overall estimated ORR was 49% with a 95% confidence interval of 39% to 58%. The estimated median DOR was similar using either the definition in the final medical report or that in the protocol. However, these estimates can differ as much as 5 weeks to 9 weeks between the consistent definition and the final medical report. Using the definition from the protocol, the European trial has an estimated median DOR of 38 weeks which is 11 weeks longer than the US trials (see Reviewer Figure 1). This difference was statistically significant (log-rank, p=.039; Wilcoxon, p=.052).

Reviewer Table 1

ORR and DOR Analyses in second line breast cancer Trials

Study# (country)	#patients treated	ORR (#CR + #PR)	Range DOR(wks) protocol definition	Median DOR(wks) final medical report (1)	Median DOR(wks) calculated from response documentation (2)	Median DOR(wks) protocol definition (3)	95%CI DOR protocol
221 Europe	28	50% (1 + 13)	4 + to 57	38	32	38	29-49
233 US	41	46% (0 + 19)	12 to 47 +	27	18	27	19-36
267 US	42	50% (3 + 18)	9 to 39 +	28	23	25	20-31

Log-Rank p=.039; Wilcoxon p=.052 (Europe vs US trials)

+ indicates censoring.

For trial TAX286, an additional pivotal submission, the ORR from intent-to-treat analysis was 28.8% (15/52), a 95% C.I. of 17% to 43%. The estimated median DOR was 24 weeks, with a 95% C.I. of 21.9 weeks to 26.9 weeks based on the definition in the final medical report. The estimated median DOR became 16 weeks with 95% C.I. of 12 weeks to 19 weeks when the DOR was computed from the documentation of tumor response excluding the time to first tumor response.

OTHER EFFICACY ENDPOINT: TFR, TTP, SURVIVAL

The time to first response (TFR), time to disease progression (TTP) and survival were also analyzed by the sponsor, though not protocol-defined objectives (see attached Appendix II.19). The sponsor's estimated TFR was 13 weeks to 15 weeks (range: 1+ to 31+ weeks). For the TTP analysis, this reviewer confirmed the sponsor's TTP estimates. The sponsor's estimated survival was 9 to 12 months (range: 0 to 15+ months).

The study duration contains the accrual period and the follow-up period. In the European trial, the accrual period was only 4.5 months. In the US trials, the accrual period

was a little over a year, 13 months for TAX233 and 14 months for TAX267. However, the follow-up period from the last patients accrued was 15 months in the European trial and was only 2.7 months to 3 months in the US trials, TAX267 and TAX233, respectively. This leads to the study duration of 19.5 months for the European trial and 16.25 months to 16.7 months for the US trials. For the two US trials, the follow-up period was only 1 week longer than the median time to first treatment response.

Reviewer Table 2
TTP Analysis in second line Breast Cancer Trials

Study# (country)	#patients treated	# censor (%)	accrual*	cutoff	accrual + cutoff	Median TTP(wks)	95%CI TTP
221 Europe	28	8 (29)	5/06/92 9/23/92 (4.5 mon)	12/15/93 (15 mon)	19.5 mon	25.6	17.0-37.7
233 US	41	7 (17)	6/23/92 7/29/93 (13 mon)	10/31/93 (3 mon)	16.25 mon	12.7	10.0-21.9
267 US	42	17 (41)	6/09/92 8/10/93 (14 mon)	10/31/93 (2.7 mon)	16.7 mon	19.6	18.1-31.1

* date of accrual was taken from the sponsor table 6 of final medical report, which was defined as the day of the first infusion for the first and last patients treated.

This indicates that the follow-up period from the last patients accrued may not be reasonable. The study duration for the European trial was 3 months longer. Therefore, the similar accrual and follow-up between the two US trials may be poolable for a possible comparison with the Taxol being approved at Dec. 1993 ODAC meeting (Supplement to NDA #20-262). The results of the TTP comparison revealed that 29% (2/7) of the censoring occurred before 27 weeks from initial Docetaxel treatment in the TAX233 trial and 94% (16/17) of the censoring occurred before 27 weeks in the TAX267 trial. In addition, the censoring rate was 17% and 41% ($p=.029$, Fisher's exact test) for TAX233 and TAX267, respectively (see reviewer Table 2). The insignificant results obtained from the log-rank test ($p=.115$) and the significant Wilcoxon ($p=.019$) TTP comparison between TAX233 and TAX267 point to the possibility that combining the two trials for median TTP estimate may be misleading due to different censoring patterns (see Reviewer Figure 2) and censoring rates. A time-dependent explanatory variable, defined as the natural logarithm of the time, was used to assess the validity of the proportional hazard (PH) assumption. The result shows that there is evidence of an increasing trend over time in the hazard ratio ($p=.028$) between the two US trials. Therefore, these trials were not pooled for further TTP comparisons with Taxol.

For study TAX286, the estimated median TTP was 16 weeks with a 95% C.I.of 11.7 week to 21.9 weeks, the censoring rate was 21% (11/52).

COMPARISON BETWEEN DOCETAXEL AND TAXOL

Bristol-Myers Squibb Co. conducted a randomized controlled phase III trial on Taxol, comparing two treatment dose regimen (175 mg/m^2 and 135 mg/m^2), in patients with metastatic breast cancer after failure of standard therapy. In this trial, 471 patients were accrued between March 9, 1992 and June 30, 1992 (3.8 months). The study cutoff date was Oct. 19, 1993, a total study duration of 18.5 months.

In the introduction of the final medical report, the sponsor used some published results including the Taxol to elucidate the importance of doing Docetaxel trials. This reviewer provides a crude comparison between Docetaxel and Taxol using review results reported at the Dec. 1993 ODAC meeting (Taxol-3) and a phase I/II trial of 96 hour infusion (Taxol-2) for doxorubicin-refractory or mitoxantrone-refractory patients (J. Clin. Oncol., Vol.12, #8, 1994:1621-1629). The study duration varies among the trials. Reviewer Table 3 presents the result of the ORR, DOR, and TTP efficacy comparisons.

The ORR was 1.7 times higher with Docetaxel than with Taxol-3 (42% vs 25%) but was no different with Taxol-2 (48%). The median DOR was shorter in Docetaxel US trials (6.7 months, 7.0 months and 6.0 months for TAX233, TAX267 and TAX286, respectively) and was longer in Docetaxel European trial (TAX221, 9.4 months) in comparison to the DORs of Taxol-3 (8.1 months) and Taxol-2 (7.75 months). It is noted that the median follow-up time was 10 months for Docetaxel (see appendix II.21 of the final medical report) and 8.6 months for Taxol-2. For the median TTP, Taxol-2 (6.75 months) was about 1.9 to 3.5 months longer than Docetaxel for trials TAX233: 3.2 months, TAX267: 4.9 months, and TAX286: 4.0 months and was about the same as Docetaxel for trial TAX221 (6.4 months). The censoring rate was higher in TAX267 (41%) and TAX221 (29%) of

Reviwer Table 3
A crude comparison between TAXOL and DOCETAXEL

	TAXOL-3	TAXOL-2	TAXOTERE
DESIGN	**Phase III,** **controlled,** two dose arms, **second line**	**Phase I/II,** **non-random** **second-line,** 120-160mg/m^2	**Phase II,** **non-random,** **single arm,** **second line,** 100mg/m^2

ORR	ITT:25%(116/471) 175mg/m² :28%(65/235) 135mg/m² :22%(51/236)		48%(16/33)	TAX233: 46.3% (19/41) TAX267: 45.2% (21/42) TAX221: 50.0% (14/28) TAX286: 28.8% (15/52)	
DOR*	Median(95%CI) OVERALL:8.1mon(6.6-8.9) 175mg/m²:8.2mon(6.6-9.9) 135mg/m² :8.0mon(5.6-9.2)		Median(range) 7.75 mon (5.5-11.5)	Median(95%CI) TAX233:6.7mon(4.7-9.0) TAX267:7.0mon(4.9-8.5) TAX221:9.4mon(7.5-12.3) TAX286:6.0mon(5.5-6.7)	
TTP	Median(95%C.I.)	%censor	Median	Median(95%C.I.)	%censor
	175mg/m² : 4.2mon(3.2-4.6) 135mg/m² : 3.0mon(2.5-3.8)	12%(29/235) 8%(19/236)	6.75 mon	TAX233: 3.2mon(2.5-5.5) TAX267: 4.9 mon(4.5-7.8) TAX221: 6.4 mon(4.3-9.4) TAX286: 4.0 mon(2.9-5.5)	17%(7/41) 41%(17/42) 29%(8/28) 21%(11/52)

*The definition of DOR is consistent between the two drugs.

Taxol-3 Supplement to NDA #20-262, the ODAC meeting Dec. 15, 1993

Taxol-2 Wilson MW, Berg SL, Bryant G et al: Paclitaxel in Doxorubicin-refractory or Mitoxantrone-refractory Breast Cancer: A phase I/II trial of 96 hour infusion. J. Clin. Oncol., Vol, 12, #8, 1994:1621-1629.

Docetaxel than in Taxol-3 (8% to 12%), which is similar to TAX233 (17%) and TAX286 (21%) of Docetaxel. However, for Taxol-3, the accrual period was one third of TAX233 of Docetaxel and the follow-up period was five times longer than that of TAX233. The study duration was different between TAX233 of Docetaxel and Taxol-3. Thus, a straight comparison among these trials is difficult to be reconciled.

CLINICAL BENEFIT

The sponsor presented two parameters on clinical benefit: (1) analgesic requirements - a prospective analysis and (2) performance status - a retrospective analysis. Tables 34 and 35 of the final medical report are for patients with stable or improved performance status from baseline to cycles 4 and 6, respectively. Changes in analgesic usage by type of response and by patient was presented in the sponsor's Table 38 of the final medical report. The clinical benefit summary includes only patients who had baseline and cycle 4 and/or cycle 6 measurements. Patients without clinical benefit data on cycles 4 and 6 are likely to be those who had withdrawn, loss to follow-up or discontinued from the treatment due to toxicity, death, progression etc. It is difficult to generalize the results of the clinical benefit.

INTEGRATED SAFETY

The sponsor's integrated safety was summarized by using US/Canada/Europe data related to safety that are available to RPR in the phase II clinical program. The sponsor stated that *the objective was that a better precision on the estimates of the incidence, duration and severity of various toxicities will be obtained and that additional exploratory analyses are possible by a larger sample size. The emphasis is on consistency of results, robustness, and biological plausibility, rather than pure statistical significance.*

Hematologic toxicity, predominantly neutropenia, was the principal toxicity. Ninety-seven percent (97%) of the 273 evaluable patients with WBC data experienced a Grade 3 or 4 toxicity. The duration of most Grade 3 or 4 neutropenia was 7 days (range: 1 to 7 days). Febrile neutropenia (defined as fever > 38°C with grade 3 or 4 neutropenia) occurred in 27% of the patients. Thrombocytopenia was less common. Anemia was experienced by 92% of patients.

Non-Hematologic toxicity was discussed only for 228 high dose patients as the sponsor claimed that "no difference was observed between patients treated with a planned dose of 100 or 75 mg/m^2". Twenty-eight percent of the 64 patients experienced accute HSR, with 5% having grade 3 or 4 reactions. For cumulative toxicities, fluid retention (including peripheral, localized or generalized edema, pleural effusion, ascites, pericardial effusion, weight gain) was reported in 65% of the patients and 15% of them was severe, and skin toxicity (including erythema, pruritus, macular rash, swelling, papulae, desquamation, hyperpigmentation, dry skin and pain) was observed in 72% of the patients.

Eighty-seven patients (31%) was prematurely discontinued the treatment due to adverse events. The most frequent cause of treatment discontinuation was fluid retention which contains 44 patients excluding 29 patients with multiple event. Among patients discontinued from the treatment, more than half of them resulted from fluid retention. Instead of the sponsor's classification of premedication as type I, II, III etc., a simple comparison was considered. Reviewer Table 4 presents the effect of premedication in fluid retention reduction. There was an indication that the premedication may help reduce the non-hematologic fluid retention toxicity (75% in no pre-medication group vs. 60% in some pre-medication group; Chi-square test, p=.039). The estimated reduction was 15%.

Reviewer Table 4
The Effect of Premedication on Fluid Retention Reduction

		No Premedication	Some Premedication
Fluid retention	Yes	45 (75%)	101 (60%)
	No	15	67

Chi-square test, p=.039

OVERALL SUMMARY AND CONCLUSIONS

1) The sponsor included the time to first response in the calculation of duration of tumor response. This is equivalent to the time to disease progression for the responders. It is possible, based on this approach, that the estimated DOR has been inflated by 1.3 to 2.3 months in these trials.

2) The study duration was 3 months longer in the European trial than in US trials. For the European trial (TAX221), the accrual period was one third of the US trials (4.5 months in the European trial and 13.5 months in US trials) and the follow-up period was five times longer than US trials (15 months in the European trial vs. 3 months in US trials). Combining all three pivotal trials of previously treated patients with respect to the duration of response, the time to disease progression, and the survival analyses in the final efficacy report could be misleading. The results of these time-to-event analyses is confounded by the European's longer study duration.

3) Study duration was comparable for the US trials (TAX233 and TAX267). The estimated DOR was similar for these two trials (27 weeks and 25 weeks). However, the TTP analysis shows that censoring patterns (for TAX233: 29%(2/7) before 27 weeks of the Docetaxel treatment; for TAX267: 94%(16/17) before 27 weeks) and the censoring rate (17% vs 41%) were different. These differences indicate that possible biases may result from these nonrandomized, noncomparative, and open labelled trials, e.g., patient selection bias, investigators' and/or patients' early decision of treatment change, possible non-unique administration criteria applied by different investigators, etc. There is an indication that the PH assumption is violated ($p=.028$), and that the hazard ratio increased over time. Thus, the estimated TTP may not be combined. The estimated TTP was 12.7 weeks (95% C.I. - 10 weeks to 22 weeks) for TAX233, 19.6 weeks (95% C.I. - 18 weeks to 31 weeks) for TAX267, and 16 weeks (95% C.I. - 12 weeks to 22 weeks) for TAX286. Note that the TTP was not a protocol-defined efficacy endpoint.

4) From comparisons of phase II results, the ORRs for Docetaxel (42%) and Taxol-2 (48%) were similar, the median DORs were also similar (Docetaxel - 6.7, 7.0, 9.4, 6.0 months for TAX233, TAX267, TAX221, and TAX286, respectively and Taxol-2 - 7.75 months), and Taxol-2 has longer estimated median TTP (6.75 months) than those of Docetaxel (3.2, 4.9, 6.4, and 4.0 months, respectively).

Taxol was approved after the ODAC meeting held in December, 1993, based on evidence from 471 patients, a phase III, controlled trial comparing two dose regimen for second line breast cancer treatment. The response rate for Taxol dropped from 48% to 25% from a phase II noncomparative to a phase III controlled trial. No phase III data has been submitted to the agency from the sponsor as of this review though the sponsor has designed a phase III, comparative trial for the comparison between Taxol and Taxotere, viz., TAX311 an ongoing trial. The relative merit of Docetaxel and Taxol may become apparent when this

phase III trial is completed and its data analyzed. The sponsor has three ongoing randomized phase III trials for second-line treatment. These comparative studies may provide statistical evidence of efficacy for DOR and/or TTP.

Note: This review is based on the original NDA submission and the report of an additional pivotal trial (TAX286) submitted on Nov. 7, 1994.

Sue-Jane Wang

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Wilson 9-7-95

for Dr. Dubey 9-8-95

cc:

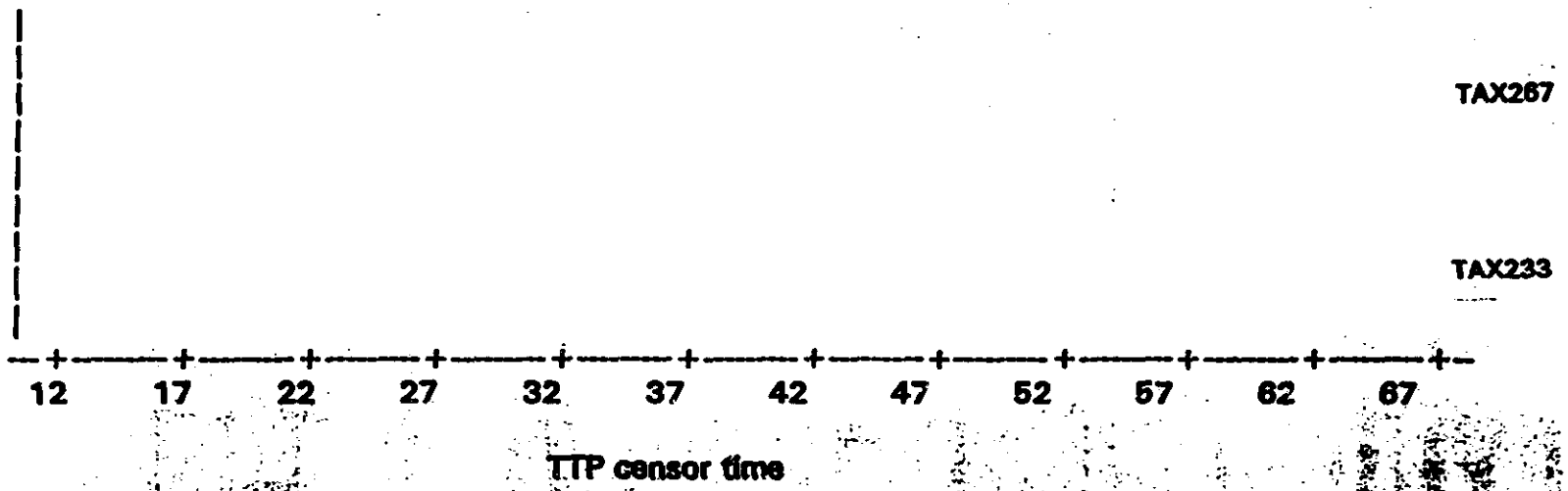
NDA 20-449
HFD-150
HFD-150/ Dr. Justice
Dr. Beitz
Ms. Pease
HFD-344/ Dr. Lisook
HFD-713/ Dr. Dubey [File: DRU 1.3.2. NDA]
Dr. Wilson
HFD-713/ Dr. Wang

SWANG/11-14-94/WP60-TAXOTERE.BR

This review consists of 14 pages of text, 12 tables from the sponsor, 4 tables and 2 figures from the reviewer.

Reviewer Figure 2

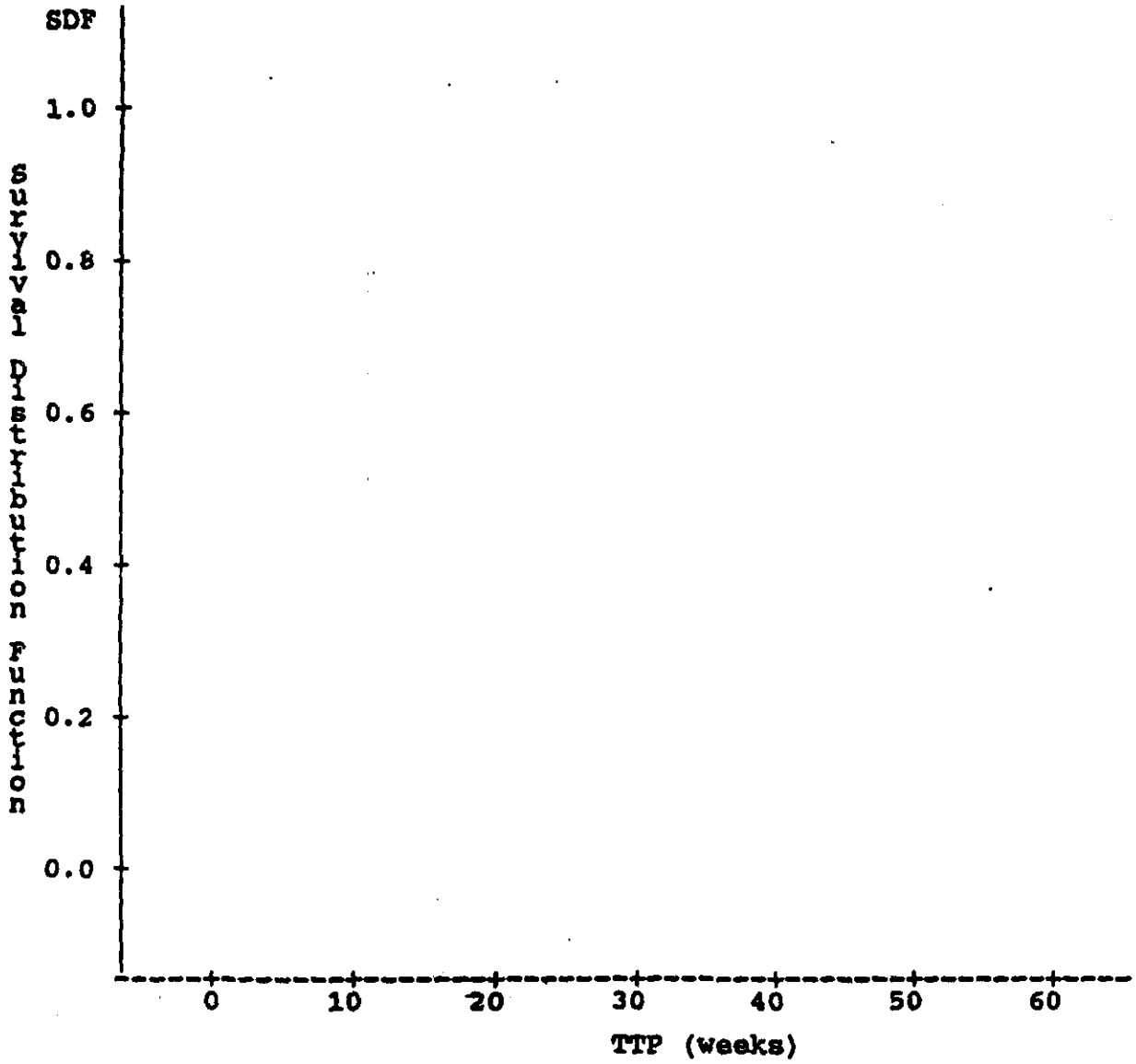
The censoring pattern for TAX233 and TAX267
The censoring rate was 17% (7/41, TAX233) vs 41% (17/42, TAX267)



Reviewer Figure 1

Response Duration Between Tax221 vs. Tax233&Tax267
Calculation was based on the protocol

Survival Function Estimates



A: TAX221
B: TAX233 & TAX267

Trial	Quantile	Point Estimate	95% Confidence Interval [Lower, Upper)	
TAX221	50%	37.7143	28.8571	49.4286
TAX233+267	50%	26.5714	21.0000	27.8571

Trial	Total	Failed	Censored	%Censored
TAX221	14	9	5	35.7143
TAX233+267	40	27	13	32.5000

VII.5.3 Adverse events leading to premature treatment discontinuation

A total of 87 adverse events (not all of them were serious adverse events) led to premature treatment discontinuation :

- Single event : 58

fluid retention	44
skin disorder	3
allergic reaction	3
infection	2
paresthesia	2
dyspnea	2
malaise	1
chest pain	1

- Multiple events : 29

VIII.5.4 Non fatal adverse events

The overall analysis of non fatal adverse events is presented table 66.

CONTENTS OF DATABASE

- A total of 10 fully completed phase II studies with docetaxel as single-agent chemotherapy in metastatic breast cancer were analyzed (table1).
  - 3 studies conducted in the U.S. — 8/10-38, 42,
  - 3 studies conducted in Europe — 8/10-50, 67,
  - 1 study conducted in Canada — 8/10-62
  - 3 studies conducted in Japan. — 8/10-74

TABLE 1 BREAST CANCER STUDIES

STUDY CODE	INVESTIGATOR	COUNTRY	REGISTERED PATIENTS	DOSE (mg/m²)	PRIOR THERAPY YES	PRIOR THERAPY NO	
*233	VALERO	U.S.	41	100	Anthracycline /anthracenedione resistant		8/10-38
*267	RAVDIN	U.S.	42	100	Anthracycline /anthracenedione resistant		8/10-44
*221	TEN BOKKEL	EUROPE	39	100	X	X	8/10-50
*228	TRUDEAU	CANADA	51	100 - 75		X	8/10-62
*237	CHEVALIER	FRANCE	35 **	100		X	8/10-67
266	SEIDMAN	U.S.	37	100		X	8/10-56
*280	FUMOLEAU	FRANCE	40 ***	75		X	8/10-70
*242	TAGUCHI	JAPAN	51	60	X	X	8/10-74
*279	TAGUCHI / ADACHI	JAPAN	74	60	X	X	8/10-74
*289	TAGUCHI / ADACHI	JAPAN	81	60	X	X	8/10-74

491

* multicentre studies
** one patient did not receive study treatment
*** no data are available for one patient who did not receive study treatment, therefore the patient does not appear on any data listings or statistical table.

- It is to be noted that 9 out of 10 studies were multicentric

- Data are presented on a total of 491 patients :
  - 120 patients from U.S.studies
  - 114 patients from European studies
  - 51 patients from the Canadian study
  - 206 patients from the Japanese studies

Within the intent to treat analysis, comparison of patient and tumor characteristics (see table 2 for details) between the untreated patient populations (75 mg/m² and 100 mg/m²) or between the two patient populations scheduled to receive docetaxel at 100mg/m² (previously untreated and previous treated for advanced disease) revealed no statistically or clinically significant differences (table 11). In the untreated patient populations (75 mg/m² and 100 mg/m²) , comparisons of two factors were, however, close to statistical significance :

- Time from first diagnosis to first infusion was longer in the 75 mg/m² subgroup with a median of 37.6 months compared to 29.0 months in the 100 mg/m² subgroup (p=0.06). Add. Item 10, Vol 1 b : table 2.02
- A higher percentage of patients in the 75 mg/m² subgroup had a WHO performance status score of 0 (47.3%) compared to those in the 100 mg/m² subgroup (29.1%) (p= 0.06)

No further differences in the above comparisons were observed in relation to the anthracycline resistant or refractory patient subgroups. The evaluable patient analysis also revealed similar trends (Add. Item 10, Vol 1 B tables 2.01a, 2.01b, 2.02a, 2.02b)

8/10-38, 44

TABLE 11 SUMMARY PATIENTS AND TUMOR CHARACTERISTICS

	PREVIOUSLY UNTREATED 75mg/m² nb (%)	PREVIOUSLY UNTREATED 100mg/m² nb (%)	PREVIOUSLY TREATED 100mg/m² nb (%)	ANTHRACYCLINE RESISTANT 100mg/m² nb (%)
Number of patients	55	117	111	83
Age - < 50	25 (45.5%)	43 (36.8)	51 (45.9%)	36 (43.4%)
- ≥ 50	30 (54.5%)	74 (63.2)	60 (54.1%)	47 (56.6%)
PS (*)				
- 0 - I	46 (83.6%)	95 (81.2)	91 (82.0%)	68 (81.9%)
- ≥ 2	9 (16.4%)	16 (13.7)	20 (18.0%)	15 (18.1%)
Metastatic site :				
- visceral	43 (78.2%)	88 (75.2)	85 (76.6%)	61 (73.5%)
- non visceral	12 (21.8%)	29 (24.8)	26 (23.4%)	22 (26.5%)
- liver	28 (50.9%)	53 (45.3)	51 (45.9%)	35 (42.2%)
Organ involved				
1	15 (27.3%)	23 (19.7)	22 (19.8%)	17 (20.5%)
2	19 (34.3%)	46 (39.3)	38 (34.2%)	26 (31.3%)
3	12 (21.8%)	28 (23.9)	28 (25.2%)	22 (26.5%)0
≥ 4	9 (16.4%)	20 (17.1)	23 (20.7%)	18 (21.7%)

(*) missing : 6 patients / Add. Item 10, Vol 1B : tables 2.01a, 2.03a, 2.05a

IX.3 OVERALL RESPONSE RATE : (O.R.R.) : INTENT TO TREAT ANALYSIS

IX.3.1 Overview

- The O.R.R. by study of the 228 patients treated at the dose of 100 mg/m² ranged from 45.5% to 64.7% (table 20). For the 55 patients studied at 75 mg/m² the ORRs were 43.8% and 48.7% (table 20).

TABLE 20 O.R.R. : INTENT TO TREAT

PATIENT POPULATION (Initial dose : mg/m²)	STUDY CODE	PATIENTS TREATED	O.R.R. N (%)	95% C.I.	C.R. N (%)	P.R. N (%)	Item/Volume
Previously Treated	221	28	14 (50.0)	31 - 69	1 (3.6%)	13(46.4%)	8/10-50
Anthracycline Resistant (100)	233	41	19 (46.3)	31 - 63	0	19(46.3%)	8/10-38
	267	42	21 (50.0)	34 - 66	3 (7.1%)	18(42.9%)	8/10-44
Untreated Patients (100)	221	11	5 (45.5)	17 - 77	2(18.2%)	3(27.3%)	8/10-50
	266	37	20 (54.1)	37 -71	2 (5.4%)	18(48.7%)	8/10-56
	228	35	19 (54.3)	37 - 71	2 (5.7%)	17(48.6%)	8/10-62
	237	34	22 64.7)	46 - 80	5(14.7%)	17 (50%)	8/10-67
Untreated Patients (75)	228	16	7 (43.8)	20 - 70	1 (6.3%)	6(37.5%)	8/10-62
	280	39	19 (48.7)	32 - 65	4(10.3%)	15(38.5%)	8/10-70

Table 21 shows the overall response rate and the complete response rate by the different subgroups.

Table 20: Overall Response in All Treated Patents and Evaluable Patients

Overall Response	All Treated Patients			Evaluable Patients		
	N	(%)	95% Confidence Interval	N	(%)	95% Confidence Interval
Complete Response (CR)	-	-		-	-	
Partial Response (PR)	19	(46.3)		18	(54.5)	
Response Rate (CR+PR)	19	(46.3)	[30.7;62.6]	18	(54.5)	[36.4;71.9]
Stable Disease	7	(17.1)		4	(12.1)	
Progression	12	(29.3)		11	(33.3)	
Not Evaluable	3	(7.3)		-	-	
All Patients	41	(100.0)		33	(100.0)	

REF: Appendix III.3, Tables 4.01 and 4.02.

7.2. DURATION OF RESPONSE

The median duration of response in all responding patients (intent-to-treat) was 27 weeks (95% CI = [19 ; 36], range: 12-47+ weeks). Fourteen responding patients had progressive disease and 5 were censored due to no documentation of PD before the cutoff date (Appendix III.3, Table 4.03).

The median duration of response in evaluable responding patients was 27 weeks (95% CI = [19 ; 36], range: 12-47+ weeks) (Appendix III.3, Table 4.04a).

Similar results for median duration of response were observed among the 17 evaluable responding patients resistant to doxorubicin (median = 27 weeks, range: 12-47+). The one evaluable responding patient resistant to mitoxantrone had a 16+ week duration of response (no documentation of PD before cutoff date) (Appendix III.3, Table 4.04a).

Table 20: Overall Response in All Treated Patients and Evaluable Patients

Overall Response	All Treated Patients			Evaluable Patients		
	N	(%)	95% Confidence Interval	N	(%)	95% Confidence Interval
Complete Response (CR)	3	(7.1)		3	(8.6)	
Partial Response (PR)	18	(42.9)		17	(48.6)	
Response Rate (CR+PR)	21	(50.0)	[34.2%; 65.8%]	20	(57.1)	[39.4%; 73.7%]
Stable Disease	13	(31.0)		11	(31.4)	
Progression	5	(11.9)		4	(11.4)	
Not Evaluable	3	(7.1)		-	-	
All Patients	42	(100.0)		35	(100.0)	

REF: Appendix III.3, Tables 4.01 and 4.02.

All three complete responders had disease limited to soft tissue.

No discrepancies remained in the final analysis between the independent panel review and the internal final assessment performed by R-PR.

7.2. DURATION OF RESPONSE

The median duration of response in all responding patients (intent-to-treat) was 28 weeks (95% CI = [20 ; 34], range: 9-66+ weeks) (Appendix III.3, Table 4.03).

The median duration of response in evaluable responding patients was 27 weeks (95% CI = [20 ; 34], range: 9-66+ weeks) (Appendix III.3, Table 4.04).

Similar results for median duration of response were observed among the 12 evaluable responding patients resistant to doxorubicin (median = 28 weeks, range: 11-66+). A slightly shorter median duration of response was observed among the eight evaluable responding patients resistant to mitoxantrone (median = 21 weeks, range: 9-34) (Appendix III.3, Tables 4.04a and 4.04b).

The duration of response was censored in eight of the 21 responders (38.1%). The reasons for censoring before PD were further chemotherapy in one patient and no documentation of progressive disease before the cutoff date (still responding as of the study cut-off date) in seven patients. The durations of complete responses were 23 weeks, 25 weeks and 39+ weeks (Appendix III.3, Table 4.03).

Table 32 : Overall Response in All Evaluable Patients

Overall Response	1st Line			2nd Line		
	N	(%)	95 % Confidence Interval	N	(%)	95 % Confidance Interval
Complete Response (CR)	1	12.5		1	4.3	
Partial Response (PR)	2	25.0		13	56.5	
Response Rate (CR+PR)	3	37.5	[8%;75%]	14	60.9	[38%;80%]
No Change	4	50.0		6	26.1	
Progression	1	12.5		3	13.0	
All Evaluable Patients	8	100.0		23	100.0	

Among the three complete responders in the intention to treat population (Appendix IV : table 23A) :

- one patient had locally advanced disease with two bidimensionally measurable chest wall lesions,
- one patient had a bidimensionally measurable chest wall lesion and contralateral lymphnode involvement,
- the third patient had a single bidimensionally measurable supraclavicular lymph node.

Four discrepancies in the evaluation of the best overall response, remained in the final analysis between the independent panel review and the internal final patient assessment performed by RPR-RD :

- Patient was evaluated as PD by the independent panel review and as NC by the internal final patient assessment since NC lasted more than 41 days following the first infusion.
- Patient was evaluated as PD by the independent panel review and as NC by the internal final patient assessment since NC was assessed after cycle 2 and 3 and lasted more than 41 days following the first infusion.

APPENDIX II.19

POPULATION INTENT TO TREAT

TIME OF FIRST RESPONSE AND TIME TO PROGRESSION : BREAST CANCER (100 mg/m²)

STATUS	STUDY CODE	T.F.R. (weeks) (range)	T.T.P. (weeks) (range)	SURVIVAL (month) (range)
Previously treated	221	15 (1+ - 28+)	28 (1 - 49)	
Anthracycline resistant	233	13 (1+ - 31+)	13 (1 - 47+)	9 (0 - 14+)
	267	13 (3 - 30+)	20 (5-6 . 6+)	12 (2 - 15+)
Untreated patients	221	**	**	**
	266	9 (2+ - 24+)	19 (2 - 59+)	* (0 -1 3+)
	228	8 (3+ - 29+)	19 (3 - 49)	11 (3 - 15+)
	237	11 (2+ - 27+)	37 (2 - 69+)	16 (0 - 19+)

* median not yet reached
** no analysis performed

TIME OF FIRST RESPONSE AND TIME TO PROGRESSION : BREAST CANCER (75 mg/m²)

STATUS	STUDY CODE	T.F.R. (weeks) (range)	T.T.P. (weeks) (range)	SURVIVAL (month) (range)
Untreated patients	228	12 (6 - 24+)	15 (3 - 30+)	* (3+ - 8+)
	280	12 (3 - 35+)	44 (0 - 42+)	* (1 - 12+)

* median not yet reached

DESCRIPTION OF CLINICAL BENEFIT PARAMETERS

In most of the phase II studies conducted, although no specific questionnaire on Quality of Life had been addressed, 2 parameters were taken into account :

- analgesic requirements (prospective analysis, US studies only)
- Performance Status (retrospective analysis)

PERFORMANCE STATUS

Patients were evaluable for this analysis of performance status evolution if performance status was recorded at baseline and at the time points for comparison i.e. cycle 4 and/or cycle 6..

The following table (34) show the number of patients with a given baseline performance score which improved or remained stable at cycle 4. Table 35 show the comparison between performance score at baseline and at cycle 6

34 PERFORMANCE STATUS : STABLE OR IMPROVED STATUS BETWEEN BASELINE AND CYCLE 4 100 mg/m²

ATUS	NUMBER OF STUDIES	PATIENTS EVALUABLE FOR P.S. EVOLUTION	BASELINE PERFORMANCE STATUS					
			0 (%)	1 (%)	2 (%)	3 (%)	ALL (%)	
ously ted	3	70	10/18 (55.6)	38/41 (92.7)	10/10 (100.0)	1/1 (100.0)	59/70 (84.3)	8/10-38, 44, 50
ated	4	62	19/25 (76.0)	29/31 (93.5)	6/6 (100.0)	/	54/62 (87.1)	8/10-50, 62, 67, 58
cycline ent	2	57	7/14 (50.0)	32/34 (94.1)	8/18 (100.0)	1/1 (100.0)	48/57 (84.2)	8/10-38, 44

dd Item 10 - Vol 2.B : table 4.20a

34 PERFORMANCE STATUS : STABLE OR IMPROVED STATUS BETWEEN BASELINE AND CYCLE 4 -75 mg/m²

	PATIENTS EVALUABLE FOR P.S. EVOLUTION	BASELINE PERFORMANCE STATUS					
		0 (%)	1 (%)	2 (%)	3 (%)	ALL (%)	
d	40	11/21 (52.4)	10/12 (83.3)	7/7 (100.0)	/	28/40 (70.0)	8/10-62, 70

d Item 10 - Vol 2.B : table 4.20a

Baseline 4 6
283 → 172 → 100

or all subgroups, the performance scores of the majority of patients mained either stable or improved. In the little groups receiving docetaxel 100 mg/m², 87% of performance scores remained stable or improved though it must be noted that 29 patients (20.4% of the 132 patients valuable for this analysis) were assessed as remaining stable at a erformance score of 0. The percentage of patients with stable or improved erformance scores at cycle 4 in the previously untreated 75 mg/m² ubgroup was slightly lower at 70%.

35 **STABLE OR IMPROVED PERFORMANCE STATUS BETWEEN BASELINE AND CYCLE 6 -100 mg/m²**

TUS	NUMBER OF STUDIES	PATIENTS EVALUABLE FOR P.S. EVOLUTION	BASELINE PERFORMANCE STATUS				
			0 (%)	1 (%)	2 (%)	3 (%)	ALL (%)
ously ted	3	38	3/11 (27.3)	16/20 (80.0)	7/7 (100.0)	/	26/38 (68.4)
ted ite	4	35	6/11 (54.5)	18/20 (90.0)	4/4 (100.0)		28/35 (80.0)
cycline tant	2	33	2/8 (25.0%)	15/19 (78.9%)	6/6 (100.0)	/	23/33 (69.7%)

dd Item 10 Vol 2.B : table 4.19a

35 **STABLE OR IMPROVED PERFORMANCE STATUS BETWEEN BASELINE AND CYCLE 6 - 75 mg/m²**

TUS	NUMBER OF STUDIES	PATIENTS EVALUABLE FOR P.S. EVOLUTION	BASELINE PERFORMANCE STATUS				
			0 (%)	1 (%)	2 (%)	3 (%)	ALL (%)
ted ite	2	27	5/13 (38.5)	9/10 (90.0)	3/4 (75.0)	/	17/27 (63.0)

dd Item 10 Vol 2.B : table 4.19a

he percentage of patients with performance scores which remained stable r improved when compared between baseline and cycle 6 was lower for ost subgroups with between 63.0% (untreated patients at 75 mg/m²) and 9.7% (anthracycline resistant patients at 100mg/m²). The percentage of reviously untreated patients at 100 mg/m² with stable or improved erformance scores remained higher at 80.0%.

8/10-38, 44, 50

8/10-50, 62, 67, 56

8/10-38, 44

8/10-62, 70

EVOLUTION OF ANALGESICS USAGE FOR TUMOR RELATED PAIN

8/10-38, 56, 44

The evolution of analgesic usage was recorded in the 3 U.S. studies : TAX233, TAX266 and TAX267. A comparison was made for all patients with data at baseline and cycle 4.

Out of the 51 patients having analgesic usage recorded at baseline and cycle 4, 12 (23.5%) had an improvement of the analgesic usage at cycle 4, as defined by a change from narcotic to non-narcotic medication or from analgesic (non narcotic or narcotic) to non-analgesic medication. For 34 patients (66.6%) no change was observed and 5 patients (9.8%) had a worsening of the analgesic usage. The worsening was defined as the reverse of improvement, i.e. from non-analgesic to analgesic (narcotic or non-narcotic) medication or from non-narcotic to narcotic medication.

The relationship between the response and the change in analgesic usage is presented in table 36. In the 25 responders, only 1 patient had a worsening of analgesic usage.

36 CHANGE IN ANALGESIC USAGE BY RESPONSE BY PATIENT

RESPONSE	MEDICATION CHANGE INDICATION			TOTAL
	IMPROVED	NO CHANGE	WORSENED	
	1			1
	7	16	1	24
	2	8	2	12
		3		3
	2	7	2	11
	12	34	5	51

MEDIAN FOLLOW-UP TIME AND NUMBER OF PATIENTS WHO DIED : INTENT TO TREAT ANALYSIS

Patient Population (Initial dose level : mg/m²)	MEDIAN Follow-up (months)	RANGE (months)	DEATHS (%)
• PRETREATED (100)	10	3-19	44/111 (39.6%)
• UNTREATED (100) .	14	5-20	43/117 (36.7%)
• ANTHRACYCLINE RESISTANT (100)	7	3-17	25/83 (30.1%)
• ANTHRACYCLINE REFRACTORY (100)	6	3-17	18/49 (36.7%)
• UNTREATED (75)	8	4-12	11/55 (20%)

Appendix III.3; Tables 1.03 and 4.07g

Clin. Pharm

Bio

D. Pearl
MAY 13 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-449 (BM, BL) **Submission Dates: November 21, 1995**

DOCETAXEL INJECTION **March 25, 1996**

40 mg/mL-2 mL or 0.5 mL Vial **April 5, 1996**

Taxotere™ **April 11, 1996**

Sponsor: **Rhone-Poulenc Rorer**

CollegeVille, PA 19426-0107

Type of Submission: Amendment to Approvable NDA (Second Partial Submission)/ Revised Package Insert

Reviewer: N.A.M. Atiqur Rahman, Ph.D.

BACKGROUND

These submissions include response to FDA request, response to FDA approvable letter, and revised package insert for Docetaxel Injection. These submissions were originally reviewed by Dr. Peter N. Zannikos (Primary Reviewer) and were provided for secondary review and sign off on April 25, 1996. The review was officially signed out of Division of Pharmaceutical Evaluation I by Dr. N.A.M. Atiqur Rahman (Team Leader, Oncology) on April 26, 1996. On April 29, 1996, Dr. Zannikos reported to Dr. Rahman of his acceptance of a position with Rhone-Poulenc Rorer, the sponsor of the NDA 20-449. The job interview was conducted on April 11, 1996; the invitation for interview was received on April 4, 1996; the job offer was made on April 25, 1996. Dr. Mehul Mehta (Deputy Director, Division of Pharmaceutical Evaluation I, OCPB) discussed with Dr. Rahman on April 29, 1996 regarding the acceptance by Dr. Zannikos of a scientist position at Rhone-Poulenc Rorer, review load, and oncology reviewer recruitment. On April 30, 1996, during Oncology Mini Rounds, Dr. Rahman requested Ms. Dotti Pease (Supervisory Project Manager, Oncology) not to give any new submissions of the Taxotere NDA to Dr. Zannikos and disclosed Dr. Zannikos' acceptance of a scientist position at Rhone-Poulenc Rorer. The Division of Oncology was concerned about possible conflict of interest and advised Dr. Rahman to consult with the upper management regarding this issue.

Dr. Rahman immediately contacted Dr. Mehul Mehta and subsequently Dr. Hank Malinowski (Director, Division of Pharmaceutical Evaluation I, OCPB) and was advised to re-review all the submissions, related to NDA 20-449, that were reviewed by Dr. Zannikos after April 04, 1996.

CURRENT STATUS

These submissions have been reviewed, and the comments and the requested suggestions for the package insert stated in the review dated April 26, 1996 by Dr. Zannikos are valid and stand as such. The most recent package insert drafted by Dr. Julie Beitz (Medical Officer) on May 10, 1996 has been reviewed and modified by Dr. Rahman.

RECOMMENDATION

There has been no compromise regarding the scientific integrity of the review of the submissions dated November 21, 1995, March 25, 1996, April 5, 1996, and April 11, 1996 of NDA 20-449, Docetaxel Injection by Dr. Peter Zannikos. The review fulfills the requirements of the Division of Biopharmaceutics I .

Please attach this review to the original NDA review.

5/13/96

Mehul U. Mehta, Ph.D.
Deputy Director
Division of Pharmaceutical Evaluation I

05/13/96

Atiqur Rahman, Ph.D.
Team Leader, Oncology Drug Products
Division of Pharmaceutical Evaluation I

cc:

NDA 20-449 (orig)
HFD-150 (Division file)
HFD-150 (Pease, Beitz, Justice)
HFD-850 (Lesko, Metz)
HFD-860 (Malinowski, Mehta, Rahman)
HFD-870 (Clarence Bott, Drug file)
HFD-870 (Clarence Bott, Reviewer's file)
HFD-870 (Clarence Bott, Chron file)

D. Pease
APR 26 1996

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-449 (BM, BL)
DOCETAXEL Injection
40 mg/ml - 2ml or 0.5 ml vial
Taxotere ™
Rhone-Poulenc Rorer

Submission Dates: November 21, 1995
March 25, 1996
April 5, 1996
April 11, 1996

Reviewer: Peter N. Zannikos, Ph.D.

Type of Submissions: Amendment to Approvable NDA (Second Partial Submission)/ Revised Package Insert

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Background:

Reference is made to the letter dated October 27, 1995 indicating that the NDA for Taxotere (docetaxel) is approvable. This letter includes a number of post-approval studies and analyses to be performed by the sponsor. In addition, an updated draft package insert has been submitted.

Page 8
Question 7
(FDA - Post-Approval Studies and Analyses)

Further exploration of pharmacokinetics/pharmacodynamic relationships, specifically toxicity and response. Rates of toxicity remain high, even in patients without combined alkaline phosphatase and transaminase elevations. We have been unable to verify your univariate and multivariate analyses aimed at identifying factors predictive of febrile neutopenia, perhaps because definitions of febrile neutropenia changed over time. Moreover, the multivariate analysis indicates that risk of febrile neutopenia decreases as alpha-1 acid glycoprotein (and presumably docetaxel exposure) levels increase, a surprise as the clearance of docetaxel decreases with increasing levels of alpha-1 acid glycoprotein. Exploration of pharmacokinetic/pharmacodynamic relationships may be able to identify a correlation between docetaxel exposure and response *rate. This could lead to definition of a therapeutic window and a means, eg., through use of a test dose and blood level measurement, that would allow physicians to maximize toxicity. Although this would represent considerable effort at the time of treatment, it may be that the interpatient variability associated with metabolism through cytochrome P450 3A4 will merit such an approach.*

Synopsis of Sponsor's Response:

Febrile Neutropenia

The definition of febrile neutropenia used in the PK/PD analysis of febrile neutropenia has been delineated. The SAS data files and output of the univariate and multivariate analyses have been provided.

Influence of baseline alpha-1 acid glycoprotein (AAG) levels on PK and PD

According to population pharmacokinetic model, elevated AAG decreases total docetaxel clearance which is expected to enhance drug effect/toxicity. However, the free fraction or unbound drug levels should in theory, remained unchanged. Therefore, the clinical consequences as a result of elevated AAG on docetaxel exposure and toxicity may be difficult to predict. Elevated AAG appears to have a second "indirect" pharmacodynamic effect which reduces toxicity. A proposed mechanism for this independent "protective" effect was not provided.

Further exploration of pharmacokinetic/pharmacodynamic relationships

A Phase III study (Tax 313) is planned which will include Taxotere doses of 100 mg/m^2 and 75 mg/m^2. This study will assess docetaxel exposure and response rate.

Interpatient variability associated with metabolism through cytochrome P450 3A4

A study aimed at evaluating the correlation between the activity of cytochrome P450 3A4 as estimated by the erythromycin breath test and docetaxel clearance is planned as part of Phase II study TAX 311.

Comments:

1. A detailed report describing the Phase II/III study protocols (TAX 311 and 313) prior to their commencement should be submitted for review.

2. The clinical pharmacology and precautions sections of the package insert should be revised as suggested (see below).

Pages 3-5

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Recommendation:

FT Atiqur Rahman
Atiqur Rahman, Ph.D. 4/24/96
Group Leader
Division of Pharmaceutical Evaluation I

Peter Zannikos 4-25-96
Peter N. Zannikos, Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation I

cc:
HFD-205: FOI
HFD-150: NDA 20-449
HFD-150: Div. File
HFD-150:Pease
HFD-150: Beitz
HFD-340: Viswanathan
HFD-850: Lesko
HFD-860: Malinowski, Mehta, Rahman, Zannikos
HFD-870: Chen
HFD-870: Clarence Bott (Drug File)
HFD-870: Chron File (Clarence Bott)
HFD-870: Reviewer's File (Clarence Bott)
HFD-880: Fleisher

Release
OCT 23 1995

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-449

Submission Dates: July 21, 1995
Sept. 15, 1995

DOCETAXEL Injection
40 mg/ml - 2ml or 0.5 ml vial
Taxotere ™
Rhone-Poulenc Rorer

Reviewer: Peter N. Zannikos, Ph.D.

Type of Submission: Amendment to Pending NDA

Synopsis

A major focus of this amendment is the influence of hepatic function on the disposition of docetaxel. Apparently, patients with hepatic impairment are at higher risk, than patients with normal liver function, for the development of severe side effects associated with docetaxel. Differences in docetaxel disposition (ie. lower systemic clearance in the former group) are believed to play a role. Patients which made up the population pharmacokinetic data base were divided into groups according to various indices of hepatic disease (total number of subjects was 26 and 521 from **Phase I and Phase II**, respectively). The most significant observation was made in patients with elevated levels of SGOT **and/or** SGPT **and** alkaline phosphatase. The population model indicated that, on average, a 27 % decrease in docetaxel clearance can be expected. The effects of isolated increases in transaminase levels or alkaline phosphatase appeared to have less influence. The presence of hepatic metastases per se did not appear to have any clinically relevant effect on docetaxel clearance.

Univariate and multivariate analyses of 533 phase II patients indicate that docetaxel exposure (ie. AUC) and hepatic impairment are important predictors of febrile neutropenia. However, these findings could not be verified since those individuals who exhibited this adverse effect were not identified.

The effect of concomitant dexamethasone administration on the disposition of docetaxel was also assessed. The final evaluation of dexamethasone effects included 577 **Phase II** patients in the pharmacokinetic/pharmacodynamic database. A total of 82 patients received five different steroid premedication schedules. Observations from the first cycle of docetaxel administration were analyzed. No clinically significant alteration in docetaxel clearance (and exposure) was observed by dexamethasone premedication.

Additional *in vitro* binding studies were submitted. Docetaxel serum binding was high, 93 %

on average, and comparable to those reported in the original NDA submission. Displacement of docetaxel from serum binding sites by the studied drugs was reported to be minimal. In addition, no significant digitoxin displacement by docetaxel could be demonstrated. Unfortunately, the data are highly variable resulting in a low power to detect potentially clinically relevant differences. The usefulness of these findings are therefore questionable.

RECOMMENDATION

The submission has been reviewed by the Division of Biopharmaceutics. The amendment adequately addressed some of the issues raised by the Division of Clinical Pharmacology and Biopharmaceutics. The firm needs to be sent the general and labeling comments and should address comments 1 - 4 as part of the Phase IV commitments.

FT Mwm 10/23/95
Mehul Mehta, Ph.D., Section Head
Pharmacokinetics Evaluation Branch I
Branch I

Peter Zannikos 10/23/95
Peter N. Zannikos, Ph.D.
Pharmacokinetics Evaluation

cc
HFD-150: NDA 20-449
HFD-150: Pease
HFD-150: Beitz
HFD-150: Biopharm/Drug File
HFD-426: Biopharm/Mehta
HFD-426: Biopharm/Fleischer
HFD-426: Biopharm/ChenL
HFD-340: Viswanathan
HFD-426: Malinowski

Table Of Contents Page No.

Appendix

Pages 4-7
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GENERAL COMMENTS:

1. Due to inclusion/exclusion requirements, the original population data base included only 18 out of 547 patients with elevations in both serum transaminase (ALT and/or AST) and alkaline phosphatase. The sponsor should strengthen the proposed relationship between hepatic dysfuncton and docetaxel exposure and toxicity by evaluating additional subjects with liver disease.

2. The univariate and multivariate analyses aimed at identifying factors predictive of febrile neutropenia could not be verified. Those individuals who exhibited this adverse effect were not readily identifiable. Further, the sponsor's definition of febrile neutropenia changed as new data was added to the NDA submission.

3. The clearance of docetaxel was found to decrease with increasing levels of alpha-1 acid glycoprotein. This is expected given that the clearance of docetaxel is restrictive and dependent upon, in part, free docetaxel concentration. Surprisingly, the multivariate analysis indicates that risk of febrile neutropenia decreases as alpha-1 acid glycoprotein (and presumably docetaxel exposure) levels increase. The sponsor should further investigate this incongruity and the mechanism behind the trend for AAG to be a predictor of toxicity.

4. The sponsor should continue to explore pharmacokinetic/pharmacodynamic relationships. This could include identification of a correlation between docetaxel exposure and response rate. The sponsor should consider defining a therapeutic window clinicians can aim for which would maximize the likelihood for a positive clinical response while reducing the risk of toxicity.

5. Additional *in vitro* binding studies were submitted. Docetaxel serum binding was high, 93 % on average, and comparable to those reported in the original NDA submission. Displacement of docetaxel from serum binding sites by the studied drugs was reported to be minimal. In addition, no significant digitoxin displacement by docetaxel could be demonstrated. Unfortunately, the data are highly variable resulting in a low power to detect potentially clinically relevant differences. For example, the fraction of free docetaxel in the control incubations ranged from 0.69 - 22.1 %. The usefulness of these findings are therefore questionable.

Pharmacokinetics/Pharmacodynamics: Relevance of Hepatic Disease

Background:

A population pharmacokinetic analysis (NONMEM) to evaluate docetaxel disposition was submitted as part of the original NDA submission. Various covariates were examined to help explain inter-patient variability in docetaxel systemic clearance and to identify subpopulations of patients potentially at risk of unusual exposure. Blood samples were obtained during the first cycle of decetaxel therapy from a total of 547 patients; 26 from the 2 pivotal Phase I studies (given 70 to 115 mg/m^2; intense sampling) and 521 from Phase II studies (given 75 or 115 mg/^{2}; sparse sampling). Population model building using the NONMEM program and supportive regression analyses based on individual (Bayesian) estimates demonstrated that docetaxel clearance is related to body surface area (BSA), α-1 acid glycoprotein (AAG) level, age (AGE), albumin (ALB) and hepatic function (HEP):

Model N°5 (final model): $\hat{}Cl = BSA(\theta 1 + \theta 2\ AAG + \theta 3\ AGE + \theta 4\ ALB)(1-\theta 5\ HEP12)$

where HEP12, an index of hepatic function, is equal to unity when SGOT and/or SGPT > 60 IU and alkaline phosphatase > 300 IU. HEP12 is otherwise equal to zero. Further,

$$\theta 1 = 22.1,\ \theta 2 = -3.55,\ \theta 3 = -0.095,\ \theta 4 = 0.225,\ \theta 5 = \mathbf{0.334}$$

Importantly, the model would predict a 33.4 % decrease in docetaxel clearance in patients with hepatic impairment. This prediction is limited to the degree of liver disease exhibited in these patients.

In a later submission (May 5th, 1995) the sponsor re-analyzed the data. Enzyme elevations were adjusted to normal laboratory values in order to match the groups investigated in the pharmacokinetic analysis to those involved in the clinical safety analysis. The analyses were conducted in 535 patients (normal laboratory values were not documented in the database for 12 patients). Twenty-three (instead of 18) were assigned a value of 1 for HEP12. Similar results were obtained:

$$\theta 1 = 21.6,\ \theta 2 = -3.45,\ \theta 3 = -0.088,\ \theta 4 = 0.226,\ \theta 5 = \mathbf{0.268}$$

The model would predict a 26.8 % decrease in clearance in patients with hepatic impairment (again this is limited to the degree of liver disease exhibited in the 23 patients).

In order to illustrate the relevance of liver disease on docetaxel disposition, patients were divided into subpopulations based on various indices of liver function. Docetaxel clearance between groups were compared. The impact of abnormal liver function tests at baseline on the safety profile of docetaxel was also evaluated. Results from the original analysis (n = 547) were used.

A pharmacokinetic/pharmacodynamic analysis (NDA, July 1994) was performed using data from 533 (out of 577) Phase II subjects. A number of covariates, including hepatic impairment, were evaluated for their importance in predicting febrile neutropenia.

Results:

Pharmacokinetics

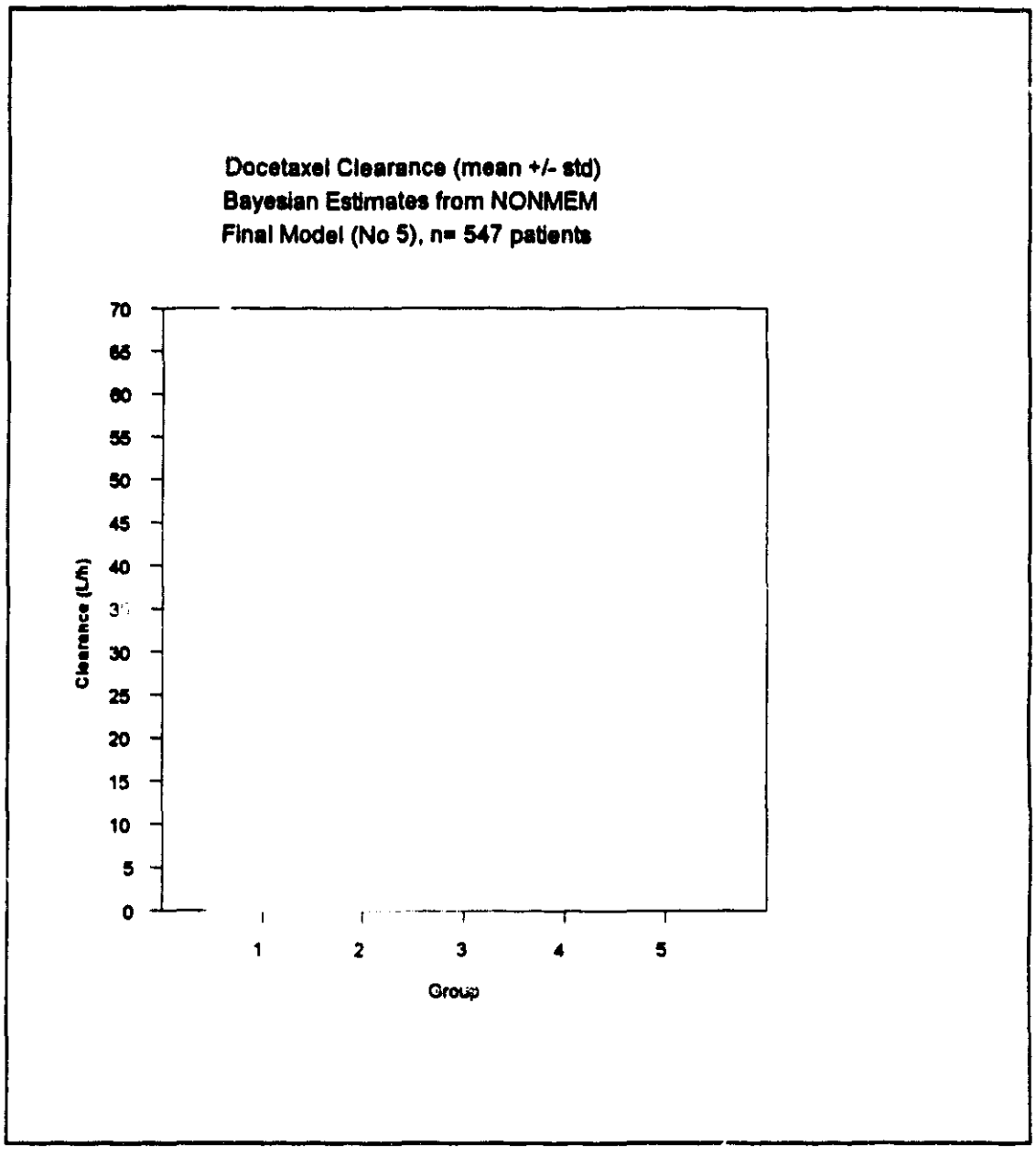
The most significant observation was made in patients with elevated levels of alkaline phosphatase and SGOT and/or SGPT (Figure 1). On average, these patients exhibited a 45 % decrease in docetaxel clearance (Group 5 versus Group 1). The effects of isolated increases in transaminase levels or alkaline phosphatase appeared to have less influence (Groups 3 & 4 versus Group 1). The presence of hepatic metastases per se did not appear to have any clinically relevant effect on docetaxel clearance (Group 2 versus Group 1).

Results from a simulation of data using the final NONMEM pharmacokinetic model (No.5) would predict that the concentration versus time profile following a dose of 75 mg/m^2 in patients with hepatic impairment, to the degree exhibited in the 18 patients, is expected to be comparable to the profile in patients with normal hepatic function administered 100 mg/m^2 (Figure 2).

Febrile Neutropenia - Pharmacokinetics/Pharmacodynamics

The occurance of febrile neutropenia in cycle 1 in the pharmacokinetic/pharmacodynamic population was investigated by univariate and multivartiate analyses. Out of 577 Phase II patients, data from 533 were available for examination. Both AUC (direct relationship) and AAG (inverse relationship) were strong predictors of febrile neutropenia (see attached). The covariate HEP12, indicating elevated serum transaminase and alkaline phosphatase levels, was also a significant covariate.

Figure I


Docetaxel Clearance (mean +/- std)
Bayesian Estimates from NONMEM
Final Model (No 5), n= 547 patients
Clearance (L/h)
70
65
60
55
50
45
40
30
25
20
15
10
5
0
1
2
3
4
5
Group

Group 1: **(-) liver metastases**
SGOT and SGPT < 60 IU
Alkaline Phosphatase < 300 IU
n = 355

Group 2: **all patients with (+) liver metastases**
n = 182

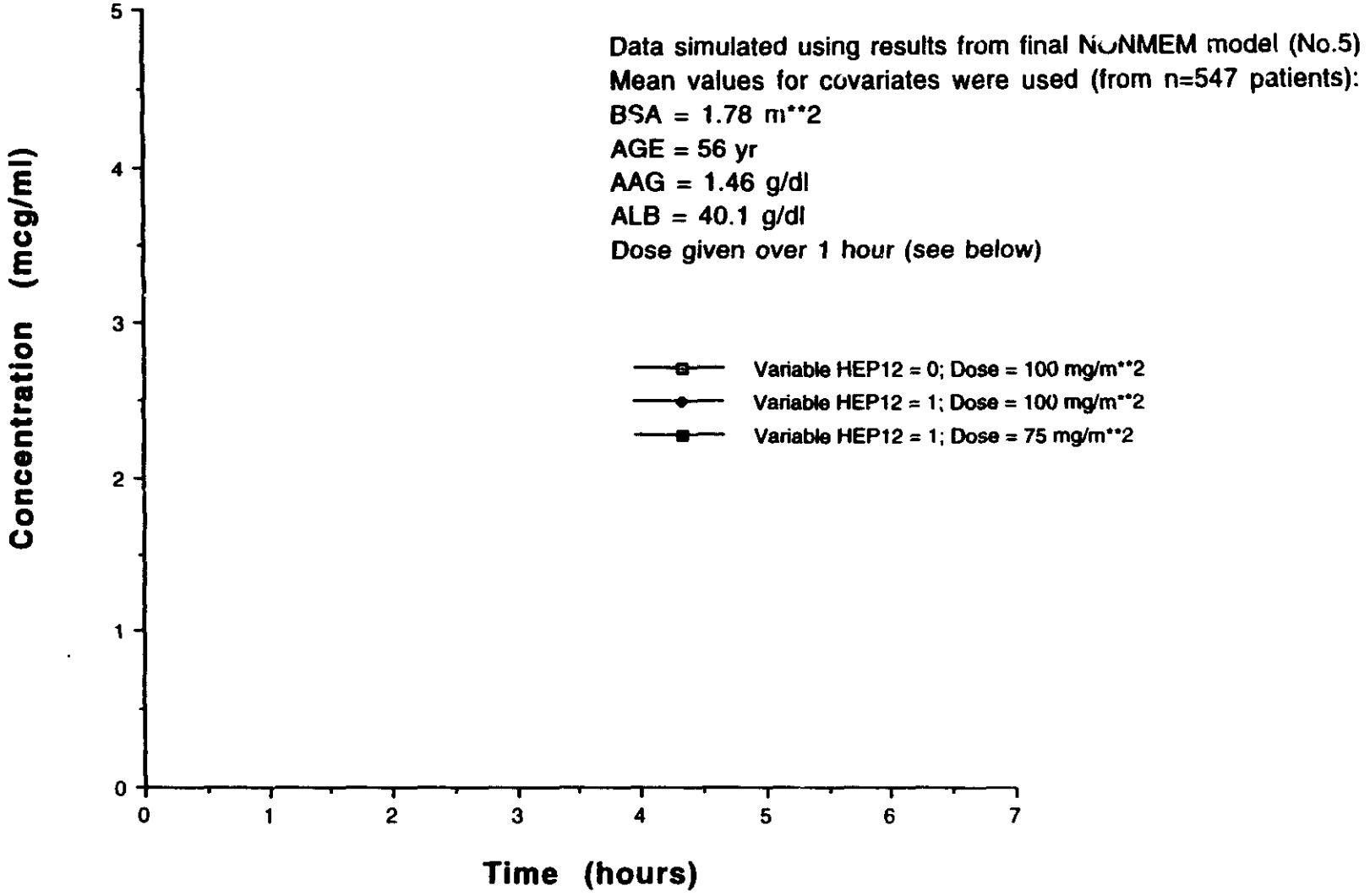
Group 3: (+/-) liver metastases
SGOT and/or SGPT > 60 IU
Alkaline Phosphatase < 300 IU
n = 25

Group 4: (+/-) liver metastases
SGOT and SGPT < 60 IU
Alkaline Phosphatase > 300 IU
n = 23

Group 5: (+/-) liver metastases
SGOT and/or SGPT > 60 IU & Alkaline Phosphatase > 300 IU
n = 18

* Statistically different from Group 1, $p < 0.05$; ANOVA/Dunnett's Multiple Comparisons Procedure (statistical analysis performed on logarithmically transformed data)

Docetaxel Disposition: Influence of Hepatic Function



PK/PD Patients Evaluable for Neutropenia Analysis, N=533
Overall Incidence is 21/533 = 3.9%

PARAMETER	N	VALUES	FEB. NEUT.	p-value*
F1	533	< 1.02	3/269 (1.1%)	p<0.001
		≥ 1.02	18/264 (6.8%)	
AUC (µg*h/ml)	533	< 4.81	4/271 (1.5%)	p=0.003
		≥ 4.81	17/262 (6.5%)	
HEP12 : hepatic impairment : SGOT/PT>60 IU and ALK>300 IU	529	no	18/513 (3.5%)	p=0.022
		yes	3/16 (18.8%)	
HEP12N : hepatic impairment : SGOT/PT>1.5*N and ALK>2.5*N	488	no	17/466 (3.7%)	p=0.055
		yes	3/22 (13.6%)	
AAG (mg/ml)	533	< 1.37	15/268 (5.6%)	p=0.073
		≥ 1.37	6/265 (2.3%)	
performance status (PSWHO)	528	0 or 1	20/452 (4.4%)	p=0.338
		> 1	1/76 (1.3%)	
initial actual dose (mg/m²)	533	>99.91	8/265 (3.0%)	p=0.374
		≥99.91	13/268 (4.9%)	
visceral organs involved	532	no	5/90 (5.6%)	p=0.376
		yes	16/442 (3.6%)	
number of prior chemo. regimens	533	0 or 1	17/462 (3.7%)	p=0.506
		≥2	4/71 (5.6%)	
age (years)	533	<50	7/149 (4.7%)	p=0.621
		≥50	14/384 (3.7%)	
sex	533	male	9/255 (3.5%)	p=0.664
		female	12/278 (4.3%)	
baseline bone metastases	533	no	16/424 (3.8%)	p=0.782
		yes	5/109 (4.6%)	
baseline liver metastases	533	no	13/351 (3.7%)	p=0.815
		yes	8/182 (4.4%)	
prior chemotherapy	533	no	12/323 (3.7%)	p=0.821
		yes	9/210 (4.3%)	
baseline neutrophil count (*10^9/l)	520	< 4.96	10/260 (3.9%)	p=0.999
		≥ 4.96	9/260 (3.5%)	
number of organs affected	533	<3	14/361 (3.9%)	p=0.999
		>=3	7/172 (4.1%)	

*Fisher's exact test

Multivariate Analysis

A logistic regression model with febrile neutropenia as the response was created using a stepwise procedure. The stepwise procedure began with all of the clinical factors listed in Table 1, with the exception of the variables HEP12 and HEP12N. Alpha level for entry was 0.10, and for the final model, an alpha level of 0.05 was required for a covariate to stay in the model.

Since the covariate baseline neutrophil count did not appear to be related to febrile neutropenia in the univariate analysis, and due to number of missing values for this covariate (n=13), the stepwise model building was done without baseline neutrophil count. The resulting model contained only the covariates F1 and AAG. Since it is easier to interpret clinically, area under the curve was substituted for F1 with no significant change in -2 LOG L.

The detail of the SAS output of the final model is as follows:

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Odds Ratio	Lower	Upper
INTERCPT	1	-2.8369	0.6102	21.6160	0.0001	0.059	0.018	0.194
AAG	1	-1.6731	0.5430	9.4953	0.0021	0.188	0.065	0.544
AUC	1	0.3310	0.0829	15.9235	0.0001	1.392	1.183	1.638

Based on this model, area under the curve (as well as F1) is a highly significant ($p<0.0001$) predictor of febrile neutropenia, along with alpha-1 acid glycoprotein.

The covariates HEP12 and HEP12N were added (separately) to this model and neither covariate was significant. However, when AUC was removed from the model i.e. the odds of febrile neutropenia was no longer adjusted for AUC effect, then those covariates entered the model significantly.

Even so this model is based on few patients with febrile neutropenia (21/533), the trends observed are consistent with previous analyses.

Reference :

1 - R. Bruno and L.B. Sheiner. Population pharmacokinetics of docetaxel (RP 56976, Taxotere®) : Analysis of data from Phase II studies - First cycle of treatment. Report IBP/Biodyn N° 1835 issued July 11, 1994. (See Document Number 6.33 found on page 6-39-6 [1.97] of NDA 20-449 filed on July 27, 1994.)

Dexamethasone-Docetaxel Interaction Analysis

Background:

On May 26, 1995, FDA expressed concerns that the reduction of fluid retention by dexamethasone premedication may be mediated by alteration of docetaxel pharmacokinetics. The population pharmacokinetic database was analyzed to evaluate any effect of the premedication. The final evaluation included 82 of 577 Phase II patients who were treated with dexamethasone. These 82 patients received five different steroid premedication schedules during the first cycle of docetaxel administration.

The population included in this analysis is slightly greater than what was studied in the initial NDA submission (n =547). The data rich 26 phase I subjects were omitted from the data file. However, these patients were replaced by 56 Phase II patients which were not part of the original data set. A limited number of samples (2 - 4/patient) were obtained from the original 521 and additional 56 study participants.

Results:

In the original NDA submission, the sponsor performed a population pharmacokinetic analysis of docetaxel using nonlinear mixed effect modeling (Method 0, NONMEM program, version III). A three-compartment structural kinetic model was used. Posterior Bayes estimates of clearance based on actual concentration measurements for each patient and parameter estimates of the final population model as priors were compared. In the most recent submission, no new or additional pharmacokinetic model was elaborated to analyze the data (ie. the original final pharmacokinetic population model, was used).

Table 1. Patient populations according to dexamethasone dosage schedule *

Schedule	Number of Patients	Days of "Relevant" Dexamethasone Exposure[$]
1 Day 0** only	44	1
2 Day 0 and Day 1	2	1
3 Day 0 for > 3 days	7	1
4 Day -1 and Day 0	2	2
5 Day -1 for > 3 days[#]	25	2
6 Unknown schedule	2	?
Total on dexamethasone	82	
0 No dexamethasone	495	0
Grand Total	577	

* except for Schedule 5, the dose of dexamethasone was NOT specified
** Day 0: day of docetaxel infusion
$ dexamethasone would be expected to have significant effects on docetaxel PK within first 24 hours.
\# recommended premedication of 8 mg po twice a day

Table 2. Docetaxel clearance and area under the plasma concentration-time curve for various dexamethasone dosage schedules (mean ± standard deviation)
- **Analysis by Sponsor**

Schedule	Number of Patients	Cl (L/h)	AUC# (mcg*h/mL)
0	495	37.0±12.3	5.34±2.3
1	44	38.4±14.5	5.47±2.5
5	25	36.9±10.8	5.34±1.9
1+2+3	53	37.5±13.7	5.54±2.4
4+5	27	35.8±11.1	5.52±1.9

$ Model $\hat{}Cl = BSA(\theta 1 + \theta 2\ AAG + \theta 3\ AGE + \theta 4\ ALB)(1-\theta 5\ HEP12)$
\# depends on clearance and the total dose administered (mg)

Our attempt to reproduce the sponsor's estimates of mean systemic clearance for each group of patients using the submitted data was somewhat successful. Upon close inspection it became apparent that clearance values for each individual from schedules 1 - 5 were identical to values obtained from the original analysis which included the Phase I subjects and a total of 547 subjects.

The data were therefore re-analyzed with only the Phase II subjects (n = 577) as initially proposed by the sponsor. The results are listed in Table 3.

Table 3. Docetaxel clearance and area under the plasma concentration-time curve for various dexamethasone dosage schedules (mean ± standard deviation)
- **Re-analysis**

Schedule	Number of Patients	Cl (L/h)
0	495	37.0±10.5
1	44	38.1±12.5
5	25	37.7±9.8
1+2+3	53	37.4±11.7
4+5	27	37.0±9.8

$ Model ^Cl = BSA(θ1 + θ2 AAG + θ3 AGE + θ4 ALB)(1-θ5 HEP12)
# depends on clearance and the total dose administered (mg)

In both analyses no clinically relevant differences were observed between the treatment schedules. This is not surprising. A disadvantage of using individual Bayes estimates is that they tend to be "centralized" towards the population mean, particularly when few observations are available from each individual. This bias creates difficulty in detecting relevant covariates.

As part of the review, an alternative method of analyzing the data was employed. The final population model was altered so a typical clearance value for each group of subjects was estimated. In this analysis, only two groups of patients were compared:

i) Phase II patients who did not receive any dexamethasone treatment; n = 495
ii) Phase II patients treated with dexamethasone on Day -1 and later (schedules 4 & 5 combined); n = 27

The dexamethasone-treated patients included were those subjects most likely to exhibit an alteration in docetaxel disposition due to dexamethasone (ie. schedules 4 & 5).

A typical value for clearance was estimated as follows:

^Cl = [BSA(θ1 + θ2 AAG + θ3 AGE + θ4 ALB)(1-θ5 HEP12)] * [1 + DEX*θ6] :

where DEX is an indicator variable equal to 1 (for + dexamethasone treatment; n=27) or 0 (for - dexamethasone treatment; n=495).

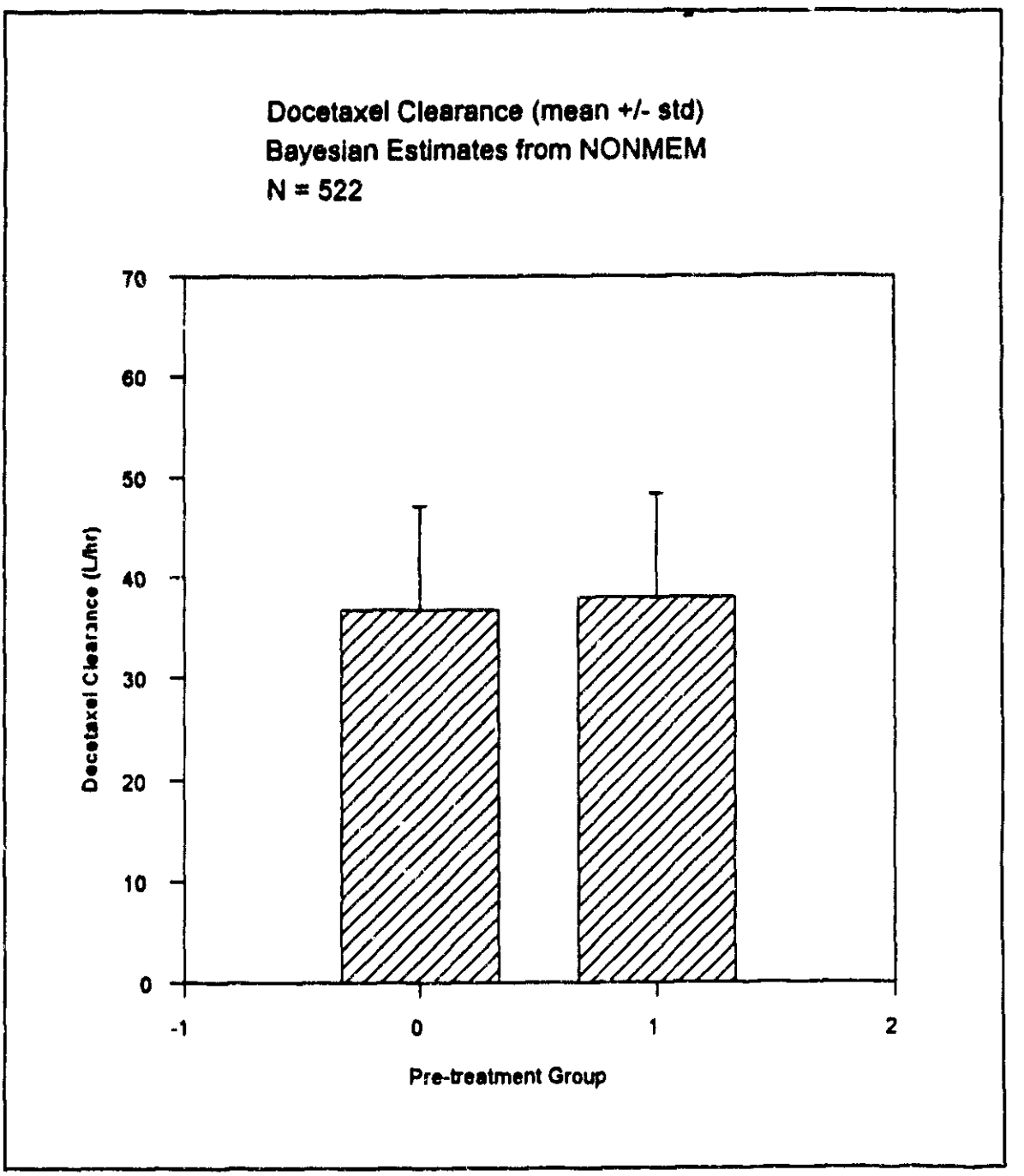
Estimates of typical docetaxel clearance for both groups of subjects are listed in Table 4. Theta 6 (= 0.092) was poorly estimated due to the small number of subjects which made up the dexamethasone-treated group. The mean (+/- std) of the Bayesian estimated clearance values are also provided (Figure 2). No clinically relevant differences could be detected.

Table 4. Docetaxel population pharmacokinetic analysis (n = 522 Phase II Patients) Parameter estimates:

Parameter	Value
θ1	26.7
θ2	-4.40
θ3	-0.134
θ4	0.183
θ5	0.35
θ6	**0.092**
V1(L)	7.52
interpatient variability:Cls*	29 %
residual variability*	37 %
Cls(L/h)**	**35.4 (DEX = 0)**
	39.7 (DEX = 1)
Vss(L)**	144.8

* expressed as coefficient of variation
** computed for mean values of covariates

Figure 2.


Docetaxel Clearance (mean +/- std)
Bayesian Estimates from NONMEM
N = 522
Docetaxel Clearance (L/hr)
70
60
50
40
30
20
10
0
-1
0
1
2
Pre-treatment Group

RP 56976, In Vitro Binding of Docetaxel to Human Serum. Drug Interactions

Protocol No.: IBP/Biodyn 93/002/1

Inverstigator:

Study Site:

Starting Date: 12-6-94
Completion: 12-9-94

Aim:

Docetaxel is bound to albumin, alpha1-acid glycoprotein and lipoprotein. The aim of this study was to evaluate the potential for interaction between a number a commonly used drugs on doxetaxel serum binding.

Protocol:

In vitro determination of docetaxel serum binding by the ultrafiltration method was performed. The potential for the following drugs to alter docetaxel free concentrations in pooled human serum was evaluated:

erythromycin
salicylate
sulfamethoxazole
diphenhydramine
propranolol
propafenone
phenytoin
sodium valproate

Methods:

Ultrafree-MC filters, cut-off 10,000 (Millipore) were used. Docetaxel, polysorbate 80 and the putative competing drug were added to the serum samples. Approximately 0.25 ml of serum was incubated at 37^0 C for 15 minutes. The pH of the incubation mixture was adjusted to 7.35 - 7.40 with lactic acid. The kit containing the sample was centrifuged. Total drug concentration was determined before centrifugation and free drug concentrations were measured from the ultrafiltrate. All experiments were replicated 5 - 29 times.

The serum concentration of docetaxel was mg/ml. In most cases, the concentration of the studied drugs were at a level achieved therapeutically. One exception was the concentration of propranolol which was fold higher than what is typically observed. All experiments were performed in the presence of polysorbate 80 (100 mg/ml).

The potential for docetaxel to displace digitoxin from serum proteins was also studied by similar methods.

The concentrations of [^{14}C]-docetaxel and [^{3}H]-digitoxin were determined by radiometry (scintillation counting).

Statistical Analysis:

Differences between group means were evaluated by an analysis of variance (ANOVA).

Results:

Docetaxel serum binding *in vitro* was high (on average 93 %). These results are comparable to those reported in the original NDA submission.

In the submission, the sponsor compared the fraction of *bound* docetaxel (and digitoxin). The putative displacers were not found to have a significant effect on the fraction of protein-bound docetaxel. No significant digitoxin displacement by docetaxel could be demonstrated as well (Tables 5 & 6). However, a more appropriate analyses would be to compare the *free* fraction of drug since the unbound species is, theoretically, the component which is pharmacologically active and available for metabolism. As part of the review, a statistical analysis of free docetaxel and digitoxin (expressed as a fraction of total * 100 %) demonstrated no significant interaction between docetaxel and the drugs studied (SAS output, Tables 7 & 8). This is somewhat expected given the high degree of variability in the data resulting in low power to detect potentially significant differences. For example, the fraction of free docetaxel ranged from % whereas the fraction of free digitoxin varied from %.

Table 5. Effect of drugs on mean docetaxel serum binding (expressed as percent bound)

Drug	Number of Replicates	Serum Concentration	Mean	Std. deviation
Control*	29	-	93.4	6.0
Erythromycin	10	7 µg/ml	92.7	3.3
Salicylate	10	300 µg/ml	91.4	7.0
Sulfamethoxazole	15	60 µg/ml	91.6	8.4
Diphenhydramine	10	100 ng/ml	89.5	8.4
Propranolol	10	900 ng/ml	96.3	3.1
Propafenone	10	3 µg/ml	90.1	10.6
Phenytoin	9**	15 µg/ml	89.7	7.3
Sodium Valproate	10	100 µg/ml	91.1	13.3

* The concentration of docetaxel in all incubations was µg/ml
** One outlying data point was removed. No further explanation provided.

Table 6. Effect of docetaxel on mean digitoxin serum binding (expressed as percent bound)

Drug	Number of Replicates	Serum Concentration	Mean	Std. deviation
Control*	5	-	98.1	2.4
Docetaxel	5	5 µg/ml	95.4	6.8

* The concentration of digitoxin was 25 ng/ml

Table 7. Effect of drugs on mean docetaxel serum binding (expressed as percent free)

Drug	Number of Replicates	Serum Concentration	Mean±Std.	Range
Control*	29	-	6.6±6.0	0.69 - 22.1
Erythromycin	10	7 µg/ml	7.4±3.4	1.3 - 11.2
Salicylate	10	300 µg/ml	7.6±7.3	0.92 - 23.7
Sulfamethoxazole	15	60 µg/ml	8.3±8.5	0.63 - 22.6
Diphenhydramine	10	100 ng/ml	10.5±8.4	0.81 - 28.4
Propranolol	10	900 ng/ml	3.7±3.1	0.43 - 9.3
Propafenone	10	3 µg/ml	9.8±10.6	0.62 - 33.9
Phenytoin	9**	15 µg/ml	10.3±7.3	0.60 - 18.9
Sodium Valproate	10	100 µg/ml	8.9±13.3	0.64 - 34.9

* The concentration of docetaxel in all incubations was µg/ml
** One outlying data point was removed. No further explanation provided.

Table 8. Effect of docetaxel on mean digitoxin serum binding (expressed as percent free)

Drug	Number of Replicates	Serum Concentration	Mean±Std	Range
Control*	5	-	1.9±2.4	0.71 - 6.2
Docetaxel	5	5 µg/ml	4.6±6.8	0.74 - 16.6

* The concentration of digitoxin was 25 ng/ml

General Linear Models Procedure

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	396.29953180	49.53744148	0.81	0.5955
Error	104	6362.41860461	61.17710197		
Corrected Total	112	6758.71813641			

R-Square	C.V.	Root MSE	Y Mean
0.058635	99.57335	7.8215793	7.8550931

Source	DF	Type I SS	Mean Square	F Value	Pr > F
X	8	396.29953180	49.53744148	0.81	0.5955

Source	DF	Type III SS	Mean Square	F Value	Pr > F
X	8	396.29953180	49.53744148	0.81	0.5955

Discussion:

It is difficult to draw firm conclusions from the present protein binding study given the high degree of variability in the data. However, the following needs to be considered when predicting the clinical relevance of these results:

i) the degree of docetaxel systemic exposure is of importance since this drug can be described as having a narrow therapeutic index

ii) the extraction ratio of docetaxel is moderately low (ER = 0.44 assuming docetaxel systemic clearance equal to 37 L/hr and hepatic blood flow equal to 84 L/hr).

Theoretically, the clearance (and therefore area under the plasma concentration vs time curve) of docetaxel is dependent upon intrinsic clearance, hepatic blood flow and the fraction of free drug. As a result, if significant displacement of docetaxel from protein binding sites were to occur, the effect on total and free drug concentrations would be offset, in part, by the dependence of docetaxel clearance on all three factors.

APPENDIX

Pages i - xii of Pharmacokinetic Review of NDA 20-449

Review: Lydia C. Kaus, Ph.D. and Peter N. Zannikos, Ph.D.

Submitted: July 10, 1995

JUL 10 1995

PHARMACOKINETIC REVIEW - FINAL

NDA 20-449
DOCETAXEL Injection
40 mg/mL -2mL or 0.5 mL vial
Taxotere™
Rhone -Poulenc Rorer

Submission Dates: July 27th, 1994
Sept 23, 1994
Oct 13, 1994
Nov 11, 1994

Reviewers: Lydia C. Kaus, M.S., Ph.D and Peter Zannikos, Ph.D.

Type of Submission: NME IP

Synopsis:
The disposition of docetaxel was studied in six Phase I clinical studies following various IV infusion schedules over a wide range of doses. Also, an excretion and metabolism study was conducted in 3 patients dosing with radiolabelled docetaxel. The main metabolic route is through a series of oxidations of the tert-butyl ester group on the side-chain. The main metabolites are 30 and 140-fold less active *in vitro* respectively than the parent. A number of *in vitro* studies were carried out to identify cytochrome P450 isoenzyme(s) involved in the metabolism of docetaxel, to investigate the plasma protein binding and to evaluate potential drug interactions. From work in human liver subcellular fractions, CYP3A isoenzymes are responsible for the metabolism of docetaxel. Potentially co-administered drugs such as cimetidine, ranitidine, paracetamol (acetominophen) or diazepam were not found to inhibit docetaxel metabolism *in vitro*. Inhibition of docetaxel metabolism was shown *in vitro* by ketoconazole and nifedipine and to a lesser degree by erythromycin. *In vitro* binding studies show that docetaxel is 94% bound at concentrations 1-5 μg/mL mainly to serum albumin, AAG and lipoprotein. In plasma samples collected from three cancer patients, docetaxel was 98% bound to protein. Neither cisplatin (50 μg/mL), doxorubicin (500 ng/mL), etoposide (10 μg/mL), vinblastine (300 ng/mL) nor dexamethasone (50 ng/mL) displaced docetaxel (1 μg/mL) from its protein binding sites (as shown *in vitro*).

Population pharmacokinetic analysis using NONMEM allowed the inter-patient variability in docetaxel clearance to be defined. The influence of age, renal impairment, hepatic impairment, race and gender on the pharmacokinetics of docetaxel were addressed by the use of covariates in the population PK analysis. Clearance was related to age, AAG level, BSA and hepatic function. The same formulation was used in all of the Phase II clinical studies. Several attempts were made to investigate a pharmacokinetic and pharmacodynamic relationship for docetaxel. A trend in AAG plasma levels as a predictor of toxicity as shown by fluid retention and Grade IV neutropenia is noted and needs further investigation.

Recommendation:
The submission has adequately addressed the Division of Biopharmaceutics requirements or guidelines. The firm needs to be sent the general comments #1-7 and the labelling comments #1-8.

-TABLE OF CONTENTS:

BACKGROUND:

Docetaxel acts by inhibiting the depolymerization of microtubules. The firm is proposing the following treatment indications for this product:

a. locally advanced or metastatic breast carcinoma in the light of previous therapy failing. The prior therapy must have included an anthracycline unless clinically contraindicated

b. locally advanced or metastatic non-small lung cancer even after failure of platinum-based chemotherapy.

Abbreviations used:

CL = total body clearance

AUC=Area under the curve

LOQ=limit of quantification for an assay

PK=pharmacokinetics

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETIC/PHARMACODYNAMICS:

I . BIOAVAILABILITY/BIOEQUIVALENCE:

Two formulations were used (No.1 and No.2) during drug development . Formulation No. 2 is the "to be marketed " formulation and was used in all pivotal clinical trials. There are two Phase 1 pharmacokinetic studies in which both the formulations were used : TAX001 and TAX004. These were dose escalation studies in design. TAX001 had two patients out of 25 on Formulation No. 2, whilst TAX004 had 11 patients out of 51 on Formulation No. 2. The infusion rates were different in the two studies. The pharmacokinetic parameters for the patients on Formulation No.2 were compared to those on Formulation No. 1 and being similar (using a comparative across study t-test), the firm concluded that the formulations were bioequivalent. Based on population PK analysis by the Division, formulation as a covariate was not significant.

II . PHARMACOKINETICS:

The label has under dose administration that docetaxel is to be given at 100mg/m^2 as a one hour infusion. Docetaxel follows a three compartment model, when plasma levels are sufficiently above the LOQ. The plasma levels obtained above a dose of 75 mg/m^2 tend to follow a three compartment model, whilst patients below this dose tend to show plasma levels that fit to a two compartment model. Terminal half-life is unaffected by infusion duration (two-, three- or six-hour infusion times tested in TAX004). Mean CL in the same study was slightly lower after the six-hour infusion (16 L/h/m^2 as compared to 21L/h/m^2).

TAX002 studied docetaxel given as a 24-hour infusion. Plasma levels of docetaxel were too low to give the terminal phase. AUC (3.5 μg.h/mL at 70 mg/m^2) for this longer infusion rate was

similar to shorter infusions of one to two hours. At highest dose of 90 mg/m^2 there was some non-proportionality shown (mean clearance was 46% lower than clearance after 70 mg/m^2 dose). TAX005 studied docetaxel as one-hour infusion given on a biweekly basis. Inconsistent results regarding comparison AUC Day 1 vs. Day 5 were shown in two patients with full PK samples available: one patient showed AUC for Day 1 being higher in value than for Day 5 and in the second patient the reverse was shown. Docetaxel was measured in the pleural fluid of one breast cancer patient given a dose of 50 mg/m^2 and levels peaked at 50 ng/mL (less than 5% of mean peak plasma level) and remained measurable for up to 18 hours. In measurements taken 4 days post-dose, docetaxel could no longer be measured in the effusion. Note in this study almost all patients including the one with pleural measurements were given docetaxel as Formulation 1.

TAX003 studied multi-dose PK. Docetaxel was given as a 1 hour infusion daily every day for 5 days every 3 weeks. $AUC_{0\text{-}5h}$ was compared since much lower doses at any one time were being given and the LOQ was reached sooner. Assay validation information was incomplete for this supportive study.

The pharmacokinetics were described from a population analysis model using NONMEM program (version IV). The pharmacokinetic information used in the population model was collected from several ongoing clinical trials; most of the patients were on the 100mg/m^2 dose as a one hour infusion and all information was from the first cycle of treatment. The influence of patho-physiological covariates on the clearance of docetaxel was investigated in the population model. An index set of 280 patients were initially analyzed which included 26 Phase I patients. Validation was obtained from a separate set of 267 patients (Phase II alone). The model was then refined using a combined set of 547 patients. The basic model showed inter-patient variability of 50 % CV. Clearance was related to age, AAG level, BSA and hepatic function. The hepatic function index was set to one when SGOT>60 IU or SGPT>60 IU and ALKPH>300 IU, otherwise it was set to zero. AAG level and the hepatic function index have the greatest influence on inter-patient clearance variability. Later model refinements included albumin as a covariate also influencing clearance. Final population model:

$$\hat{}CL = BSA\,(\theta_1 + \theta_7\,AAG + \theta_8\,AGE + \theta_9\,ALB)\,(1-\theta_{14}\,HEP12)$$

where $\theta_1 = 22.1$, $\theta_7 = -3.55$, $\theta_8 = -0.095$, $\theta_9 = 0.225$, $\theta_{14} = 0.334$

HEP12 represents an interaction term between HEP1 and HEP2. HEP1 is defined as SGOT>60 or SGPT>60, HEP2 is defined as ALKPH>300.

The final model showed that the unexplained variability in clearance was reduced from around 50% to 33%. The residual variability was low at a CV% of 20.5 in that it was close to the assay variability (%CV) of up to 15 at the LOQ.

Pharmacokinetic parameters from the Phase I (expressed as means) and from the final population model for an average patient with mean covariate values can be compared:

PK Parameter	Phase I Studies Mean	Population Model Average Patient
t1/2 hours	11.1	11.4
CL L/h/m^2	21.0	20.6
Vss l/m^2	113	83.2

The parameters are close except for Vss which is more a reflection of the two methods of determination.

The Phase I trials TAX001 and TAX006 pharmacokinetic data were analyzed both by the two-stage approach and were incorporated into the population analysis.

The effect of several cycles of therapy was addressed in TAX001 and TAX006. This was not a formal study, just observations on the terminal half-life and CL values in two patients in each study who were followed anywhere from 2 cycles to 7 cycles; clearance was stable across cycles for patient with a mean of 19.4 L/h/m^2 (±2.05).

Protein binding:
In vitro binding studies show that docetaxel is 94% bound at concentrations μg/mL mainly to serum albumin, AAG and lipoprotein. Polysorbate 80 which is an excipient in the IV formulation, at concentration range of μg/mL, did not significantly affect the serum binding of docetaxel. In plasma samples collected from three cancer patients (TAX016) docetaxel was 98% bound to protein. Neither cisplatin (50 μg/mL), doxorubicin (500 ng/mL), etoposide (10 μg/mL), vinblastine (300 ng/mL) nor dexamethasone (50 ng/mL) displaced docetaxel (1 μg/mL) from its protein binding sites.

Binding parameters to isolated proteins were estimated and simulations predicted a slight increase in binding to 95.1 % (f_u decreased by 20 %) in cancer patients with severe biological syndrome of inflammation (increased 1-acid glycoprotein levels).

III. METABOLISM:

From a study in 3 cancer patients where ^{14}C-docetaxel (100 mg/m^2 was infused in 1 hour) it was found that fecal excretion is the major route of elimination of docetaxel -related radioactive compounds. (TAX016- ^{14}C labelled docetaxel mass balance study in cancer patients) . The firm accounted for about 70% of total dose administered in the feces. About 6-7% of the total dose administered was found in the urine. 78-81% of the total dose administered was accounted for in this radioactive mass balance study. The main metabolic route is through a series of oxidations of the tert-butyl ester group on the side-chain. The alcohol derivative is identified as RPR 104952 (metabolite VI) and is the main one found in the urine, but is also produced by degradation of docetaxel. Less than 8% of the total radioactivity was parent compound. In the feces the main metabolite identified is cyclized acid XVI (RPR 104943). These metabolites are 30 and 140-fold less active in vitro respectively, than the parent. See the review of this study for structural identity of the metabolites mentioned here.

From work in human liver subcellular fractions, CYP3A isoenzymes are responsible for the metabolism of docetaxel. Potentially co-administered drugs such as cimetidine, ranitidine, paracetamol (acetominophen) or diazepam were not found to inhibit docetaxel metabolism in vitro.

IV. DOSE AND DOSAGE FORM PROPORTIONALITY:

The effect of dose was investigated in TAX004 where patients were given increasing doses from 40 to 100 mg/m^2. AUC showed dose proportionality between 40 to 100 mg/m^2. The study used a 6-hour infusion time. Dose proportionality was also investigated in TAX001 where AUC was dose proportional between 70 to 115 mg/m^2.

V. SPECIAL POPULATIONS:

a. Renal Impairment:

This was not studied as a separate study, however plasma creatinine was a covariate used in the population pharmacokinetic analysis. Inclusion of this covariate did not improve the model. Creatinine concentration for the full dataset ranged from μmol/L (mean 83.5 ± 18.70). Extremes in plasma creatinine clearance were not in the dataset. Only a small amount of unchanged drug is excreted renally.

b. Hepatic Impairment:

Several covariates were used in the population PK model to address the effect of markers of liver dysfunction on clearance. The effect of moderate hepatic dysfunction (as shown by elevation of SGOT or SGPT and alkaline phosphatase) may be of clinical relevance, since there can be a 33 % decrease in clearance. This was apparent in a small number of patients in the study group (18 patients out of 547 i.e. 3.3 % of the whole population). It should be noted that patients with severe hepatic impairment were not eligible to participate in these Phase II trials. An observation was made that the presence of liver metastasis per se was not found to alter clearance. The effect on the metabolites was not addressed by the firm.

c. Elderly:

Age was used as a covariate in the population PK model. The magnitude of age and albumin effects were relatively unimportant in the final model. The need to dose adjust in the elderly is not considered to be necessary since there is a 6.7 % decrease in clearance for patients 70 year old and the effect of body size is already accounted for by adjusting the dose to body surface area.

d. Gender:

Gender was used as a covariate in the population PK model. No difference in clearance was shown between males and females.

e. Race:

The firm did not address the effect of race on clearance since the European studies did not record the race of the patient. This was analyzed as a separate analysis by the Division (Dr. Zannikos) and found not to impact on the population pharmacokinetics.

VI . DRUG INTERACTIONS:

No formal *in vivo* drug interactions were studied. Implied drug interactions are from drugs that are common substrates for the cP450 3A pathway and in vitro inhibition of docetaxel metabolism was shown by ketoconazole and nifedipine and to a lesser degree by erythromycin. In study Biodyn #1728, docetaxel at 5μM was not inhibited by the CYP3A -mediated metabolized drugs 5-fluorouracil, cytarabine and cisplatin *in vitro*. Anticancer agents that did not have the CYP3A common pathway and were able to inhibit the metabolism of docetaxel *in vitro* were doxorubicin (100μM), vinorelbine (100 μM) and vinblastine (100 μM) at 86%, 63% and 44% inhibition *in vitro*. This study can be described as an attempt to address drug interaction *in vitro* but is not definitive (see comments to send to firm).

VII . PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Some attempt was made using sigmoid Emax model to look at maximum neutrophil decrease vs. AUC relationship. TAX002 also looked at same PK/PD model , but the parameter AUC_{50} was higher than after shorter infusions. The firm also undertook further PK/PD modelling using logistic regression and hazard analysis. Clearance estimates were obtained from Bayesian estimates using parameter estimates from the final population model as priors and also from predictions by the final population model using only individual covariates. The clearance estimates were then expressed in terms of factors or ratios, so that CLj is an individual clearance and mean CL is the average clearance for the population. The following summarizes the results from the PK/PD analyses:

Multiple factors were assessed by adding to a core model and testing using the log liklihood statistic. In terms of response:

AAG plasma level proved to be significant as a predictor of response ($p=0.02$) in breast studies. The odds of response decreased by 52% for each mg/L increase in AAG plasma level. Addition of the PK factors did not improve the model. AAG plasma level proved to be significant as a predictor of response ($p<0.01$) in lung studies. The odds of response decreased by 64% for each g/L increase in AAG plasma level.

In terms of toxicity, the odds of Grade IV neutropenia:
decreased by 16% when baseline neutrophils increased by 1 X 10^9 /L,
decreased by 85% for each g/L increase in AAG
increased by 90% for patients with prior chemotherapy
increased by 4X for each unit increase of fi (fl is a factor defined as the ratio of mean CL/CLj)
which means that clearance decreased two fold.
The risk of fluid retention was:
increased 1.6X for female patients
decreased 33% with 1g/L increase in AAG
decreased by 25% when protein levels increased by 10 g/L
decreased by 35% when steroids were included in the premedication
increased by 20% for unit increase in fl implying a two fold decrease in clearance or this can also be interpreted as an increased risk of 10% for each additional 100mg/m^2 course.
decreased by 13% with each additional organ involved.

The strong trend in AAG plasma levels as a predictor to toxicity in terms of fluid retention and Grade IV neutropenia is noted and needs further investigation. The implication of steroids being of benefit is muddied by the various premedication schedules used and needs to be clarified in some way.The firm have not addressed the mechanism behind the high incidence of fluid retention and AAG levels and the paradoxical relationship of clearance. The drug is highly bound and has a relatively low clearance (restrictive), so the expectation is as the protein levels rise, clearance decreases since the fraction unbound decreases. Therefore greater exposure to total drug as oppose to free (unbound) means the expectation of higher incidence of neutropenia. Again it must be emphasized that this analysis was from studies that were not randomized control trials.

VIII . FORMULATIONS:
Formulation 1 consists of docetaxel 15 mg in a 50:50 mix of dehydrated alcohol and polysorbate 80 in 1 or 5mL vials. Formulation 2 consists of docetaxel 80mg/2 mL or 20 mg/0.5 mL in polysorbate 80 alone. Formulation 2 is the to be marketed formulation. These are further diluted before administration.

IX . DISSOLUTION:
N/A

X . ASSAY:
HPLC with UV detection. There is a solid phase extraction step involved for sample preparation. Range = ng/mL in plasma and urine. Samples were diluted to be within the calibration range. The method used by investigators was cross-validated using selected plasma controls and patient samples at the firm's analytical laboratory.

GENERAL COMMENTS:

These comments are important and need to be addressed by the firm:

1. The firm needs to study *in vivo* potential drug interactions between docetaxel and drugs shown *in vitro* to be potential interacting agents, possibly through the use of adverse event databases. The firm need to address the effect of dexamethasone on the pharmacokinetics of docetaxel.

2. The firm needs to investigate further the mechanism behind the trend for AAG to be a predictor of toxicity and/or response.

3. The firm needs to investigate the potential interaction between itraconzole and docetaxel on the basis of an interaction being shown for ketoconazole *in vitro*.

These comments are for information and scientific interest:

4. Future submissions on PK studies should include the demographics on the patients/subjects.

5. The firm may want to consider investigating levels of docetaxel (bound and free) and its main metabolites in samples from pleural effusions over several cycles of treatment in order to relate toxicity to levels. A sparse sampling approach could also be taken .

6. From the *in vitro* liver microsomal studies: It would have been useful to have characterized the metabolites, especially the predominate metabolites M2, M3 and M4. The Dixon plots for determination of K_i's needed more experimental points, sampling between 5 and 10 μM ketoconazole (microsome batches HL 15 and HL 23) or between 2.5 and 10 μM in other batches for more scatter of points across the concentration range for linear regression determination. The authors suggest that there was a high correlation of M1, M2 and M4 with erythromycin N-demethylase activity. Correlations need to be more appropriately expressed in terms of r^2 rather than r values. The correlation with total metabolites $r=0.7698$ then becomes $r^2=0.5926$ and the highest r value for the correlation of activity with M2 where $r=0.8330$, becomes $r^2=0.6939$. At these values the correlations may not be definitive and further evaluation with for instance expressed systems is suggested. There is a need for further work using 3A expressed systems and anti-P450 3A for definitive conclusions to be made. The histogram of micosome number vs. total metabolites in (pmol/min/mg P) shows values ranging from about 20 to 160 pmol/min/mg not 6.9 to 164.7 pmol/min/mg as described in the abstract. This does not seem to suggest high variability as stated by the authors.

7. The following was noted from the report on study Biodyn #1728: the peak appearing after 15 minutes was not identified and its impact on the assay concentration of docetaxel was not described, if it is say the 7-epimer of docetaxel. From study Biodyn # 1728: no rationale was given for the incubation time of 60 minutes, this seems rather long. No rationale was given for using substrate disappearance assay for incubates with liver microsomes rather than product formation method.

The effect of anticancer drugs on docetaxel biotransformation was studied in Biodyn #1728 Exp # 27. The impact of the results would have been put into better perspective if there was an additional control substance such as ketoconozole for comparison.

Pages X-XI
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12/19/94

Lydia C. Kaus, M.S., Ph.D.
Pharmacokinetics Evaluation Branch
Biopharm Day (12-6-94): Attendees: Dr. T. Ludden, Dr. H. Malinowski, Dr. M. Mehta, Dr. J. Collins, Dr. W. Gillespie, Dr. M. Chen, Dr. N. Fleischer.
FT 7/10/95
Mehul Mehta, Ph.D., Section Head

cc
HFD-150:Orig. NDA 20-449
HFD-150: Pease
HFD-150: Beitz
HFD-150: Div. File
HFD-426:Biopharm/Drug File
HFD-426: Biopharm/Mehta
HFD-426: Biopharm/Fleischer
HFD-426: Biopharm/ChenL
HFD-340: Viswanathan

PHASE I AND PHARMACOKINETIC STUDY - pivotal

TITLE: Phase I and pharmacokinetic study of docetaxel given as a short IV infusion TAX 001, Vol. 1.61 page 6-3-15.

OBJECTIVES:
1. To determine the MTD of docetaxel when given as a short (minimum 1 hour) IV infusion.
2. To determine a) qualitative and quantitative toxic effects and then test whether a new formulation (Formulation #2) could be recommended based on observed tolerance b) a safe schedule (dose and time interval) for future Phase II trials c) basic pharmacokinetics in man, and d) any antitumor effect.

Clinical Investigator and Site:
Clinical Study Dates: June 21 1990 - May 13 1992
Subject Demographics:
(not given specific to PK patients)

Baseline Characteristics of All Treated Patients

	Initial planned dose-level (mg/m²)										All doses
	5	10	20	30	40	55	70	85	100	115	
Number of patients	3	3	6	4	4	6	5	16	11	8	66
Sex (M/F)	1/2	2/1	1/5	1/3	1/3	1/5	1/4	3/13	4/7	1/7	16/50
Age (years):											
Median	58.0	55.0	56.5	50.0	50.0	67.5	51.0	52.0	55.0	54.5	55.5
Range	(57-69)	(48-65)	(37-62)	(41-58)	(46-56)	(58-69)	(47-59)	(36-66)	(45-63)	(35-69)	(35-69)

Drug Supplies: Docetaxel 15 mg/mL in 50% polysorbate 80 and 50% dehydrated alcohol (Formulation #1) and Docetaxel 40 mg/mL in polysorbate 80 (Formulation #2).

STUDY DESIGN AND DOSAGE ADMINISTRATION:
Phase I dose-escalating, open-label, non randomized, dual-center study. Doses were escalated with three to six patients at each initial planned dose starting at 5 mg/m^2 and ending up at 115 mg/m^2 (modified Fibonacci). Doses were infused over one to two hours every 2-3 weeks.

BIOLOGICAL SAMPLING:
Blood samples were collected at pre-infusion, 0.5h after start of infusion, every hour during infusion and if infused longer than one hour, 5 min prior to end of infusion and 5, 10, 20, 30, 60 and 90 minutes, 2, 3, 4, 6, 8, 12 and 24 hours post-infusion.
Urine was collected pre-infusion and at timed intervals up to 24 hours post-dosing.. Every patient had blood and urine samples obtained for at least the first cycle of treatment and blood and urine was sampled the same in patients followed for cycle 2. One patient had ascites samples drawn as

per the sampling schedule for blood.

ANALYTICAL METHODOLOGIES:
Analytical Site: RPR, Antony, France. **Analytical Dates:** September 17, 1990 to October 31, 1992.
Specificity: Validated method used.
Linearity: 10-5000 ng/mL range
LOQ: 10 ng/mL
Precision: Inter-day %CV QC 20 ng/mL 11% and QC 1000 ng/mL 6% **Recovery:** Validated method used.

PHARMACOKINETIC RESULTS:
Two or three compartment models were fitted to the individual data.. The model that was the best fit was chosen according to the AKAIKE criterion. The maximum % decrease in neutrophil count was calculated according to the formula:

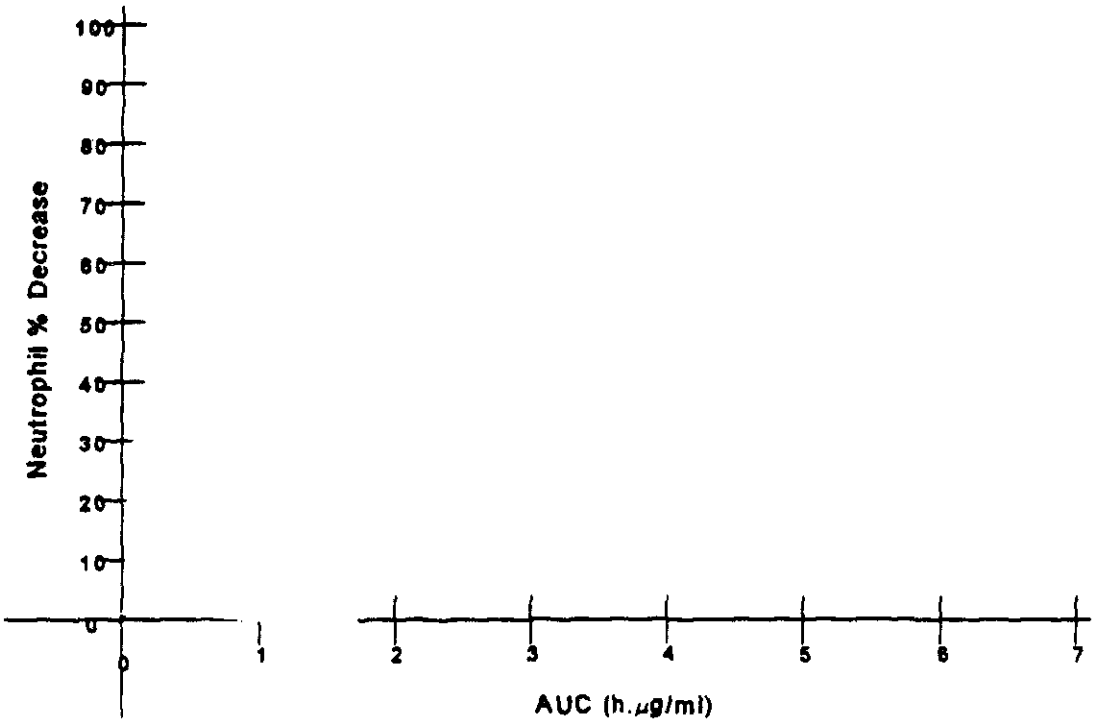
$$\%decrease = \frac{pre\text{-}treatment\ count - nadir\ count}{pre\text{-}treatment\ count} X\ 100$$

and using the following sigmoid E_{max} model:

$$\%Decrease = \frac{E_{max}(AUC)^k}{(AUC_{50})^k + (AUC)^k} \cdot (Hill\ Equation)$$

Data were available for 22 patients. A plot of the maximum neutrophil decrease (nadir) versus AUC (area under the plasma docetaxel concentration curve) shows a significant relationship (sigmoid E_{max} model, figure 1). The AUC_{50} estimate is 1.12 h.μg/ml, with a sigmoidicity coefficient k estimate of 1.36. The package used was SIPHAR (SIMED).

Figure 3 : Sigmoid Relationship Between Neutrophil Maximum % of Decrease and Docetaxel AUC



The patients receiving 5 and 10 mg/m^2 dosing had unquantifiable drug plasma concentrations.

A two compartment model was used for dose levels of 20, 30, 40, 55, and 70 mg/m^2 and a three compartmental model for dose levels 70, 85, 100 and 115 mg/m^2. Mean pharmacokinetic parameters are summarized:

Table 28 : Mean (SD) Pharmacokinetic Parameters (TAX001 Study)

Dose (mg/m²)	Nb of Pts.	Infus. time (h)	Peak Conc. (µg/ml)	t 1/2 α (min)	t 1/2 β (h)	t 1/2 γ (h)	AUC (h.µg/ml)	CL (l/h/m²)	Vss (l/m²)	Urinary excretion (% dose)
5	n=1	1.40	0.13	-	-	-	-	-	-	2.2
10	n=1	1.00	0.08	-	-	-	-	-	-	-
20	n=1	1.00	0.82	9.1	2.2	-	0.96	20.8	16	1.7
30	n=3	1.58 (0.80)	0.64 (0.45)	4.1 (1.4)	4.6 (2.8)	- -	1.26 (0.34)	24.9 (6.3)	81 (61)	- -
40	n=1	1.00	0.42	6.6	4.6	-	0.74	54.0	190	1.1
55	n=3	1.68 (0.75)	0.82 (0.38)	6.0* (2.5)	2.0* (0.5)	- -	1.42* (0.37)	40.0* (10.5)	39* (34)	2.7* (1.3)
70	n=3	1.37 (0.53)	1.91 (0.31)	3.8 (1.2)	1.3 (0.7)	4.1 -	2.79 (0.85)	26.7 (8.2)	16 (5)	3.3 (1.6)
85	n=6	1.61 (0.41)	2.42 (0.92)	4.0*** (2.7)	0.9*** (0.3)	13.6*** (6.1)	4.10*** (1.31)	22.6*** (7.7)	72*** (24)	2.1 (1.5)
100	n=4	2.03 (0.09)	2.41 (0.35)	4.5** (3.2)	0.8** (0.5)	18.5** (10.7)	5.93** (0.53)	17.0** (1.5)	95** (62)	3.0 (2.2)
115	n=4	1.84 (0.28)	2.68 (0.93)	3.0 (1.7)	0.6 (0.3)	9.5 (5.8)	5.19 (0.16)	22.2 (0.7)	53 (39)	2.6** (1.3)

*-: no result *: n=2 **: n=3 ***: n=5*

Table 32 : Individual Pharmacokinetic Parameters (TAX001 Study)

N° Pat /Ident /N°cycle	Dose mg/m²	Dose mg	Inf. Time (h)	Peak Conc. (µg/ml)	t 1/2 α (min)	t 1/2 β (h)	t 1/2 γ (h)	AUC (h*µg/ml)	CL (l/h/m²)	Vss (l/m²)	24 h Uri. excr.(% of dose)
1	5	9.5		0.13				-	-	-	2.2°
5	10	18		0.08				-	-	-	-
7	20	32		0.82				0.96	20.75	16	1.7
14	30	50		1.15				1.64	18.29	12	-
16	30	47		0.28				0.97	30.83	105	-
16	30	50		0.49				1.18	25.50	127	-
18	40	60		0.42				0.74	54.00	190	1.1°
21	55	90		1.13				1.69	32.60	15	1.8
22	55	82.5		0.40				-	-	-	-
24	55	85		0.94				1.16	47.43	63	3.6
29	70	115		2.24				1.98	35.31	13	-
29	70	115		1.61				2.71	25.82	13	2.2°
31	70	115		1.89				3.68	19.03	22	4.4°
32	85	133		1.53				3.02	28.12	78	1.3°
35	85	150		3.59				4.87	17.46	98	2.2°
36	85	135		3.43				4.28	19.84	56	0.5°
38	85	160		2.53				5.77	14.74	89	3.1°
39	85	130		1.57				-	-	-	1.6
52	85	145		1.84				2.58	32.99	40	3 7
43	100	166		2.89				5.36	18.65	30	5.1°
46	100	170		2.33				6.40	15.62	153	0.7°
47	100	140		2.35				6.02	16.62	103	4.7°
51	100	160		2.06				-	-	-	1.6°
58	115	171		2.40				5.30	21.70	104	-
59	115	173		1.97				4.98	23.10	60	1.5°
60	115	180		2.31				5.32	21.62	33	2.3°
65	115	200		4.04				5.17	22.23	14	4.0

- : no result # : formulation N°2 ° : 0 - 12 h excretion

A phase I study of RP 56976 administered as a one intravenous infusion to cancer patients

Model: MODEL1
Dependent Variable: AUC

Analysis of Variance

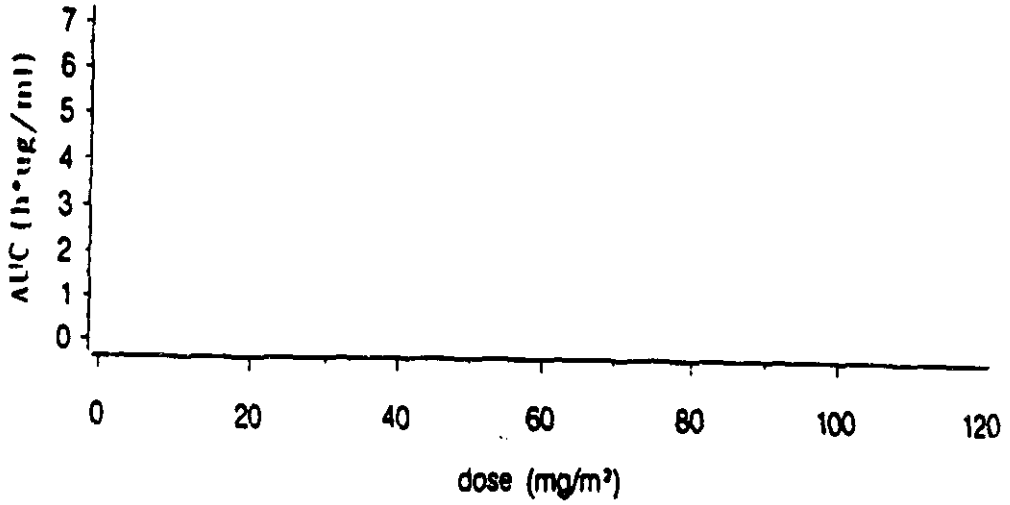
Source	DF	Sum of Squares	Mean Square	F Value	Prob>F
Model	1	62.26238	62.26238	72.536	0.0001
Error	20	17.16736	0.85837		
C Total	21	79.42975			

Root MSE	0.92648	R-square	0.7839
Dep Mean	3.44455	Adj R-sq	0.7731
C.V.	26.89706		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
INTERCEP	1	-0.755531	0.53123999	-1.422	0.1704
DOSE	1	0.055832	0.00655550	8.517	0.0001

A phase I study of RP 56976 administered as a one intravenous infusion to cancer patients – AUC vs doses



y = 0.0558 x – 0.7555 r2 = 0.7839 Prob>F = 0.0001

PK 2.4.2 OUTPUT LISTING FROM THE NON-LINEAR REGRESSION ON A SIGMOID MODEL

```
SIPHAR/PC : Version 4.0
-------------------------------------------------------------------------
Date: 04-27-1994                                          Time: 10:17:24
Title : TX-KD                                        Data set : NEUTRO%
-------------------------------------------------------------------------
The minimization algorithm used is : POWELL
The structural model is :
    Sigmoid Emax equation
The model has been fitted to data using weighted least squares algorithm
    with the weighting factor = 1

                    Pharmacodynamic Model Parameters

           CE(50) =    1.1468          gamma  =   1.42
-------------------------------------------------------------------------

  The nodrug Eff has been fixed to =    0.00
-------------------------------------------------------------------------

  The maximum Eff has been fixed to =  100.00
```

STATISTICS:

A linear regression analysis was carried out to determine the relationship between AUC and dose. AUC was found to increase proportionately to dose. A significant linear relationship was found (r^2=0.7839, $p<0.0001$) and the intercept was not significantly different from 0. Clearance was also found to be dose independent with a mean of 21.1±5.3L/h/m^2 between dose of 85 and 115 mg/m^2

The patient (No. 1st cycle, 40 mg/m^2 dose) in which measurements were made in the ascites, showed that docetaxel remained within the ascites at a level of 23.4 ± 3.5 ng/mL for 12 hours and at a level of 14 ng/mL at 24 hours. This patient had a Cmax of 420 ng/mL and a CL of 54 L/h/m^2. In TAX 005, another study, drug could not be measured in the ascites.

COMMENTS:

1. Sigmoid relationship looks quite dubious. A better attempt at investigating a PK/PD or toxicity relationship can be found later in the submission, although this was not outlined in the final summary report on the Pharmacokinetic Section.

2. Infusion times varied therefore the Cmax concentration was also variable.

3. The firm made statements comparing two individual patients' pharmacokinetic parameters who had been given Formulation #2 , to the rest who had been given Formulation #1. Comparisons were also made for two patients' pharmacokinetic parameters who had data for cycle 1 and cycle 2. Comparisons such as these can only give an impression of similarities or differences. Definitive conclusions can only be drawn from comparisons within a more formal statistical setting. Again an individual observation was made in one patient from whom docetaxel was measured in the ascites.

PHASE I STUDY WITH PHARMACOKINETICS - pivotal

TITLE: Abbreviated Phase I Study of RP 56976 Administered as One Hour Infusion to Cancer Patients (TAX006 Vol.1.67 page 6-9-6)

OBJECTIVES:
To confirm the MAD or MTD reached in the first Phase I clinical trial using the same schedule of administration but formulation #2.

Clinical Investigator and Site:

Clinical Study Dates: October 18, 1991 to May 7, 1992.

Subject Demographics: N=10, 5 female and 5 male. Median age =51.5 range 41-65. 3 patients dosed at 70 mg/m^2 and 7 patients dosed at 100 mg/m^2.

PATIENT NUMBER	AGE (years)	SEX	HEIGHT (cm)	WEIGHT (kg)	SURFACE AREA REPORTED (m^2)	SURFACE AREA CALCULATED (m^2)	WHO PERFORMANCE STATUS
	62	F	168	43.50	1.30	1.47	1
	54	M	172	81.50	1.95	1.95	0
	50	M	170	71.00	1.81	1.82	1
	49	M	181	72.00	1.90	1.92	1
	53	F	172	64.00	1.76	1.76	0
	43	F	167	63.00	1.72	1.71	0
	41	M	178	84.00	2.02	2.02	0
	65	M	172	60.80	1.72	1.72	1
	50	F	175	60.20	1.73	1.73	1
	56	F	172	60.50	1.72	1.72	0

Drug Supplies: Docetaxel 40 mg/mL in polysorbate 80. Formulation #2. Batch No. CB 4993 and CB 5545.

STUDY DESIGN AND DOSAGE ADMINISTRATION:
70 or 100 mg/m^2 as one hour infusion every 3 weeks. Non-randomized, open-label, dose-ranging study in patients with malignant solid tumors. Three patients were entered at 70 mg/m^2 and since there was toleration a further seven patients were entered at a dose of 100 mg/m^2. At least two cycles of treatment were given.

BIOLOGICAL SAMPLING:
Blood samples collected at pre-infusion, 0.5h after start of infusion, 5 min prior to end of infusion and 5, 10, 20, 30, 60 and 90 minutes, 2, 3, 4, 6, 8, 12 and 24 hours post-infusion. Urine was collected pre-infusion, 0-6, 6-12, 12-24 hours. Every patient had blood and urine samples obtained for at least the first cycle of treatment. Two patients had samples taken during multiple cycles (6-7).

ANALYTICAL METHODOLOGIES:
HPLC with solid phase extraction.
Analytical Site: RPR Institut de Biopharmacie, Dept. of Biodynamics ANTONY, France

Analytical Dates: October 23, 1991 to September 22, 1992.

Specificity: Run according to a validated method shown to be specific.
Linearity: 10-2500 ng/mL
LOQ:10 ng/mL

Precision: QC for low, medium and high concentrations were summarized for different dates/runs The three QC concentrations were not necessarily run on the same date. Inter-assay CV% was adequate.

Recovery: Not reported.

PHARMACOKINETIC RESULTS:
Docetaxel showed an increase in plasma concentration 30 minutes after the start of infusion. Two and three compartmental analysis of the data were undertaken. Comparing the AKAIKE criterion, the observed plasma concentrations were best fitted by the three compartmental model at both dose levels (70 and 100 mg/m^2). Mean Pharmacokinetic parameters were outlined as follows for the first cycle of treatment.

Mean Pharmacokinetic Parameters (SD) After First Cycle of Treatment

Dose mg/m^2	Nb of Patients	Peak Conc µg/ml	$t_{1/2\alpha}$ minutes	$t_{1/2\beta}$ minutes	$t_{1/2\gamma}$ hours	AUC h*µg/ml	CL l/h/m^2	Vss l/m^2	24h urinary excretion (%)
70	3	2.57	3.7	23.6	6.8	3.48	24.3	47.2	1.8**
		(0.64)	(0.5)	(7.2)	(1.6)	(1.12)	(8.2)	(13.3)	(1.5)
100	7	3.61	5.4*	45.5*	18.0*	4.59*	22.4*	149.3*	4.0***
		(0.94)	(0.9)	(14.1)	(10.3)	(0.76)	(4.1)	(137.6)	(1.2)

*$n = 6$; **$n = 2$; ***$n = 5$

The drug plasmaa profiles for individuals after the lower dose of 70 mg/m^2 showed a different terminal half-life due to the limitation of detection of the assay at these lower plasma levels. This contribution of the terminal portion of the curve is said to contribute to about 20% of the total AUC. Calculations of AUC and CL at the lower dose were said to be affected only slightly. Mean clearances were similar between the two doses. The mean Vss was difficult to compare due to not being able to describe the terminal half-life adequately for the lower dosed patients. There

was a low urinary excretion of docetaxel with a mean of 3.3 ± 1.6% in 24 hours.

After Repeat Cycles:
Two patients had the pharmacokinetics described for multiple cycles; both had received 100mg/m^2 .

Patient #	Total # cycles with data	Observation
	1 to 7	Increasing plasma conc. during 4-8h at cycles 6 and 7. PK parameters very similar to first cycle . Clearance constant across cycles.
	1 to 6	Increasing plasma conc. during 4-8 h at cycles 5 and 6. Gradual decrease in CL during treatment (41% reduction from cycle 1). Decrease possibly due to changed hepatic function.

TABLE 3 : DOCETAXEL MEAN (SD) PHARMACOKINETIC PARAMETERS IN PHASE I STUDIES FOLLOWING SHORT INTRAVENOUS INFUSION

STUDY CODE	TAX 001			TAX 006	
DOSE (MG/M^2)	70	85	100	70	100
NUMBER OF PATIENTS	3	6	4	3	7
INFUSION DURATION (H)	1.4 (0.5)	1.6 (0.4)	2.0 (0.1)	1.1 (0.1)	1.1 (0.1)
PEAK (µG/ML)	1.91 (0.32)	2.41 (0.9)	2.41 (0.35)	2.57 (0.64)	3.61 (0.94)
AUC (µG/ML.H)	2.78 (0.85)	4.1[C] (1.3)	5.93[B] (0.53)	3.48 (1.12)	4.59[C] (0.76)
T½ (H)	4.1[A] -	13.6[C] (6.1)	18.5[B] (10.7)	6.8 (1.6)	18.0[D] (10.3)
CL (L/H/M^2)	26.7 (8.2)	22.6[C] (8.2)	17.0[B] (1.5)	24.3 (8.2)	22.4[D] (4.1)
VSS (L/M^2)	16 (5)	72[C] (24)	95[B] (62)	47 (13)	149[D] (138)
24H-URINARY (% OF DOSE) EXCRETION	3.3 (1.6)	2.1 (1.5)	3.0 (2.2)	1.8 (1.5)	4.0 (1.2)

[A]: N=1 (ONLY ONE PATIENT HAD A TRIPHASIC PROFILE).[B] : N=3.[C]: N=5[D]: N=6.

Figure 1 : Plasma Concentration Profile Following First Cycle of Treatment (Patient

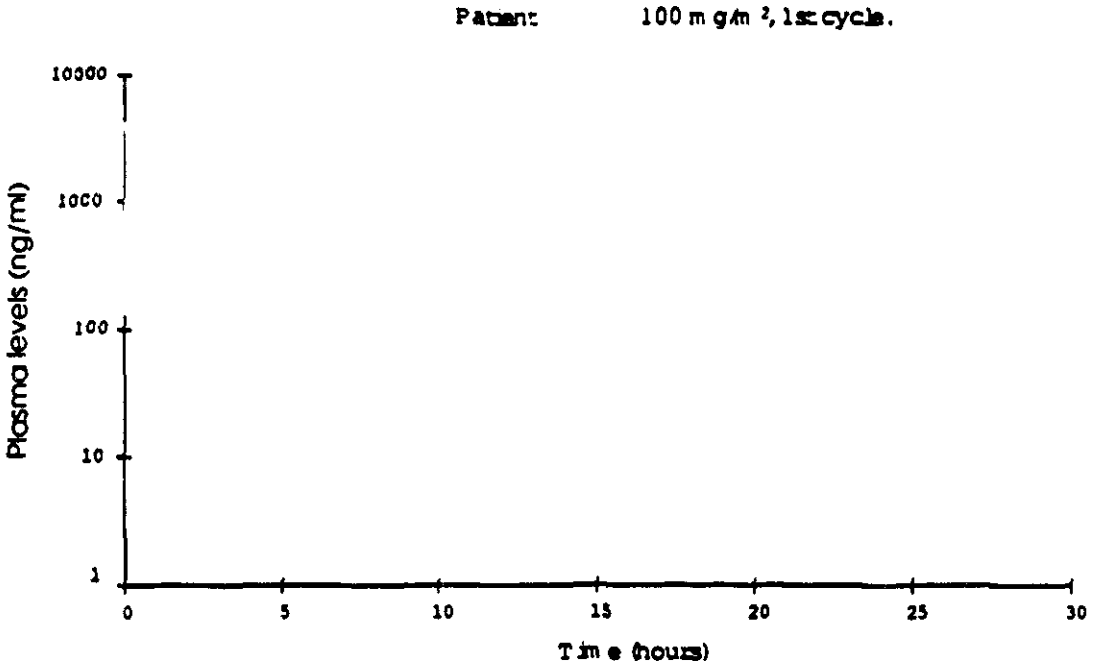
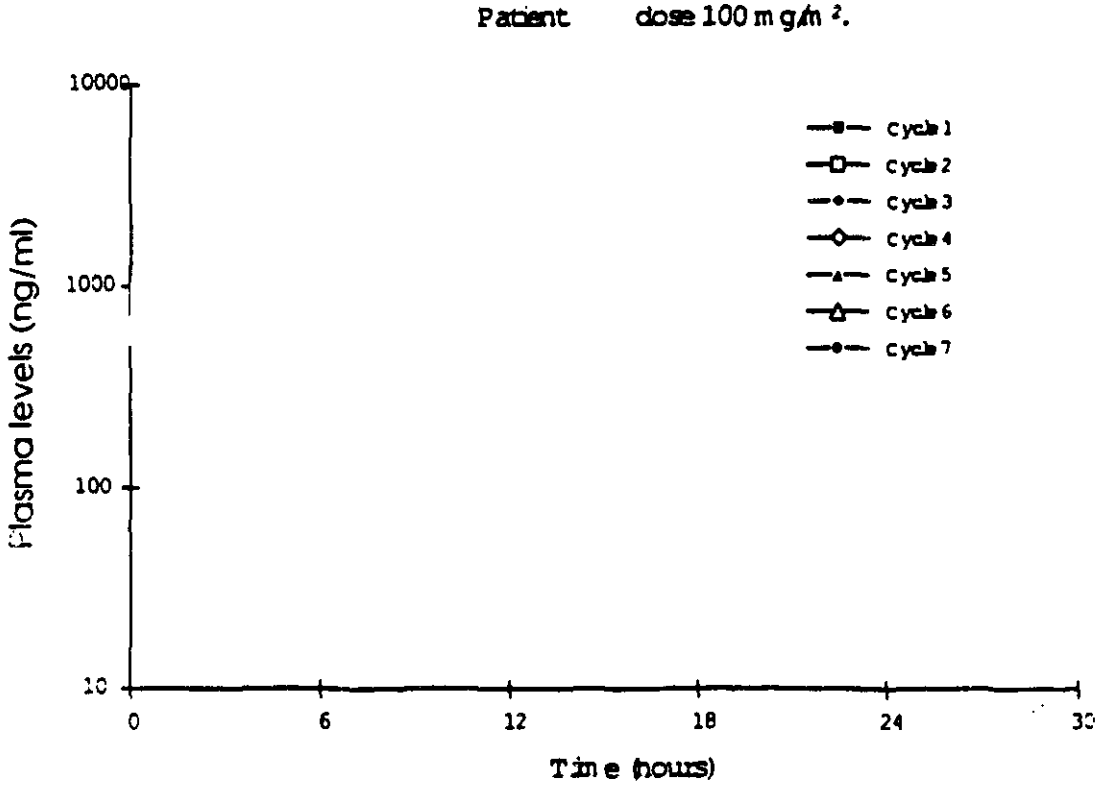


Figure 2 : Plasma Concentration Profiles Following 7 Cycles of 1 Hour Docetaxel Infusion Every 21 Days



CONCLUSIONS: .

The firm conclude that the pharmacokinetic profile was similar to that observed with Formulation #1 in other studies particularly TAX 001 (observational).

COMMENTS:

One patient followed over multiple cycles gave some indication of consistent clearance over time.

The mean clearance was similar at the two dose levels of 70 and 100 mg/m^2 .

DOSE ESCALATION AND PHARMACOKINETIC STUDY - supportive

TITLE: Phase I trial of RP56976 administered as a six hour infusion every 21 days (TAX 004, Vol.1.77, page 6-19-17)

OBJECTIVES:
To determine:
1. the maximum tolerated dose of docetaxel administered as a six-hour infusion every 21 days
2. the qualitative and quantitative toxicities
3. recommended dose and schedule (6 hour and 2 hour) for phase II studies
4. basic pharmacokinetics in man
5. any antitumor effect.

Clinical Investigator and Site:
Clinical Study Dates: Dec. 14 1990 to Sept. 10 1993.
Subject Demographics:
Not given for PK patients.

Baseline Characteristics of all Treated Patients

	Initial Planned Dose Level (mg/m^2)								All Doses
	5	10	20	40	60	80	100	115	
Number of Patients	3	3	3	3	9	14	30	6	71
SEX (M/F)	1/2	1/2	1/2	1/2	0/9	3/11	8/22	3/3	18/53
AGE (years) Median Range	73.0	57.0	38.0	40.0	57.0	51.5	56.0	52.5	56.0

Drug Supplies:
Batch #'s CB 4579, CB4587: Docetaxel 15 mg/m^2 in 50% polysorbate 80 and 50% dehydrated alcohol (Formulation #1) and Batch #'s CB 5140, CB 5327, CB 5363, CB 5545: Docetaxel 40 mg/m^2 in polysorbate 80 (Formulation #2).

STUDY DESIGN AND DOSAGE ADMINISTRATION:
Phase I, dose escalating, open-label, nonrandomized, single-center study with groups of 3 new patients at each initial dose level. Pharmacokinetic data were obtained in 51 patients who received docetaxel dose levels ranging from 5 to 115 mg/m^2 as 2-, or 3- or 6-hour infusions. Thirteen patients receiving docetaxel dose levels 100 and 115 mg/m^2 as 2- or 3- hour infusion were also investigated for pharmacokinetics of the vehicle polysorbate 80.

BIOLOGICAL SAMPLING:

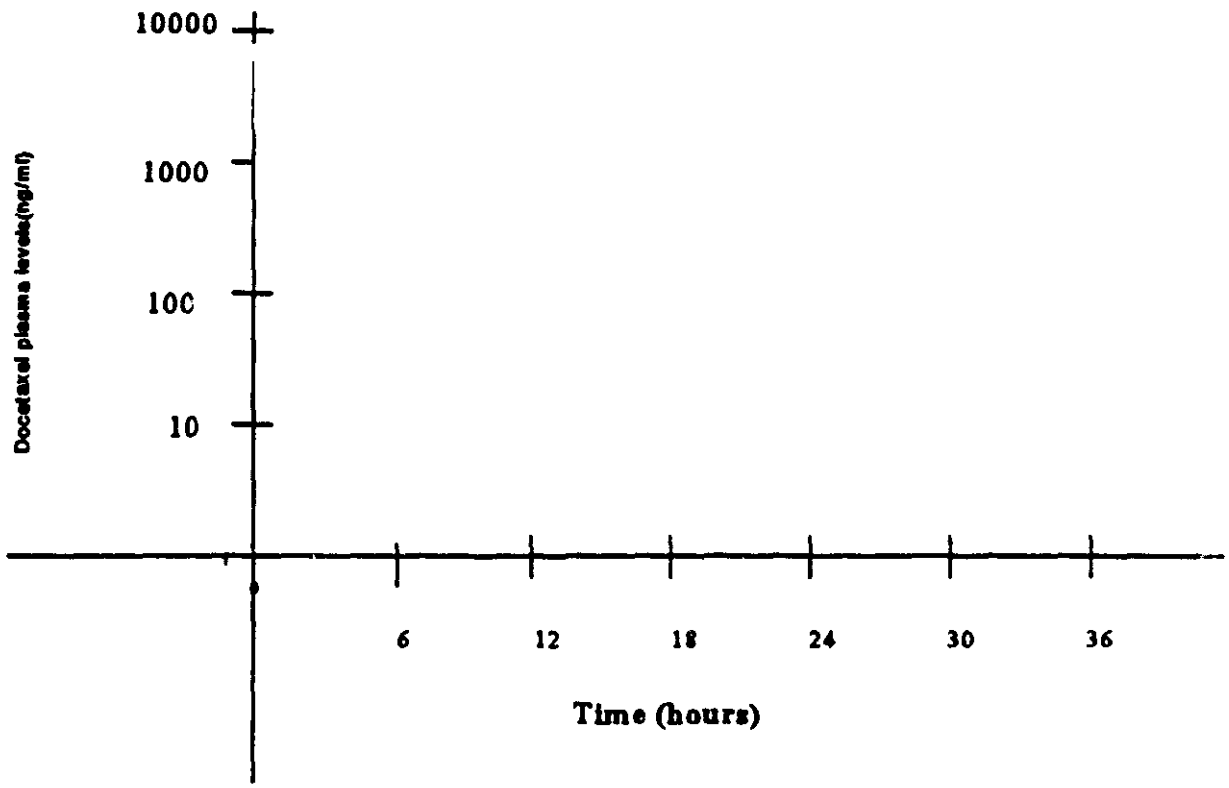
BIOLOGICAL SAMPLING:
Blood sampling varied according to the rate of infusion:
6 hour infusion: 30, 60 minutes and 2 hours, 4 hours into infusion, end of infusion and 5, 15, 30, 60, 90 minutes and 2, 3, 4, 6, 8, 12 and 24 hours post infusion.
2 hour infusion: 30, 60, 115 minutes into infusion, at end of infusion and 5, 10, 20, 30, 60, 90 minutes , 2, 3, 4, 6, 8, 12 and 24 hours post infusion.
3 hour infusion: 30, 90, 115 minutes into infusion, at end of infusion and 5, 10, 20, 30, 60, 90 minutes and 2,3, 4, 6, 8, 12 and 24 hours post infusion. Urine was collected pre-treatment and daily over two days following administration.
The sampling for polysorbate was the same as that for docetaxel.

ANALYTICAL METHODOLOGIES:
HPLC with UV detection.
Analytical Site:
Analytical Dates:11/91 to 9/92
Specificity: Not given as chromatograms but some patients excluded due to interfering peaks
Linearity: Range 15 to 1500 ng/mL plasma and 15 to 4000 ng/mL for urine.
LOQ:15 ng/mL
Precision: No inter or intra-assay given. Only some cross-validation information to RPR method. Different extraction method used to that of RPR. Up to 35% difference in accuracy shown for some QC samples. Cross-validation continued with patient data sent to RPR. Again differences shown, but overall noncompartmental derived pharmacokinetic parameters close but individual concentrations differed as much as 44%.

PHARMACOKINETIC RESULTS:
Irrespective of the dose or the duration of the infusion, postinfusion concentrations declined rapidly in a multi-phasic profile. Mean half-lives of the first two phases were 5 minutes and 1.6 hours, respectively and mean half-life of the terminal phase determined at dose levels ≥ 100 mg/m² was 13.6 ± 9.6 hours (n=28). Total clearance estimated at dose levels 40 to 115 mg/m² was constant with a mean value of 22.2 ± 7.1 l/h/m² (n=42). Thus, pharmacokinetic parameters estimated in this study were similar to those found in the two pivotal studies TAX001 and TAX006).

The influence of the infusion duration on pharmacokinetic parameters at a constant dose level (100 mg/m²) showed that, Cmax and the average concentration during infusion increased significantly from 1043 to 2469 ng/ml and 802 to 1804 ng/ml respectively, when infusion duration diminished from 6 to 2 hours, respectively. Terminal half-life was not influenced by infusion duration. Clearance estimates following a 6 hour infusion (16.0 ± 4.9 l/h/m², n=6) were slightly lower than after the 2 or 3-hour infusions (24.5 ± 7.4 l/h/m², n=14 and 23.4 ± 6.4 l/h/m², n=5) (p = 0.0499). Typical profiles after 2, 3 and 6 hour infusions are shown in the figure overleaf:

FIGURE 4 : DOCETAXEL PLASMA PROFILES AFTER 2, 3 AND 6 HOUR INFUSIONS AT A DOSE OF 100 MG/M² FOR TYPICAL PATIENTS



The effect of dose on docetaxel pharmacokinetics was evaluated in patients receiving a 6-hour infusion at doses of 40 to 100 mg/m². AUC showed a good proportionality with the dose, increasing from 1.9 to 6.8 h.μg/ml. No dose dependence of clearance was observed. This result is consistent with linear pharmacokinetics of docetaxel. Urine excretion of unchanged docetaxel was at the same level as in the pivotal studies. Mean value was 4.6 % of the administered dose.

Table 21 : Mean (SD) Docetaxel Pharmacokinetic Parameters.

Dose (Infusion)	Nb of Pat.	Cmax ng/ml	Cave° ng/ml	Terminal# t 1/2 (hr)	AUC h.μg/ml	CL l/h/m²	Vss l/m²
5 mg/m² (6 hr)	3	113.9 (50.3)	56.3 (17)	- -	- -	- -	- -
10 mg/m² (6 hr)	2	86.2 (36.3)	69.8 (22.1)	- -	- -	- -	- -
20 mg/m² (6 hr)	1	181.9 -	151.6 -	- -	- -	- -	- -
40 mg/m² (6 hr)	2	305.7 (149.0)	210.4 (66.8)	16.4 (18.8)	1.9 (0.2)	21.0 (1.9)	246 (304)
60 mg/m² (6 hr)	2	898.2 (362.9)	482.1 (12.2)	3.0 (0.0)	3.7 (0.4)	16.5 (1.9)	29 (11)
80 mg/m² (6 hr)	9	867.1 (302.2)	540.0 (197.7)	4.0 (2.7)	3.9 (1.6)	23.2 (8.0)	38 (21)
100 mg/m² (6 hr)	6	1042.6 (393.4)	801.9 (225.5)	17.9 (11.3)	6.8 (2.3)	16.0 (4.9)	108 (101)
100 mg/m² (3 hr)	5	1774.0 (652.6)	1431.0 (432.1)	13.9 (13.0)	4.5 (1.1)	23.4 (6.4)	93 (99)
80 mg/m² (2 hr)	1	1486.8 -	1238.7 -	1.95 -	2.7 -	29.3 -	19 -
100 mg/m² (2 hr)	14	2468.8 (1091.5)	1804.1 (566.4)	11.2 (7.1)	4.4 (1.4)	24.5 (7.4)	76 (43)
115 mg/m² (2 hr)	3	2475.4 (707.0)	2104.2 (557.1)	15.6 (12.3)	5.8 (1.8)	21.0 (6.1)	112 (74)
Overall Mean SD	**all**	- -	- -	13.6* 9.6		22.2 7.1	81 86

° : average concentration during infusion

: here are computed arithmetic mean of T 1/2 to be homogenous with other reports (investigator computed the harmonic mean, see Appendix II)

* : for dose levels ≥ 100 mg/m² (n=28)

Polysorbate 80 results.

Polysorbate amount administered to the 13 patients investigated for polysorbate 80 pharmacokinetics were 2.7 g/m² (10 patients), 3.6 g/m² (2 patients) and 4.1 g/m² (1 patient), depending on docetaxel dose and formulation (table 5).

A typical polysorbate plasma profile is shown in figure 5 and mean pharmacokinetic parameters are presented in table 5.

Table 5: Polysorbate 80 Pharmacokinetic Parameters.

Patient No.	Inf. dur (h)	Docetaxel (mg/m²)	Poly. 80 (g/m²)	Cmax µg/ml	t 1/2 (h)	AUC (h.µg/ml)	CL (l/h/m²)	Vss (l/m²)
								23.80
Mean				120.0	2.12	543.0	5.06	16.35
SD				30.2	0.71	81.2	0.78	5.07
Mean				122.4	4.42	402.4	6.99	30.99
SD				37.7	4.99	82.4	1.68	29.39
Mean				175.9	1.52	593.6	6.12	13.34
SD				36.8	0.21	79.8	0.82	1.13
All mean							6.13	18.03
SD							1.48	12.70

* : formulation N°1

° : not included in mean

Figure 5 : Polysorbate plasma profile of a patient receiving a 2-hour infusion of 100 mg/m² docetaxel.

Polysorbate pharmacokinetic was mono-compartmental with a t1/2 of 3.1 ± 3.5 hours. Cmax ranged from 120 to 202 μg/ml depending on the dose given and duration of infusion.

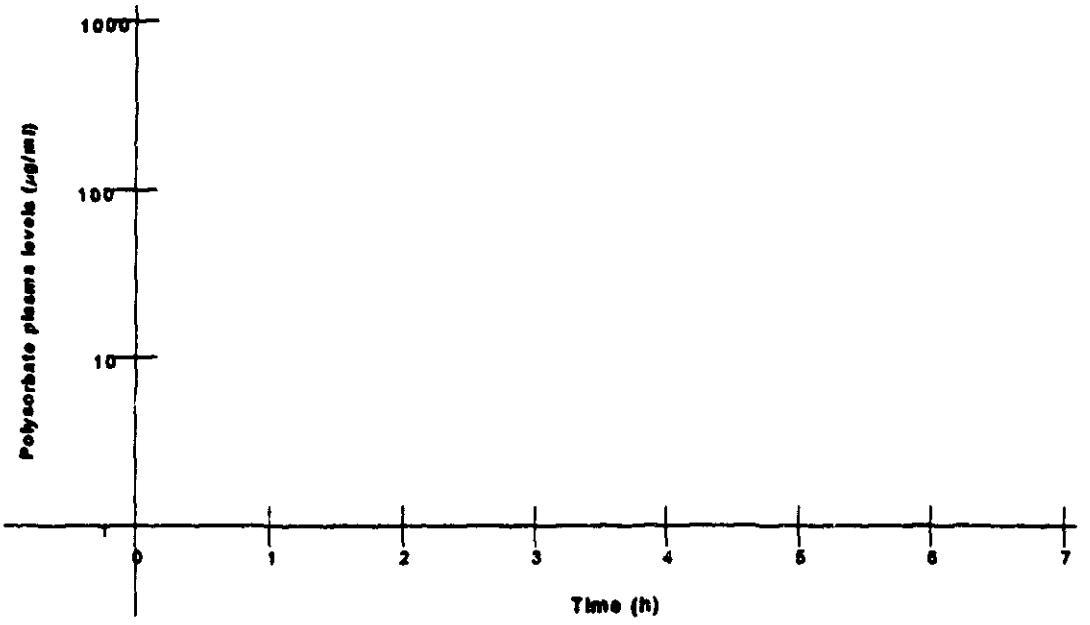


Table 5 : Mean (SD) polysorbate 80 pharmacokinetic parameters.

Formul	Inf.	Docet.	Poly.	N	Cmax	t 1/2	AUC	CL	Vss
2	3.00	100	2.70	4	120.0 (30.2)	2.12 (0.71)	543.0 (81.2)	5.06 (078)	16.35 (5.07)
2	2.00	100	2.70	6	122.4 (7.7)	4.42 (4.99)	402.4 (82.4)	6.99 (1.68)	30.99 (29.39
1	2.00	100	3.60	2	175.9 (36.8)	1.52 (0.21)	593.6 (79.3)	6.12 (0.82)	13.34 (1.13)
1	2.00	115	4.14	1	201.9	2.62	790.6	5.23	17.07
All SD						3.13 (3.48)		6.13 (1.48)	18.03 (12.70

STATISTICAL ANALYSIS:

The effect of infusion duration was examined by GLM procedure in SAS with Tukey's multicomparison test. As expected Cmax and Cave were significant, but other pharmacokinetic parameters such as Vdss, half-lives and total clearance were independent of infusion. However AUC was also shown to be significant.

Linear regression analysis was carried out to determine if there was a relationship between rash and polysorbate 80 pharmacokinetics. This approach seems naive since the grade of rash is a discontinuous variable. Logistic regression seems a more appropriate approach. Also there were only two patients studied on Formulation #1.

COMMENTS:

There seemed to be a trend toward higher exposure of polysorbate 80 for the same infusion rate in Formulation 1 vs. Formulation 2. However this is a comparison of N=2 vs. N=6 for the same dose administered. So only very approximate information is available for conclusions to be drawn or comparisons made. (If linearity is assumed and one normalizes for dose the difference is about 11%).

No trend toward nonlinear pharmacokinetics was observed for different infusion rates.

DOSE ESCALATION STUDY - supportive

TITLE: A Phase I study of RP 56976 (Doxcetaxel) administered as a twenty-four hour continuous intravenous infusion every three weeks to cancer patients. **(TAX002 Vol.1.69, page 6-11-14)**

OBJECTIVES:
1. To determine the MTD of docetaxel under the studied regimen.
2. To determine the qualitative and quantitative toxicities of docetaxel; the recommended dose for Phase II clinical trials: the pharmacokinetics; and antitumor levels.

Clinical Investigator and Site:

Clinical Study Dates: Nov. 7 1990 to Oct. 3 1991.

Subject Demographics:
Not given for PK p[illegible]

	INITIAL PLANNED DOSE LEVEL (mg/m² *)						
	10	20	40	55	70	90	ALL DOSES
NUMBER OF PATIENTS	3	3	3	6	5	10	30
SEX (M/F)	1/2	1/2	1/2	2/4	2/3	5/5	1[illegible]
AGE (years)							
MEDIAN RANGE	55.0 (51-56)	46.0 (44-65)	54.0 (53-55)	56.0 (22-62)	57.0 (49-58)	46.0 (24-68)	55.0 (22-68)
WEIGHT (kg)							
MEDIAN RANGE	62.8 (61-73)	62.8 (57-70)	73.2 (55-77)	63.3 (52-95)	65.0 (59-84)	54.5 (41-86)	62.3 (41-95)
PERFORMANCE STATUS :							
MEDIAN RANGE 0 1 2 3 4	1.0 (1-1) . 3 . . .	2.0 (0-2) 1 . 2 . .	1.0 (0-1) 1 2 . . .	1.0 (0-2) 2 2 2 . .	0.0 (0-2) 4 . 1 . .	1.0 (0-2) 2 7 1 . .	1.0 (0-2) 10 14 6 . .

(*) 24h c.i.v infusion every 3 weeks

Drug Supplies: Docetaxel 15mg/mL in 50% polysorbate 80 and 50% dehydrated alcohol by intravenous infusion during 24 hours once every 21 days; Batch #s CB 445, CB 4579, CB 4587.

STUDY DESIGN AND DOSAGE ADMINISTRATION:
Phase I single-center open-label non randomized study following a modified Fibonacci schedule with cohorts of three to six new patients at each initial dose level. No dose escalation within patient. Dose range studied: 10 to 90 mg/m^2.

BIOLOGICAL SAMPLING:

Blood samples (4 mL) collected pre-infusion, 6, 12 hours after start of infusion, end of infusion and 15, 30, 60, 90 minutes and 2, 3, 4, 6, 8, 12 and 24 hours post-infusion. Urine was collected pre-dose, during infusion and for 24 hours post-infusion at the following intervals: 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours.

ANALYTICAL METHODOLOGIES:
HPLC assay with UV detection. No assay validation given in terms of eg. QC sample results. Information given in text. This is not a pivotal study.

Analytical Site:
Analytical Dates: Not given.
Specificity: Validated method for pre-clinical studies.
Linearity: 15 to 500 ng/mL, r=0.97
LOQ: 15 ng/mL
Precision: Intra-assay %CV 7% to 13% over the range.

PHARMACOKINETIC RESULTS:
This study looked at a 24 hour-infusion schedule, and pharmacokinetic data were available for 16 patients at their first cycle for dose levels ranging from 20 to 90 mg/m².
For a 24 hour infusion, plasma docetaxel concentrations were low er than those observed after shorter IV infusions. End of infusion (24 hour) mean plasma drug concentrations ranged from 0.09 μg/ml at 20 mg/m² to 0.46 μg/ml at 90 mg/m². After the 24 hour infusion, plasma levels showed an apparent monophasic profile up to the limit of quantification of the assay.
The apparent elimination half-life was short and the mean ranged from 0.6 to 1.2 hours in the dose interval 40 to 90 mg/m². The monophasic behavior is probably a reflection of the third phase being unobserved since the LOQ had been reached. This apparent elimination half-life is in the order of that of the second phase of elimination observed in the short infusion studies. The mean clearance at dose levels of 20 to 70 mg/m² ranged from 30-40 l/h i.e. 18-24 l/h/m², similar to estimates following short intravenous infusion (around 20 l/h/m²). The mean exposure (AUC of 3.47 ± 0.90 h.μg/ml at 70 mg/m²) was also similar between the 24 hour infusion and the short infusion of 1-2 hours .

At the highest dose (90 mg/m²) there was some evidence of a non-proportional increase of AUC (7.81 ± 1.67 h.μg/ml) with a decrease of plasma clearance (19.5 ± 5.4 l/h). However this is inconsistent with TAX001 study's results where a more formal statistical analysis was carried out for doses ranging from 20 to 115 mg/m² .
Urinary excretion of docetaxel was approximately 2 to 4 % of the administered dose, a value similar to that found in other studies.

Again an attempt at determining a PK/PD relationship was made using the sigmoidal Emax model. A relationship was seen between plasma AUC and the fall in neutrophil count after the first course of docetaxel. AUC yielding a 50 % decrease in neutrophils was 3.5 h.μg/ml with a coefficient of sigmoidicity of 2.3. The AUC_{50} is somewhat higher than that estimated for a short

intravenous infusion.

Mean data can be summarized:

Mean plasma pharmacokinetic parameters of docetaxel after 24 h infusion

Dose (mg/m²)	No of patients		End of infusion conc (µg/ml)	AUC (µg/ml.h)	$t_{1/2}$ (h)	Vd (l)	CL (l/h)
20	1		0.09	0.92	0.2	9.1	29.1
40	3	mean	0.14	2.19	1.23	57.0	33.0
		SD	0.04	0.05	0.97	39.6	4.3
		range	0.11-0.18	2.14-2.24	0.4-2.3	23.4-100.6	29.8-37.9
55	4	mean	0.14	2.56	0.98	70.8	43.3
		SD	0.07	0.93	0.36	65.4	24.3
		range	0.06-0.23	1.19-3.28	0.7-1.5	26.5-167.7	25.0-78.8
70	3	mean	0.22	3.47	0.63	33.1	36.0
		SD	0.10	0.90	0.12	7.7	6.0
		range	0.15-0.33	2.90-4.51	0.5-0.7	28.1-42.0	29.1-40.3
90	5	mean	0.46	7.81	1.2	36.2	19.5
		SD	0.13	1.67	0.59	18.5	5.4
		range	0.27-0.57	5.95-9.82	0.6-2.1	18.2-58.8	15.0-28.6

Docetaxel plasma pharmacokinetic data after 24 hour infusion

Patient N°	Dose mg/m²	C_{24h} (µg/ml)	AUC (µg/ml.h)	$T_{1/2}$ (h)	Clearance (l/h)	V_1 (l)
	20	0.09	0.92		29.1	9.1
	40	0.11	2.18		29.8	100.6
	40	0.18	2.14		31.3	47
	40	0.13	2.24		37.9	23.4
	55	0.13	2.94		38.9	51.6
	55	0.23	3.28		25.0	26.5
	55	0.13	2.84		30.5	37.4
	55	0.06	1.19		78.8	167.7
	70	0.18	2.99		40.3	42.0
	70	0.33	4.51		29.1	29.3
	70	0.15	2.90		38.5	28.1*
	90	0.54	6.35		17.5	19.1
	90	0.39	9.05		15.0	18.2
	90	0.57	7.88		20.2	33.9
	90	0.52	9.82		16.3	51.4
	90	0.27	5.95		28.6	58.8

** Plasma data of patient N° 70 could be fitted to a two-compartement model and the calculated half-lives are t1/2α =0.7h and t1/2β =10.9 h with the corresponding distribution volumes V1=11.4 L and V_{ss}=136,5l*

STATISTICAL ANALYSIS:
Not given.

COMMENTS:
1. The labelling for Docetaxel is for a one hour infusion. This study is non-pivotal and gives information on the pharmacokinetics of docetaxel at other dosing schedules (see also TAX004 where the infusion rates were two to six hours every three weeks).

2. This study did not have complete assay validation information. Since it is not to be used as a pivotal study but supportive, the results are for cross-study comparison and not to be used for any substantial conclusions with regard to the pharmacokinetics. Should the firm want a change in labeling to support a 24 hour infusion, complete assay validation results will be needed.

DOSE ESCALATION STUDY: ONE HOUR INFUSION EVERY WEEK - supportive - pleural

TITLE:
A Phase I study of RP 56976 (docetaxel) administered as one hour intravenous infusion every week to cancer patients (**TAX 005 Vol.1.89, page 6-31-15**).

OBJECTIVES:
To determine:
1. the MTD of docetaxel under the studied regimen
2. the qualitative and quantitative toxicities of docetaxel; the recommended dose for Phase II clinical trials; the pharmacokinetics; and antitumor effects.

Clinical Investigator and Site:
Clinical Study Dates: Dec. 28, 1990 to June 22, 1992.

Subject Demographics:

	Dose-level (mg/m^2 /cycle)				
	20	80	100	110	130
No. Patients	1	1	5	3	1
Sex (M/F)	0/1	0/1	2/3	3/0	1/0
Age (years) Mean Range	 35 35	 49 49	 46 29-65	 54 38-63	 49 49

Drug Supplies:
Docetaxel in 50% polysorbate 80 and 50% dehydrated alcohol (Formulation #1, Batches CB 4445, 4579, 4587) and docetaxel in 100% polysorbate 80 (Formulation #2, Batch CB 4993).

STUDY DESIGN AND DOSAGE ADMINISTRATION:
Phase I, single-center, open-label, dose escalation study. At least three to six patients were at each dose level. There was no dose escalation within patient. Starting dose was 10 mg/m^2 and up to 110 mg/m^2 docetaxel was administered to patients. 13 of the patients had samples taken for pharmacokinetic determination. Two had insufficient information for full evaluation.

BIOLOGICAL SAMPLING:
Blood sampling was at pre-infusion, mid and end of infusion and at 5, 10, 20, 30, 60, 90 minutes, 2, 3, 4, 6, 8, 12 and 24 hours post-infusion. Urine samples were collected 0-6, 6-12 and

12-24 hours post start of infusion.

ANALYTICAL METHODOLOGIES:
HPLC with UV detection using the validated RPR method with modifications. Cross-validated with RPR assay method.

Analytical Site:
Analytical Dates: Dec. 1990-Jan. 1992

Specificity: Validated method of RPR - some differences in method used, such as manual extraction - see cross validation below.
Linearity: Validated RPR method
LOQ:15 ng/mL
Precision: Intra and inter-run reproducibility ranged from 1.7 to 23.4%.
Recovery: Validated RPR method.
Cross-validation: Comparative tables were given showing QC analysis. This information was satisfactory. The comparative concentrations from a pharmacokinetic sampling in a patient were less satisfactory. RPR method had a tendency to give higher values and some differences were as high as 32% where this particular concentration was not in the vicinity of the LOQ.

PHARMACOKINETIC RESULTS:
Pharmacokinetic data were obtained for 13 patients at their first infusion (day 1) and for 3 of them at a subsequent infusion on day 8 or day 15. Of these, 9 out 11 received doses ranging from 50 to 65 mg/m²; two others received 10 and 40 mg/m², respectively.
As in the short IV infusion studies, docetaxel plasma levels declined according to a triphasic profile. The first two phases were rapid with half-lives equal to 2.6 minutes and 0.36 hour. The third terminal phase was more prolonged with a half-life of 7.4 hours. It is important to note that in the pivotal studies where the third phase was only apparent at doses 70 mg/m², the ability to estimate a third phase of elimination at low dose (< 70mg/m²) was kept within the LOQ. In this study, however, measurements below the LOQ of 15 ng/ml were considered for data analysis. Such measurements were assigned a lower weight in the iterative no linear least squares regression than those above the LOQ.
Docetaxel clearance was not dose dependent with a mean value of 28.8 l/h/m² (data limited mostly to 50 to 55 mg/m² doses). Volume of distribution was 79 l/m². These values are in the range of those observed in previous studies.

Pharmacokinetic modeling was undertaken using ADAPT.

In this study, additional patients were investigated for end of infusion concentration both on their first day of treatment and on a subsequent infusion (21 patients). A significant diminution of the concentration was seen between first and subsequent administration. Comparison of AUC of the three patients who had a complete pharmacokinetic profile (15 samples) both at their first

administration and at a subsequent administration showed inconsistent results:

Patient # AUC_{0-24}

1782 (Day 1) 1388 (Day 15)
2195 (Day 1) 1719 (Day 5)
1289 (Day 1) 1674 (Day 5)

To compare a biweekly dose, the firm essentially has provided full pharmacokinetic data on just two patients (

An observation from this study: pharmacokinetic data obtained from the pleural fluid of one patient during two consecutive dosages (day 1 and day 15) - see the next figure - "showed that i) docetaxel concentration in pleural fluid (around 30 ng/ml) changed slowly and ii) docetaxel was present in pleural effusion at least 17 hours after infusion; at a time when simultaneous plasma docetaxel is not measurable."

. : Docetaxel Pharmacokinetic Parameters

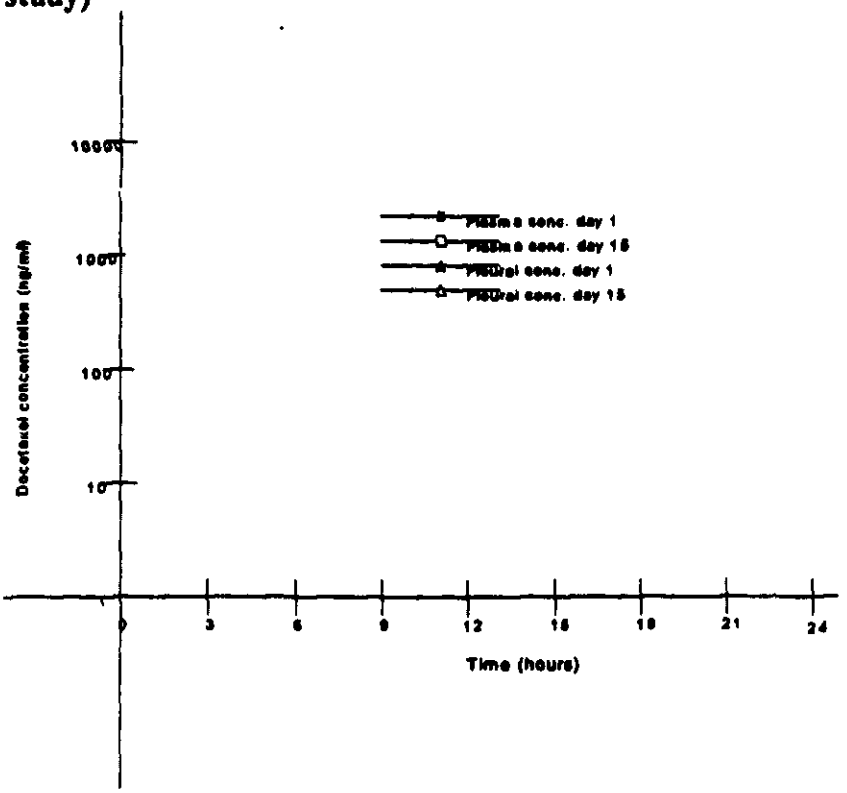
N° Pt	Day/ cycle	Dose mg/m²	Cmax * ng/ml	t 1/2 α min	t 1/2 β h	t 1/2 γ h	AUC h*ng/ml	CL l/h/m²	Vss l/m²	24 h Ur. Excr. % of dose
	1/1	10	275				300	33.4	11	-
-	1/1	40	1223				1654	24.2	30	1.6#
-	1/1	50	1452				1783	28.1	22	4.3
	15/1	50	1176				1388	36.0	16	3.3
-	1/1	50	1160				1844	27.1	249	3.4
-	1/1	50	1354				1744	28.7	78	3.0
-	1/1	50	1146				1242	40.3	16	0.4
-	1/1	50	2174				3341	15.0	278	3.2
-	1/1	55	1548				2479	22.2	166	1.9
	8/1	55	1610				1719	32.0	6	2.6
-	1/2	55	1022				1298	42.4	77	3.5
	8/2	55	1145				1700	32.4	43	2.8
-	1/1	55	1223				2105	26.1	123	3.3
-	1/1	65								2.0
	1/1	65	2676				4224	15.4	21	3.4
Mean				2.6**	0.36**	7.4**		28.8	79	2.8
CV%				34	45	73		28.2	100	42

Statistics on the results have been done on 10 patients and considering only the first dose administered. Patient has been excluded of the mean calculation because of the too large confidence interval of its terminal half-life.

** : actual peak level. # : 12 h interval = : formulation N°2.*

** : plasma parameters not available due to a discontinuous infusion ** : n = 9 (without*

Figure 6 : Plasma and pleural fluid docetaxel levels (Patient N°222, 50 mg/m², TAX005) study)



STATISTICAL ANALYSIS:

Intrapatient variability of end infusion concentrations was carried out comparing Day 1 and Day 8, using Wilcoxan's for matched data and t-test for single mean. AUC varied linearly with dose (N=13) in 10 patients, $r=0.786$, $p< 0.001$. However most of the data was collected from patients on either 50 or 55 mg/m² = 100 or 110 mg/m² /cycle.

COMMENTS:

This study is limited by the unsatisfactory assay cross-validation of pharmacokinetic plasma samples and the data being mostly from patients on two doses. One observation on pleural concentrations is supplied, but this can only give a very rough estimate of levels in the pleural cavity.

Note that Formulation 1 was used in this study except for one patient: the one on Formulation 2 showed very different PK parameters compared to those on Formulation 1 (CL of 15 l/h/m² for patient compared to the mean of 28.8 L/h/m² (%CV 29) and t1/2β of 63.8 h vs. mean of 7.4h (%CV 73)).

TABLE 1. PATIENT CHARACTERISTICS

#	SEX	AGE	PS (WHO)	WEIGHT (Kg)	HEIGHT (m)	TUMOR TYPE	PRETREATMENT	PK
	F	40	0	66.5	1.70	Humeral osteosarcoma with lung metastasis	2 CT regimens	
	F	35	0	47.0	1.62	Ovarian cystadenocarcinoma	2 CT regimens, 1 RT and 1 IT	+
	F	50	1	48.5	1.61	Ovarian adenocarcinoma	2 CT regimens	
	F	57	0	70.0	1.62	Ovarian adenocarcinoma	5 CT regimens	+
	F	55	2	54.0	1.56	Ovarian adenocarcinoma with pelvic, abdominal and inguinal metastasis	5 CT regimens and 2 RT	
	F	47	0	60.0	1.63	Ovarian adenocarcinoma	2 CT regimens and 1 RT	
	F	49	0	49.0	1.56	Stade III ovarian serous adenocarcinoma	4 CT regimens	+
	M	47	0	100.0	1.90	Non small cell lung carcinoma with left shoulder metastasis	None	
	F	44	2	60.0	1.64	Ovarian adenocarcinoma	1 CT and 1 RT	
	M	60	0	82.0	1.80	Sigmoid adenocarcinoma with hepatic metastasis	4 CT regimens	+
	F	42	0	58.0	1.55	Breast adenocarcinoma	6 CT and 1 RT	
	M	62	0	60.0	1.56	Caecal adenocarcinoma	1 CT	
	F	56	0	67.0	1.53	Bilateral ovarian adenocarcinoma	2 CT regimens	
	M	59	0	57.5	1.65	Adenocarcinoma of unknown origin	4 CT regimens	

F	65	1	69.0	1.58	Thyroid anaplastic epithelioma	RT	
F	52	1	55.0	1.55	Breast adenocarcinoma	4 CT regimens and 2 RT	
F	59	1	50.0	1.60	Ovarian adenocarcinoma	2 CT regimens	
M	38	0	56.0	1.68	Sigmoid adenocarcinoma	2 CT regimens	+
F	46	2	55.0	1.63	Adenocarcinoma of unknown origin with hepatic and pulmonary metastasis	1 CT regimen	
F	64	1	59.0	1.51	Stade IV ovarian adenocarcinoma	3 CT regimens	
M	63	1	84.0	1.70	Mesothelioma		+
F	38	3	47.0	1.67	Breast cancer with pulmonary and bone metastasis	4 CT regimens and 1 RT	+
F	51	1	60.0	1.71	Breast cancer with hepatic and bone metastasis	3 CT regimens and 1 RT	
F	54	1	90.0	1.70	Breast cancer	3 CT regimens	
F	53	2	53.0	1.66	Ovarian adenocarcinoma	2 CT regimens	
F	64	0	46.0	1.58	Ovarian adenocarcinoma	1 CT regimen	+
F	48	1	56.0	1.69	Colon adenocarcinoma with hepatic metastasis	1 CT regimen	+
F	48	0	61.0	1.55	Ovarian adenocarcinoma	3 CT regimens	
F	61	1	85.0	1.75	Colon adenocarcinoma with supra clavicular metastasis	2 CT regimens	
M	42	1	55.0	1.78	Small cell lung cancer	1 CT regimen	
M	29	1	47.0	1.80	Femoral osteosarcoma with mediastinal and pulmonary metastasis	2 CT regimens and 1 RT	+
M	55	0	80.0	1.79	Adenocarcinoma of unknown origin	1 RT	+

	F	40	0	67.0	1.79	Breast cancer	2 CT regimens	
	F	65	1	54.0	1.62	Ovarian cystadenocarcinoma	4 CT regimens	+
	F	42		57.0	1.55	Breast cancer with axillary metastasis	4 CT regimens and 1 RT	+

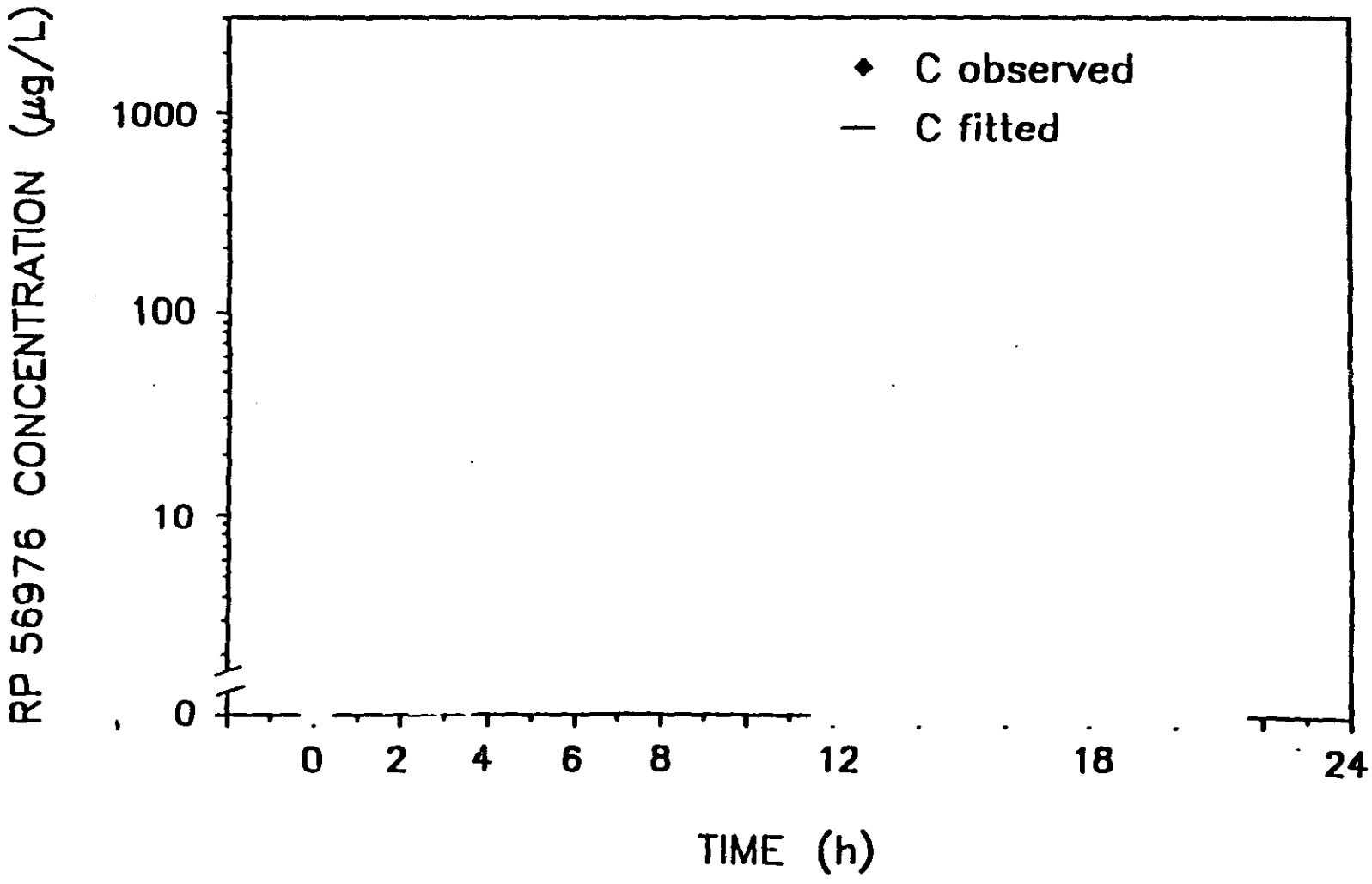
PK, pharmacokinetic study; CT, chemotherapy; RT, radiotherapy; IT, immunotherapy

TABLE 5. RP 56976 PHARMACOKINETIC PARAMETER VALUES AT MTD AND PHASE II DOSE

n/pt	Dose mg/m²	TotDose mg	Cpeak µg/L	T½α min	T½β min	T½γ h	AUC_{24} µg/L*h	AUC_{∞} µg/L*h	TBC L/h/m²	VSS L/m²
5/3	55	101.2	1282				1772	1860	31	83.0
			(23.2)				(19.3)	(24.1)	(24.7)	(76)
5/4	50	82	1148				1537	1600	32	76
			(15.8)				(14.4)	(16.7)	(18.1)	(132)

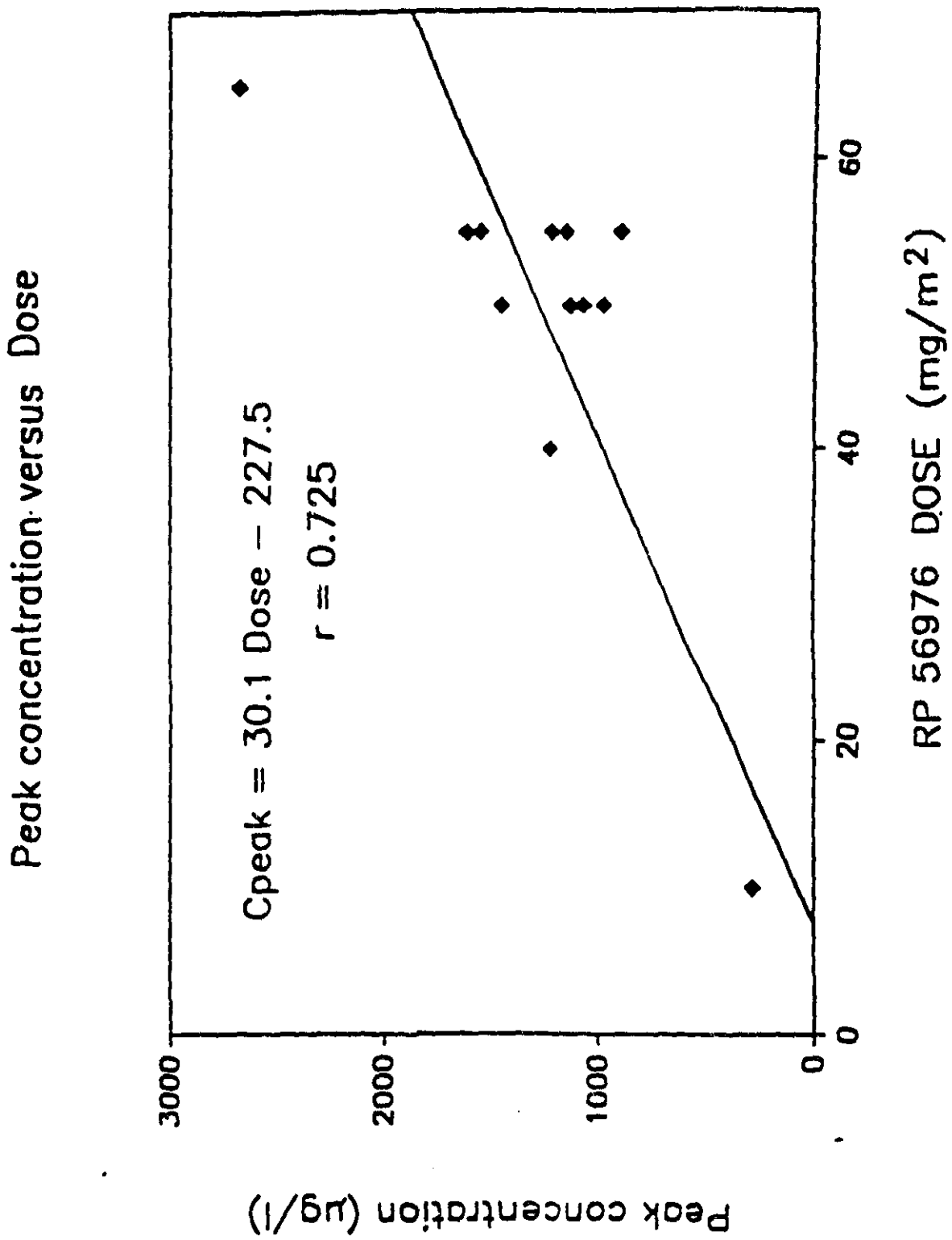
(CV %)

PLASMA CONCENTRATION VERSUS TIME PROFILE (50 mg/m^2)

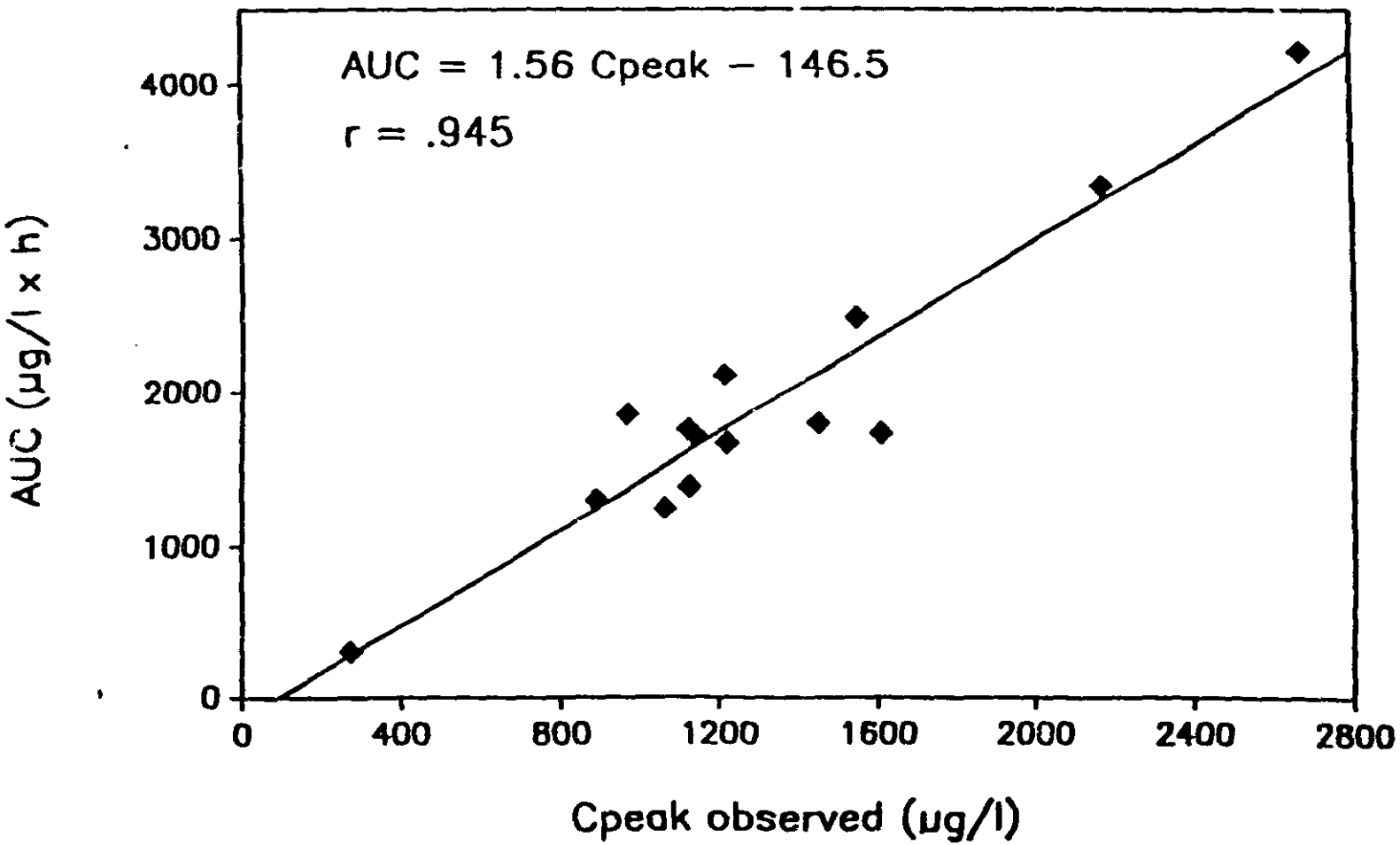


GRAPH 1

6-31-293


Peak concentration versus Dose
Cpeak = 30.1 Dose – 227.5
r = 0.725
Peak concentration (µg/l)
RP 56976 DOSE (mg/m2)
3000
2000
1000
0
0
20
40
60

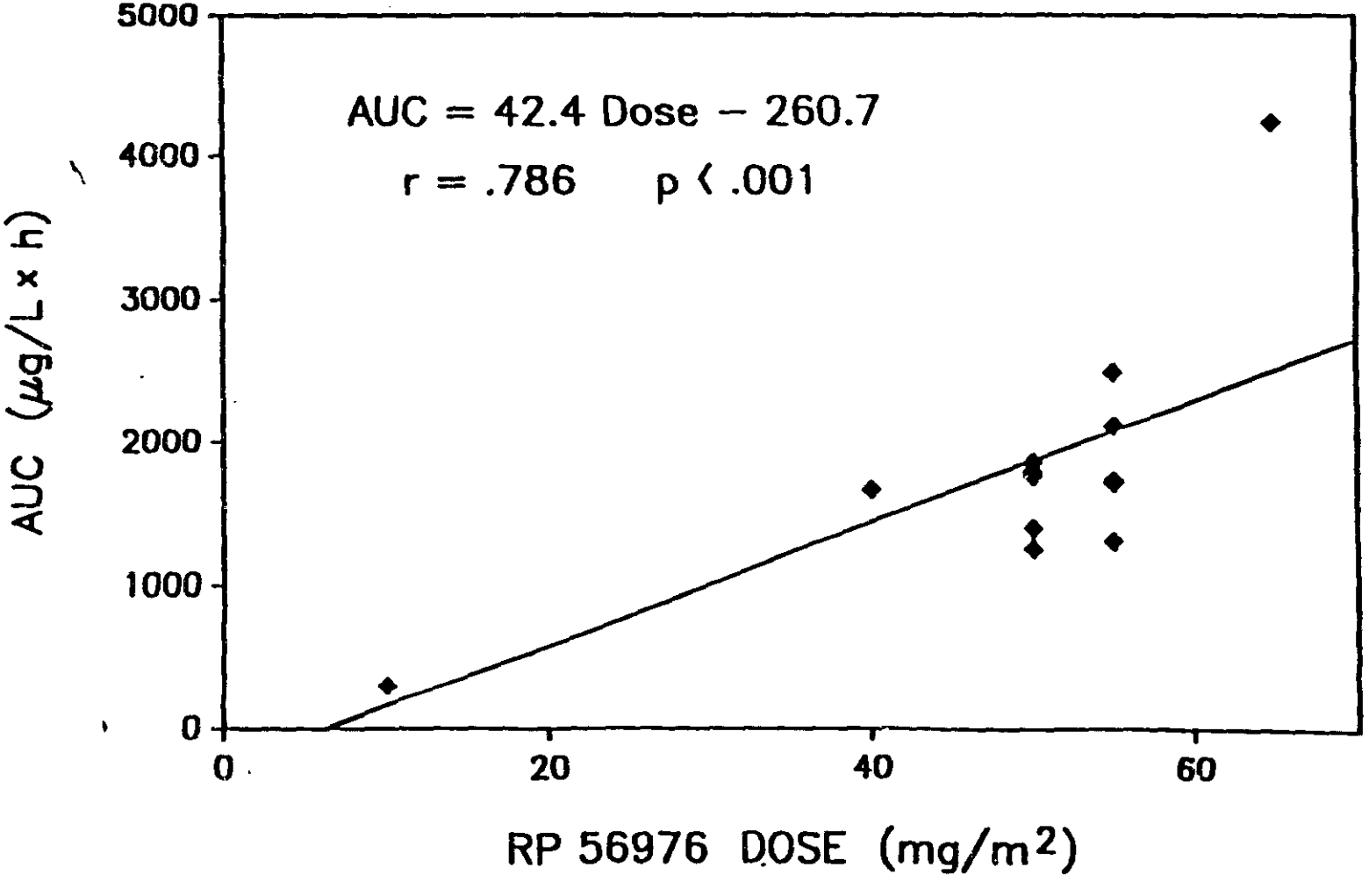
AUC o–infinity versus Concentration at time of the peak



GRAPH 3

6-31-295

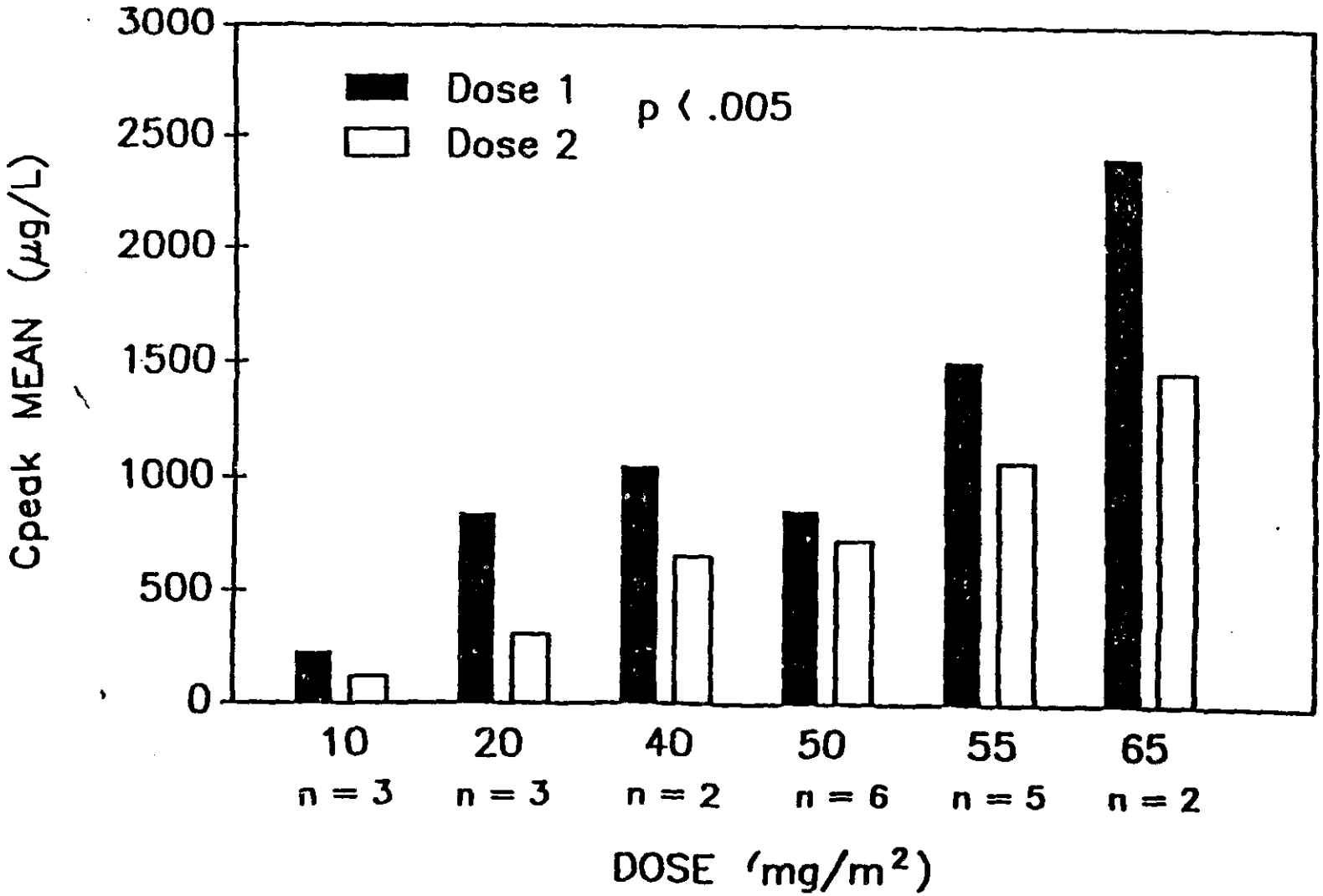
RP 56976 AUC VERSUS DOSE



GRAPH 4

6-31-296

RP 56976 INTRAPATIENT VARIABILITY



6-31-297

GRAPH 6

37

RP 56976 CONCENTRATION VERSUS TIME PROFILES

GRAPH 6

6-31-298

DOSE ESCALATION STUDY - used to illustrate multi-dose
TITLE: Phase I trial of RP 56976 administered as a single daily infusion for 5 days every 3 weeks (TAX003 Vol. 1.72, page 6-14-15).

OBJECTIVES:
1. To determine the MTD of docetaxel administered as a single daily infusion for 5 consecutive days every 3 weeks.
2. To determine the qualitative and quantitative toxicity and reversibility of toxicity of docetaxel when administered as such.
3. To determine the clinical pharmacology of docetaxel.
4. To determine any antitumor effect.

Clinical Investigator and Site:
TX Clinical Study Dates: December 27 1990 to January 21 1993.
Subject Demographics:
1 male, 11 females
Male Age=55 yr, Height=180 cm, Weight=91.6 Kg, BSA=2.11m^2
Females Means (SD) Age=61(9.4) yr, Height=166 cm (8.1), Weight= 69.4 Kg(17.3), BSA=1.77m^2 (0.22).
Drug Supplies:
Batch #'s CB 4579, CB4587: Docetaxel 15 mg/m^2 in 50% polysorbate 80 and 50% dehydrated alcohol (Formulation #1, used before May 1991) and Batch #'s CB 5140, CB 5327: Docetaxel 40 mg/m^2 in polysorbate 80 (Formulation #2, used after May 27th, 1991).

STUDY DESIGN AND DOSAGE ADMINISTRATION:
Phase I dose-escalating open-label nonrandomized single-center study. pharmacokinetic sampling taken during cycle 1 Day 1 through Day 5. Docetaxel was infused over one hour. The vials are diluted to give a concentration of polysorbate 80 of no greater than 2% (more often 1% v/v?) for Formulation #1 and a concentration of 2.5% of polysorbate for Formulation #2 .
BIOLOGICAL SAMPLING:
Blood samples were obtained at pre-infusion, 20 and 40 minutes during infusion, end -of infusion and then 5, 10, 15, 30, 60, 90 and 2,4, 6, 8 and 12 hours post-infusion on Day 1Day 5 (with additional sample at 24 hours). Day 2, 3, 4 sample times were pre-infusion, 20 and 40 minutes during infusion and at the end of infusion.

ANALYTICAL METHODOLOGIES:
HPLC with UV detection. Little assay details given. The firm response 11/7/94 to enquiries on assay validation for this study . They re-affirmed that no formal validation of the assay was available. There was some cross-validation between RPR and this group, bu the results were not considered reliable. THe MD Anderson assay gave consistently lower estimates compred to RPR. Therefore conclusions drawn from this study can only be tentative.
Analytical Site:
Analytical Dates: Not given

Specificity: Not given
Linearity: Not given. Range stated to be 15 to 750 ng/mL
LOQ:15 ng/mL
Precision: Values for standard curves run for each patient given. No statistics (such as %CV).
Recovery: Not given.

PHARMACOKINETIC RESULTS:
The daily dose was 1/5 of the single infusion protocols and therefore daily dose escalation ranged between 12 and 16 mg/m². The time interval over which docetaxel was quantified was 5 hours. The LOQ of the assay was reached fairly rapidly. Plasma profiles showed only the first 2 phases of the higher dose studies (ie >70 mg/m²): the mean apparent terminal half-life was 4.7 hours. Pharmacokinetic parameters were obtained on days 1 and 5 at dose level 16 mg/m² (6 patients) and showed that the mean Cmax, AUC and CL did not differ between occasion, consistent with lack of drug accumulation.
Total clearance was similar at all doses administered. Mean estimates were higher (41.3 l/h/m² or 28.4 l/h/m²) than those determined in studies carried out at higher doses. Vdss was highly variable (%CV 94% - probably a reflection of poor estimation of the terminal rate constant, since the method of estimation was Vdss=Dose $(A/\alpha^2 + B/\beta^2)/AUC^2$).

Individual pharmacokinetic parameters can be summarized:

Table 22: Mean (SD) Docetaxel Pharmacokinetic Parameters

DOSE mg/m²	DAY	NUMBER OF PATIENTS	CMAX, RANGE NG/ML	AUC ng.h/ml	T 1/2 α h	T 1/2β h	CL l/h/m²	VSS l/m²
12	1	3	55-286	565 (406)	.012*	9.6*	52.3 (64.5)	311 (118)
14	1	3	219-521	392 (151)	0.05*	1.0*	39.9 (16.7)	11 (6)
16	1	6	124-631	488 (319)	0.09 (0.06)	3.8 (2.4)	43.5 (22.0)	133 (125)
16	5	5	211-685	580 (273)	0.11 (0.07)	3.6 (1.6)	32.9 (15.1)	73 (67)
ALL	ALL	ALL	55-685		0.10 (0.6)	4.7 (1.7)	41.3 (28.4)	125 (133)

The investigator calculated harmonic mean for t 1/2α and t 1/2β at 12 and 14 mg/m²

The investigators also looked at a possible relationship between AUC and % decrease in absolute granulocyte count modeled using sigmoidal Emax model. This was part of a published paper. No details (results, data used etc.) were given in the volume submitted

COMMENTS:

1. A more accurate estimate of Vdss may have been obtained using moment analysis and AUC, since AUC's probably are more accurately determined and not dependent on capturing sufficient information from the terminal portion of the plasma-time curve.

2 Incomplete information was given on the assay in terms of validation and in 11/7/94 correspondance this will not be available.

3. Individual results from Emax published study requested but will not be available according to the firm.

Taxotere Pharmacokinetics

Patient	Cmax (ng/ml)		Vdss (L/m^2)		AUC (ng·h/ml)		Clt L/h/m^2		t½α (h)		t½β (h)	
mg/m^2	Day1	Day5	Day1	Day5	Day1	Day5	Day1	Day5	Day1	Day5	Day1	Day5
Mean	163.8		310.7		564.9		52.3		0.12 *		8.6 *	
±	116.1		118.2		407.9		64.5					
	70.7%		37.9%		72.2%		123.3%					
m/m^2												
Mean	366.8		11.1		391.6		39.9		0.05 *		1.0 *	
±	151.3		5.5		150.8		16.7					
	41.1%		49.6%		38.5%		41.9%					
m/m^2												
11												
12												
Mean	365.2	411.5	132.8	72.7	487.6	580.0	43.5	32.9	0.09	0.11	3.8	3.6
SD ±	204.0	226.0	125.4	67.0	318.8	273.3	22.0	15.1	0.06	0.07	2.4	1.6
CV	55.9%	54.9%	94.4%	62.3%	65.4%	47.1%	50.0%	45.8%	66.7%	63.6%	63.2%	44.4%
h	198.9	323.4	20.6	38.9	340.4	486.7	27.9	27.6	0.06	0.06	1.7	3.2

ND - Not Done, SD - Standard Deviation, CV - Coeffiecient of Variation, h - Harmonic Mean for 16 mg/m^2, * - Harmonic Mean

POPULATION PHARMACOKINETICS:

META-ANALYSIS OF PHASE I STUDIES

TITLE:
Meta-analysis of data from two Phase I studies (**TAX001,TAX006**) and design of a limited sampling strategy for Phase II studies (**Vol. 1.96, page 6-38-6**).

OBJECTIVES:
1. To estimate the preliminary docetaxel population pharmacokinetic parameters
2. To design a limited sampling strategy

Number of Subjects: 26 (There were potentially 35 with pharmacokinetic data . Those patients with data who were dosed from 5 to 55 mg/m^2 were not included).

METHODOLOGY:
A population pharmacokinetic approach using NONMEM (nonlinear mixed effect modeling) was applied to the Phase I data. APIS is a local French program used in the limited sampling strategy. A sparse sampling strategy was implemented in Phase II studies to perform a prospective population PK/PD analysis of docetaxel.

The NONMEM program used was double precision, version III, level 1.2 with the NMTRAN pre-processor on a Digital DEC station 5000/240 and an ULTRIX operating system.

ADVAN 3, TRANS 3 and ADVAN 5, TRANS 1 were subroutines tried from PREDPP.

Inter-patient variability was modeled according to the constant CV model for CL and residual variability was also modeled as constant CV model. The difference in the objective functions was used to compare the models. Plots of PRED the model prediction vs. measured concentrations, DV and weighted residuals (WRES) vs. time and PRED were used to compare outputs.

Optimal sampling times (OST) were obtained using the D-optimality theory from simulation of docetaxel plasma profiles for typical patients and parameter estimation from NONMEM. Secondary pharmacokinetic parameters were also calculated. All of this was computed using APIS.

RESULTS:
The optimal sampling results indicated core times (see following tables). These were modified for the purpose of a population sampling strategy to vary across patients and take into consideration time constraints of patients who are outpatients.

Table 3 : RP 56976 (docetaxel) TAX 001 - TAX 006 studies population PK analysis : Optimal sampling times (h:min) over various observation intervals for a 1 hour infusion of docetaxel

Interval	Times								Information
0:00 - 24	0:0	0:41	-	-	1:39	3:40	8:19	24:00	21.08
0:92 - 24	-	-	1:00	1:15	1:46	3:46	8:19	24:00	21.11
0:30 - 24[a]	-	0:30	-	1:15	1:45	3:45	8.22	24:00	21.19
	-	-	1:0	1:15	1:45	3:45	8.22	24:00	21.11
Core times	-	0.30 - 1:00		1:15	1:45	3 - 4	8 - 9	24	

[a] estimates for different initial values with similar information content

Table 4 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Sampling strategy implemented in Phase II studies

Protocol N°	Sampling times			
	0 Pre-drug	1 During Infusion	2[a] After Infusion (min)	3 After Infusion (hours)
1	before inf.	5 min before end	10	2
2	before inf.	30 min after start	20	3
3	before inf.	5 min before end	30	4
4	before inf.	30 min after start	60	5

[a] when possible this sample will be replaced by a blood sample obtained at a later time : any time between 12 and 24 hours post infusion

The NONMEM analysis indicated that a three compartmental model was more appropriate. The results can be found in the following tables:

Table 2 : RP 56976 (docetaxel) TAX 001 - TAX 006 studies population PK analysis : Docetaxel pharmacokinetic parameters estimated using a 3 compartment pharmacokinetic model for different PK data bases

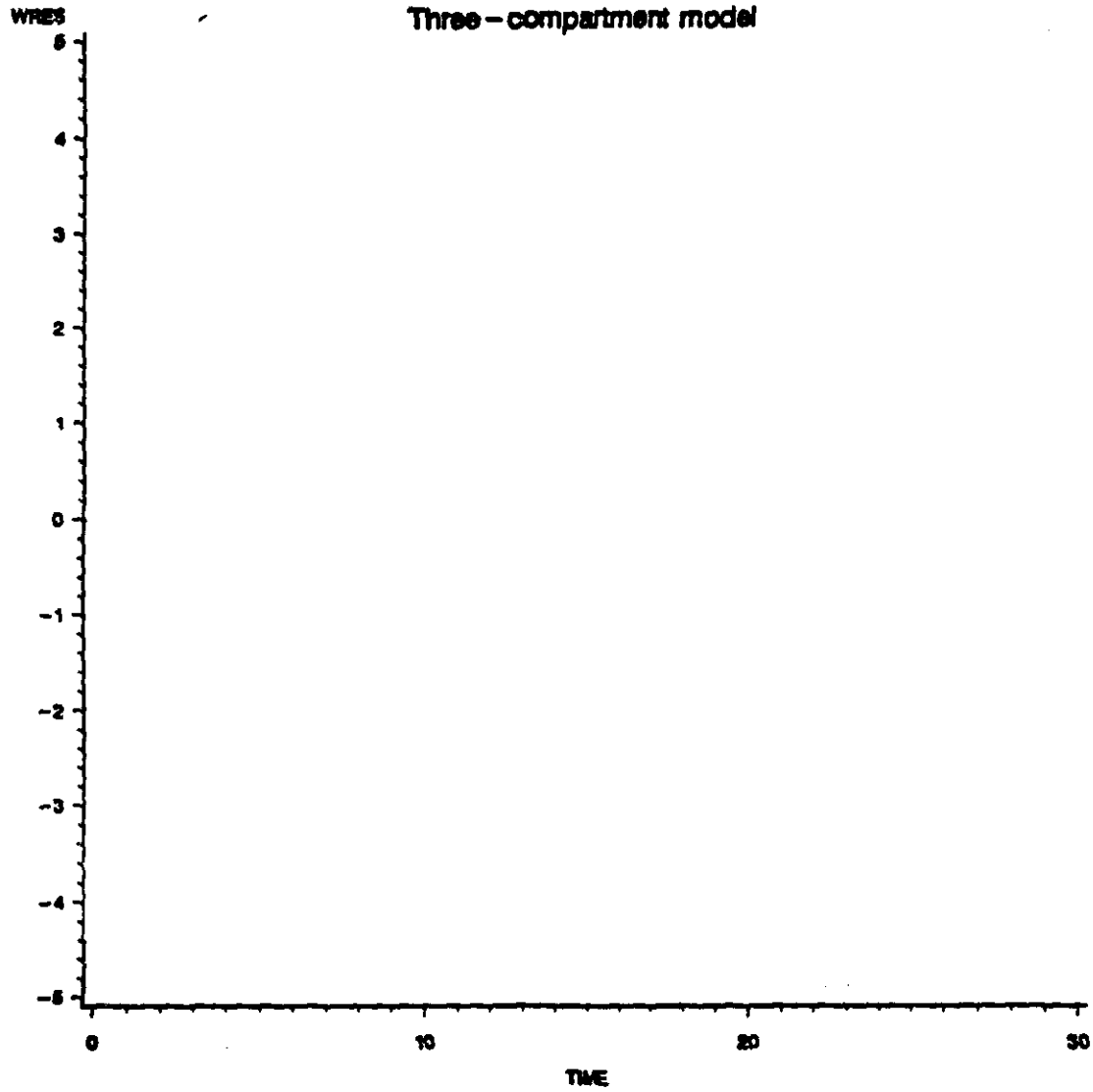
Data base	preliminary	final (1st course)
Patients	24	26
Courses	28	26
CL (l/h)	36.8 (5.8)	35.3 (6.0)
V_1 (l)	6.34 (18.8)	5.39 (16.2)
K_{12} (h^{-1})	1.12 (23.2)	1.45 (20.8)
K_{21} (h^{-1})	1.07 (26.7)	1.39 (21.9)
K_{13} (h^{-1})	1.25 (14.4)	1.46 (12.9)
K_{31} (h^{-1})	0.068 (22.9)	0.077 (16.1)
ω CL (%)	21.0 (30.2)	21.7 (30.7)
σ (%)	27.0 (14.0)	25.1 (13.9)
K_{10} (h^{-1})	5.8	6.5
Vss (l)	129	113
$t_{1/2\alpha}$ (min)	5.0	4.3
$t_{1/2\beta}$ (min)	45.8	36.2
$t_{1/2\gamma}$ (h)	12.4	11.1

( ) CV of estimation

DOCETAXEL

Phase I Studies

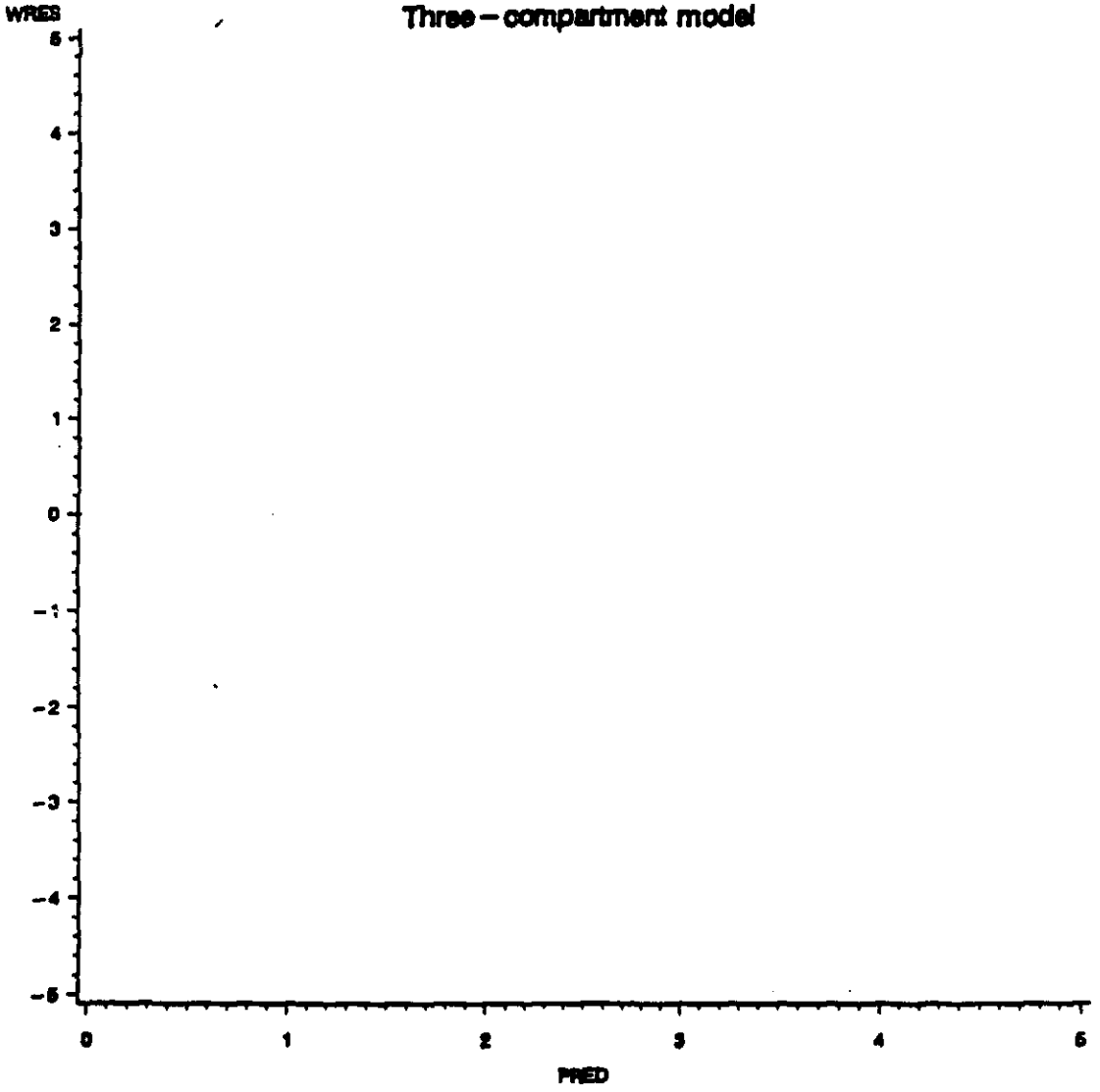
Three – compartment model



DOCETAXEL

Phase I Studies

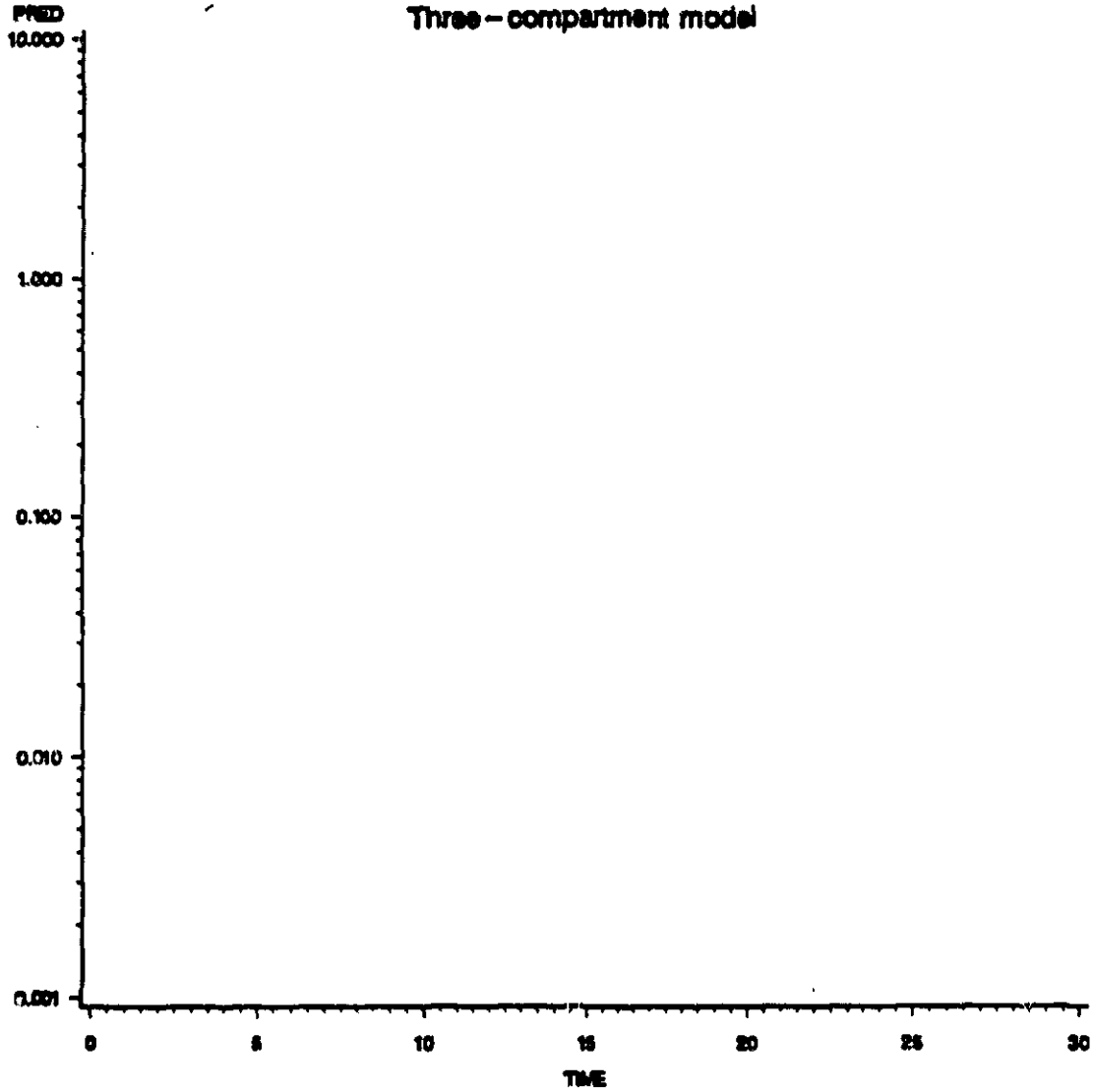
Three – compartment model



DOCETAXEL

Phase I Studies

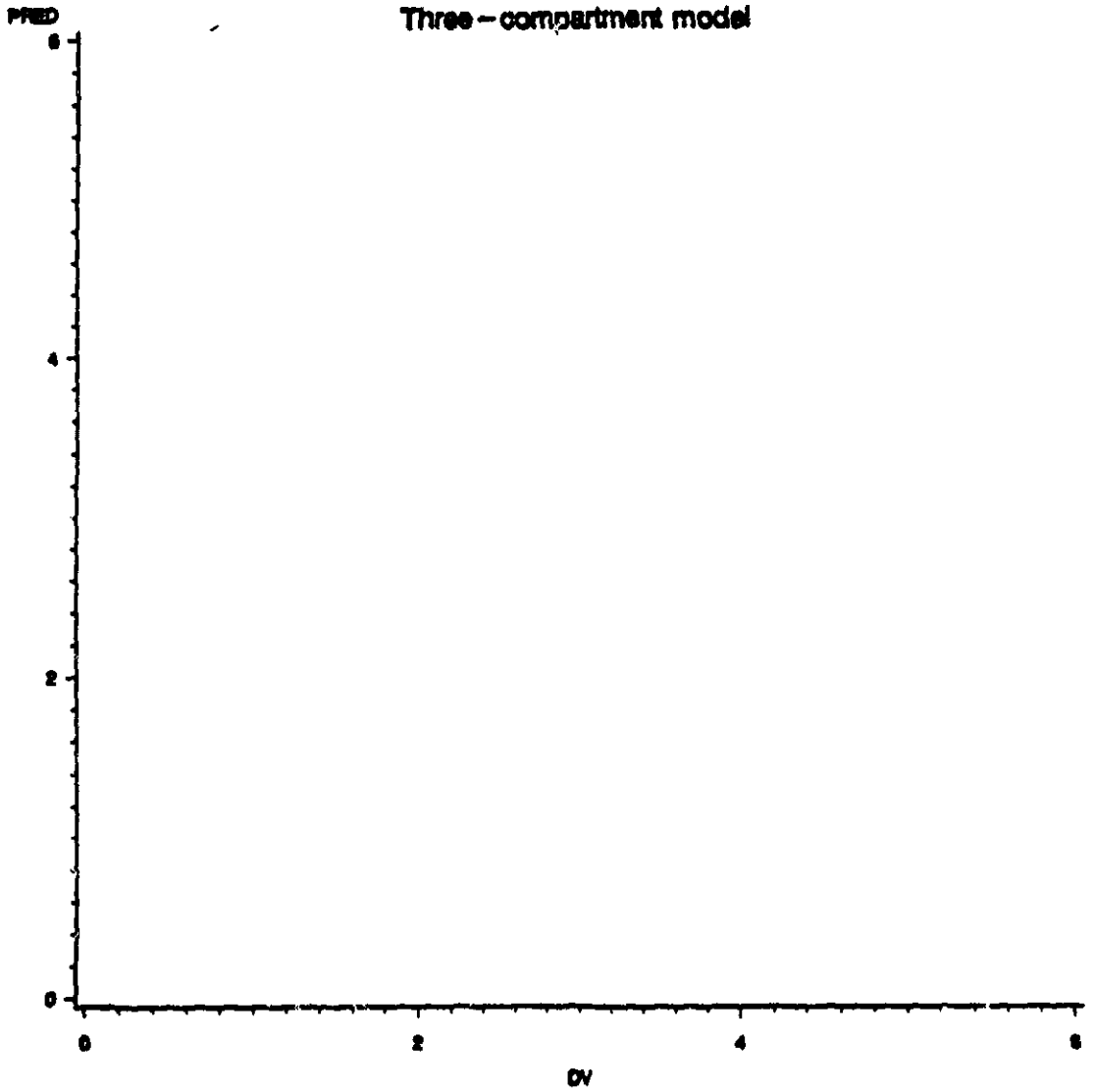
Three-compartment model



DOCETAXEL

Phase I Studies

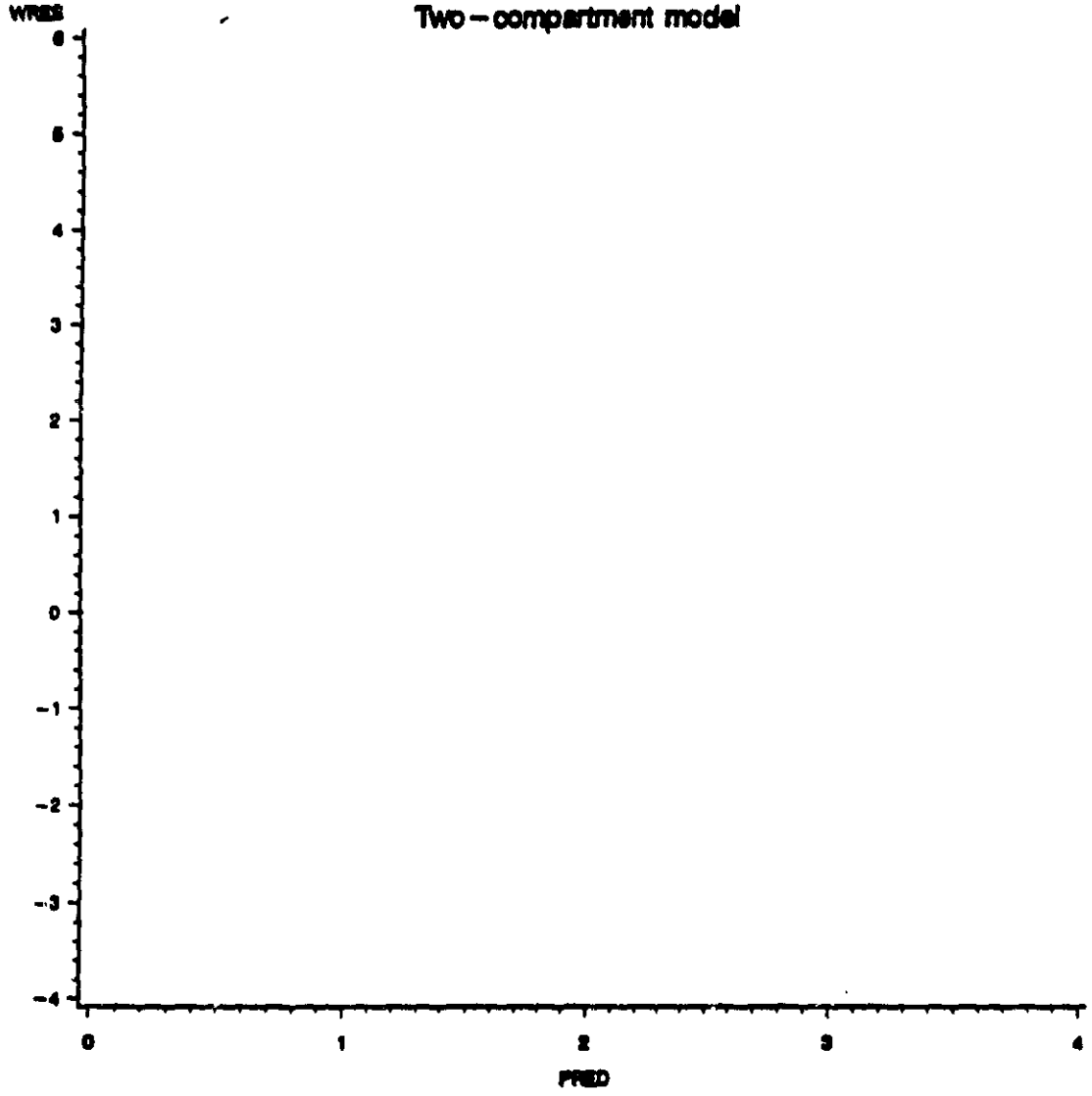
Three – compartment model



DOCETAXEL

Phase I Studies

Two – compartment model



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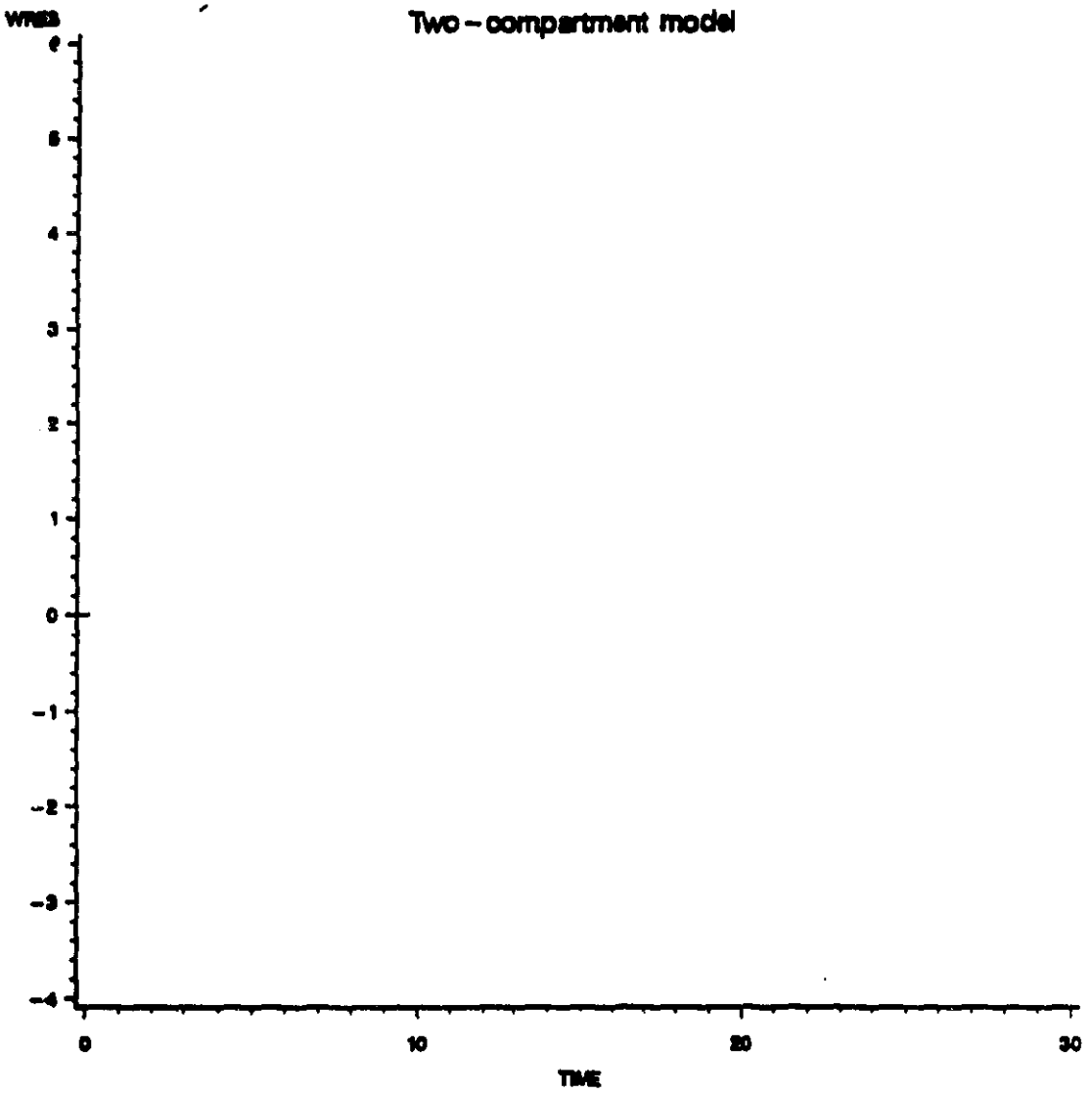
DOCETAXEL

Phase I Studies

Two – compartment model



DOCETAXEL

Phase I Studies

Two – compartment model

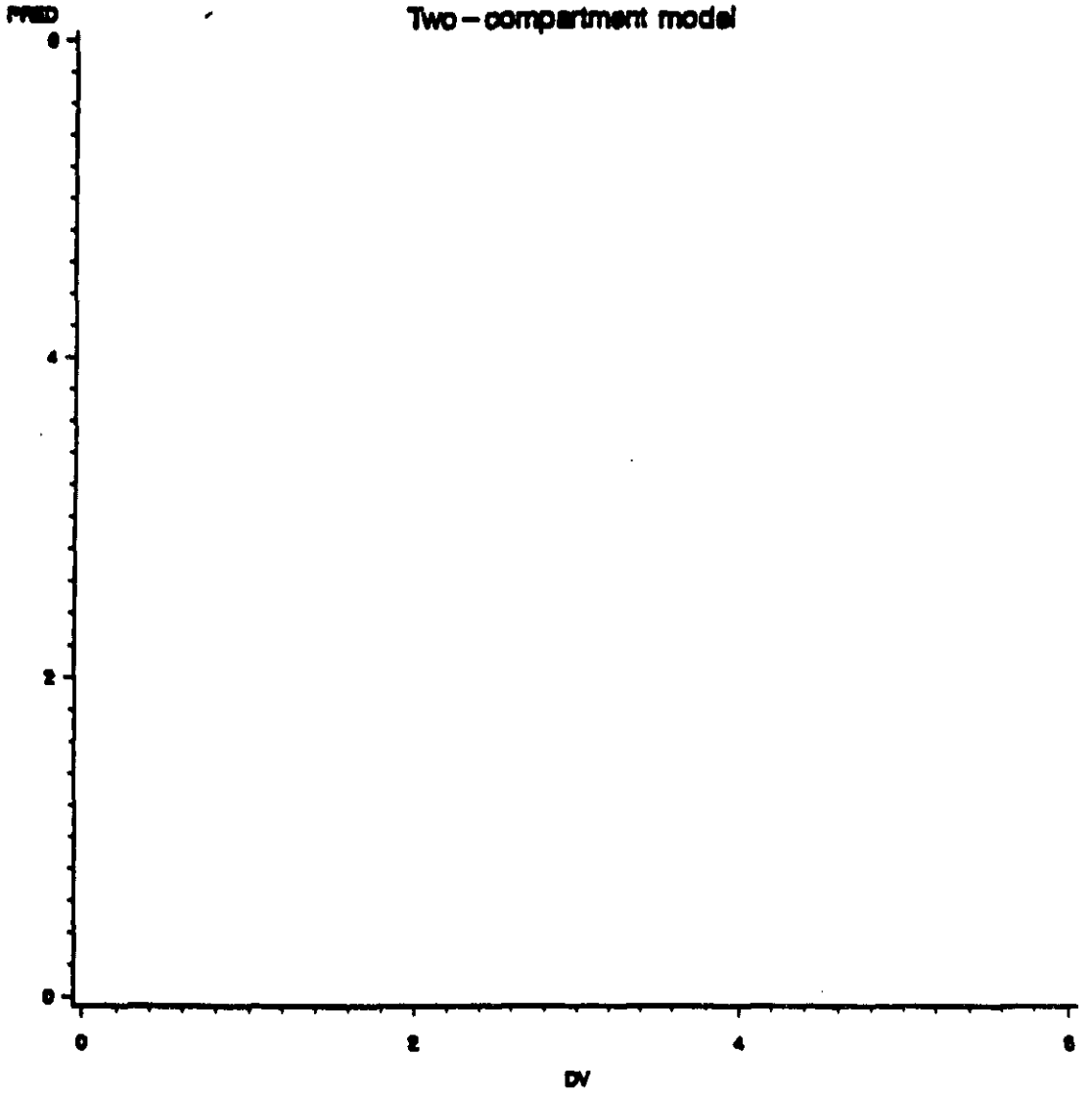


Figure 2

Pooled data from Phase I studies

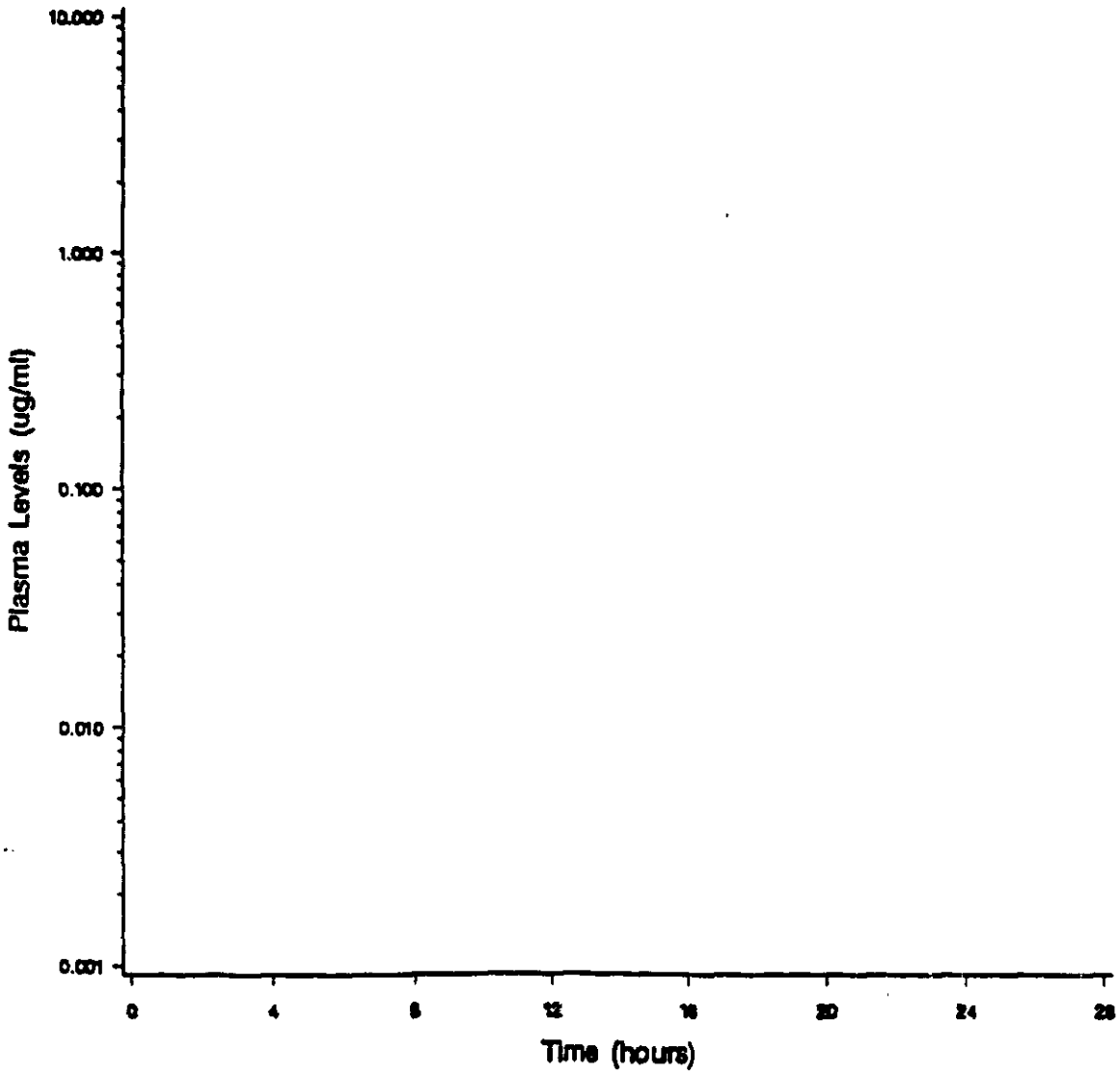


Figure 4

Optimal sampling times

(1-hour infusion)

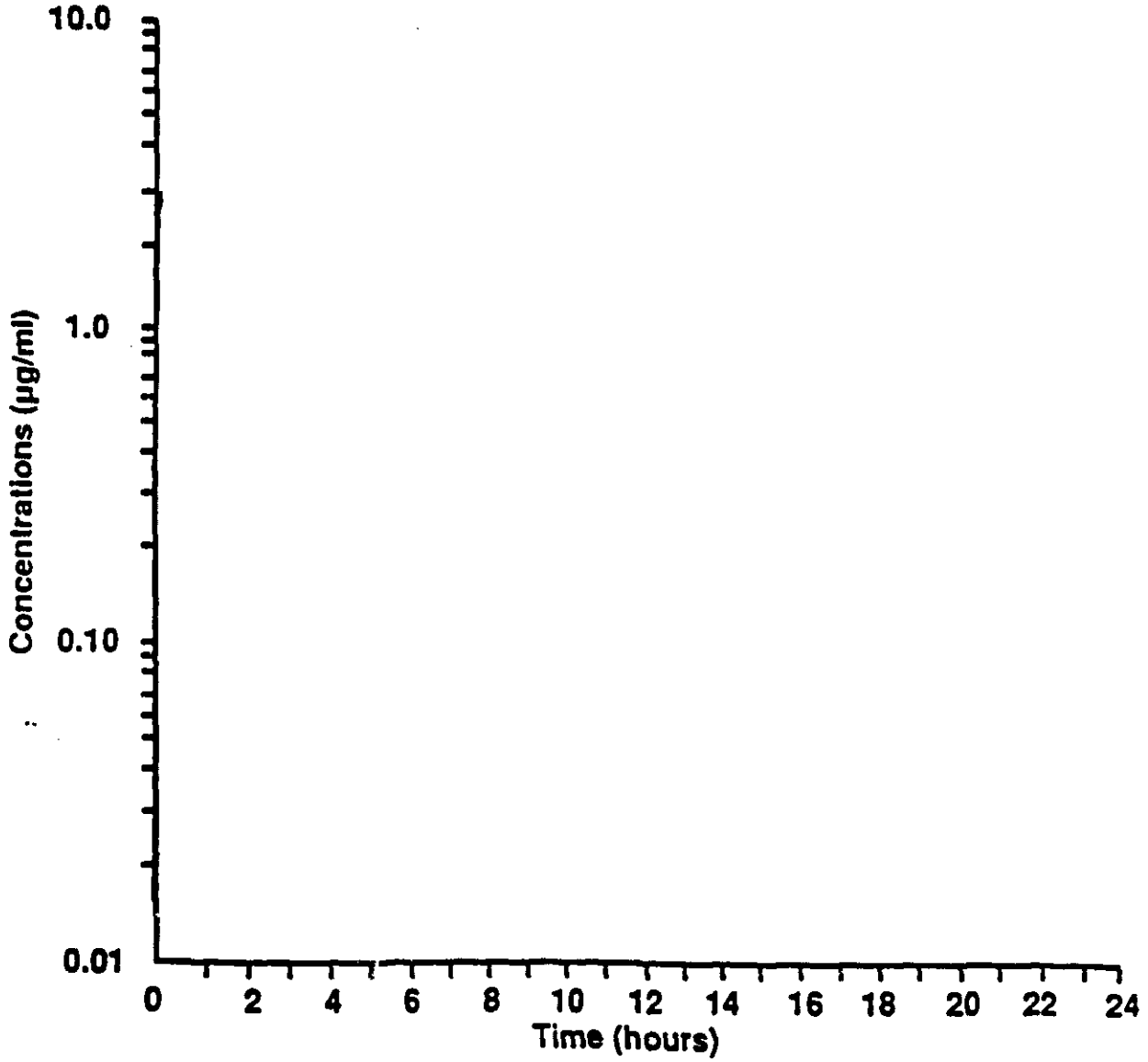


Figure 3

Simulated profiles following dosing of 100 mg/m² (168 mg, 1-hour infusion)

Two-compartment① vs. three-compartment② models

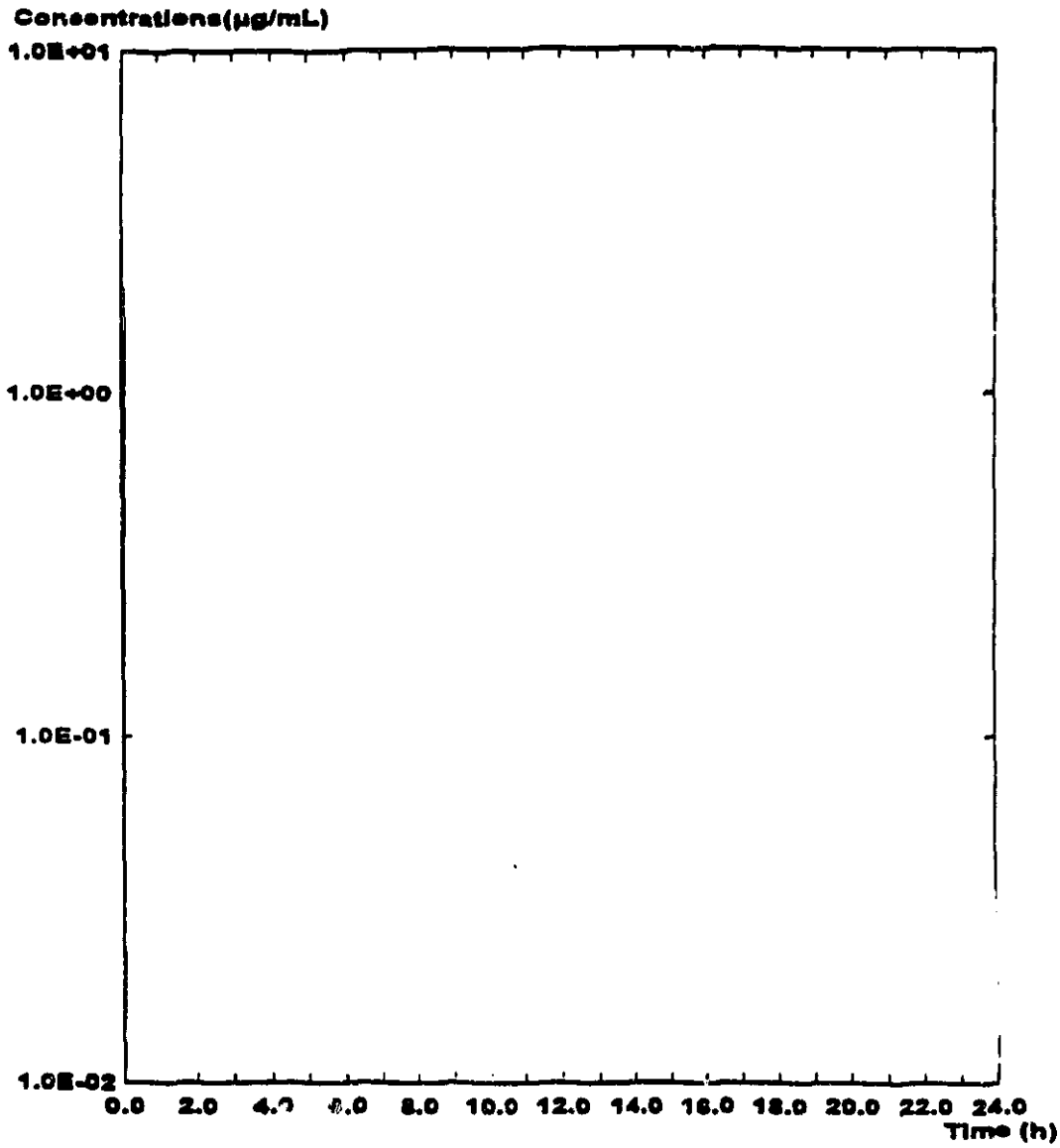


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Figure 1

Typical individual pharmacokinetic profiles

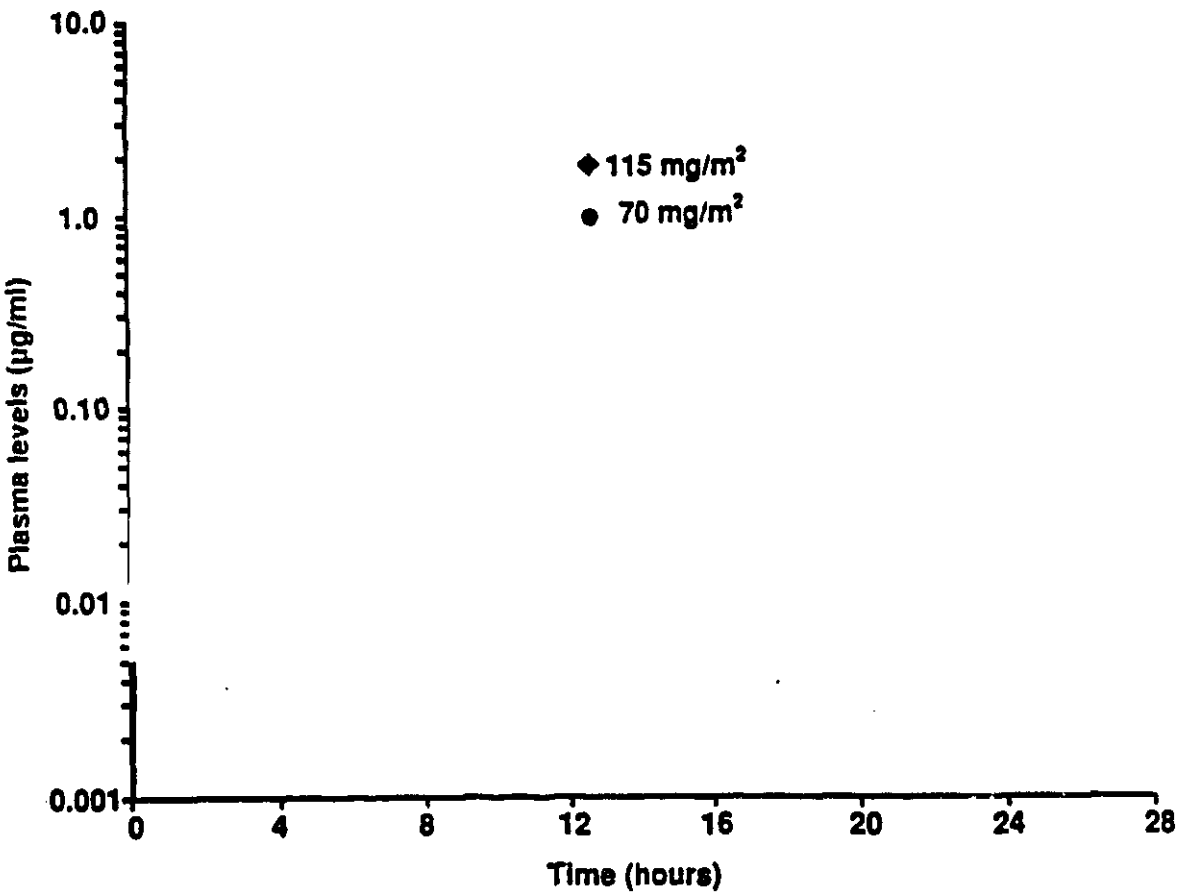

Table I : RP 56976 (docetaxel) TAX 001 - TAX 006 studies population PK analysis : Summary of patient characteristics (n = 26 patients)

	Mean (SD)	Range
Age (years)	52.3 (8.0)	
Weight (kg)	61.4 (10.7)	
Height (cm)	168.0 (6.2)	
Body surface Area (m^2)	1.68 (0.16)	
Alanine Amino Transferase [a] (IU/L)	27.9 (20.6)	
Bilirubin [a] (µmol/L)	9.6 (4.8)	
Total protein[a] (g/L)	68.9 (7.8)	
Plasma creatinine [a] (µM)	87.1 (17.8)	
Formulation (1/2)	14/12	
Sex (M/F)	9/17	
Performance Status (0/1/2)	8/17/ 1	
Hepatic Metastasis (Yes/No)	8/18	

[a] n=25 patients

No Page
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Patients were entered into the database as their clinical data were made available, so the index set consisted of the first patients entered into the studies and the validation set consisted of subsequent patients ie. the patients were not randomized between the two sets.

Table 4 (page 72) shows the patient population and Table 9 (page 77) shows the patient population in terms of the different sets.

Phase II trial design and treatment:

These were nonrandomized open studies.

Dose: Docetaxel 1 hr infusion every 3 weeks

Formulation: Formulation #2

Patient inclusion restrictions to note: Adequate renal function ie creatinine ≤ 140μmol/L. Adequate hepatic function ie total bilirubin ≤ 1.25 upper normal limit, SGOT (AST) ≤ 2 upper normal limit and ≤ 3 upper normal limit in liver metastases.

Comment: The database is limited in testing extremes because severe renal and/or liver impaired patients have been excluded.

Blood sampling:

The sampling strategy was based on practicality and optimal sampling times (see page 44 on this) and is repeated for clarity in the table:

Table 3 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Sparse sampling strategy implemented during first cycle in Phase II studies

Schedule N°	Sampling times			
	0 Pre-drug	1 During Infusion	2[a] After Infusion (min)	3 After Infusion (hours)
1	before inf.	5 min before end	10	2
2	before inf.	30 min after start	20	3
3	before inf.	5 min before end	30	4
4	before inf.	30 min after start	60	5

[a] when possible this sample will be replaced by a blood sample obtained at a later time any time between 12 and 24 hours post infusion

Actual sampling times and the begin and end times of infusion were recorded by investigators.

Phase II assay:

Analytical sites: RPR, France and Pharmaco LSR, Inc. Richmond, VA, USA.

Analysis dates: Sept. 8 1992 to March 25 1994 (RPR analytical site).

For validation see Assay Validation section as part of this review (page 113).

The assay information given: specificity, reproducibility, precision, assay system for RPR site was acceptable and very similar to that of the assay validation report for RPR site.

NONMEM Analysis:

The NONMEM program used was double precision, version IV, level 1.0 with the NMTRAN pre-processor running on a Digital DEC station 5000/240 and the ULTRIX operating system. A three compartment model with first order elimination was used ie PREDPP subroutines ADVAN 5, TRANS 1, so the basic parameters were CL, Volume of distribution of central compartment V_1 and inter- compartmental rate constants K_{12},K_{21},K_{13},K_{31} h^{-1} and the elimination constant K_{14} was defined as CL/ V_1.

Inter-patient variability was modelled for example CL, as:

$CL_j = {}^{\wedge}CL_j \exp(\eta_j CL)$

$\eta_j CL$ is the proportional difference between the true parameter CL_j of the j individual and the typical value ${}^{\wedge}CL_j$ for an individual in the population.

The inter-patient variability being ω^2

The residual variability was modelled as a proportional error model:

$Cp_{ij} = \sim Cp_{ij}(1 + \epsilon_{ij})$

ϵ_{ij} is the residual intra-patient random error with variance σ^2

Cp_{ij} is the ith measured concentration

$\sim Cp_{ij}$ is the model predicted concentration

An alternative model which combined the additive and constant CV error models was also evaluated:

$$Cp_{ij} = \sim Cp_{ij}(1 + \epsilon_{1ij}) + \epsilon_{2ij}$$

The regression model for clearance was built from looking at the influence of covariates introduced one by one, then significant covariates were incorporated into the basic model and finally looking at the full model compared to restricted models to give the final model. Comparisons were made from the relative objective functions and using the χ^2 test with $p<0.005$ for statistical significance. Model diagnostics were also performed from graphical outputs of

DV vs. TIME

PRED and IPRED vs. TIME

PRED and IPRED vs. DV

WRES and IWRES vs. TIME and DV

ABS(IWRES) vs. IPRED

DV represents dependent variable ie concentration.

PRED is the prediction from the population parameter and IPRED is the prediction from the individual parameters.

Supportive exploratory analysis of the influence of covariates was undertaken using MLR from SAS and GAM from S-plus.

Model validation:

A new set of data was compared on a clinical than statistical basis for validation.

Qualitative assessment was made through the firm asking itself the following questions:

"1. Are most or all sub-populations at risk properly identified?

ie. a) Do the "true " clearances from the validation set patients exhibit the same qualitative dependence on covariates as described by the index set? b) Do the validation set clearances suggest qualitative dependence on covariates not appearing in the index population model?"

The simple mean of "true " clearance estimates is referred to as the best naive predictor.

Quantitative assessment was made by estimating the prediction error ($\hat{}pe_j$ (%) = ($\sim CL_j$ - CL_j)/ $\sim CL_j$ X 100) and looking st the bias and precision of a prediction.

Model refinement:

The index set population model was finalized using the index set and validation set of patients. This allowed the firm to refine the parameter estimates and look at any dependence of clearance on patho-physiologic covariates.

RESULTS:

Inter-patient variability in clearance was analyzed since it is considered to be the most important

(clinically relevant) PK parameter, determining (with the dose) the systemic exposure to the drug.

Basic population model:

A three-compartment model was evaluated with different Ω matrix structures for assessing inter-patient variability. The Ω matrix structure with ω^2_{CL} was used to identify outliers. Ten data points were discarded with WRES >± 5. This resulted in a reduction of the residual variability, σ from 54.2 to 36.1%. After assessing other matrix structures the one shown to be most adequate was the DIAG(5) model: this gave important information for Bayesian estimation of individual parameters (using POSTHOC) in later data analyses.

Exploratory data analysis

Univariate regression analysis showed that AAG correlated strongly with CL, also WT, BSA and enzyme levels associated with hepatic dysfunction (ALKPH, SGOT or HEP indices) correlated significantly. No correlations were found between clearance and AGE, LIVER and SEX

MLR resulted in AAG, WT or BSA, HEP1 or SGOT and SEX being considered significant in the model for clearance.

GAM analysis resulted in selection of AAG, WT, SGOT, AGE AND TPROT, the first three being the most significant covariates.

POPULATION PHARMACOKINETIC MODEL BUILDING

Inter-patient variability of docetaxel clearance (CL, l/h) was 50 % CV in the basic model involving no covariate. CL was related to the following patient characteristics: 1-acid glycoprotein (AAG) level, hepatic function (HEP), body surface area (BSA) and age (AGE) as follows **(Index set population model)**:

$$\hat{}CL = BSA\,(\theta_1 + \theta_7\,AAG + \theta_8\,AGE)\,(1 - \theta_{14}\,HEP12)$$

where HEP12 is an index of hepatic function equal to 1 when SGOT > 60 UI or SGPT > 60 IU and ALKPH> 300 IU, and equal to zero, otherwise. HEP12 is essentially the interaction HEP1*HEP2

The CV of clearance inter-patient variability remaining not explained by the covariates is 35 % in the final population model. The most prominent effects are those of 1-acid glycoprotein and

hepatic function.

POPULATION PHARMACOKINETIC MODEL VALIDATION

The index set population model was evaluated using a validation set of 267 patients from Phase II studies. All patients had received 100 mg/m^2 except 12 who received 75 mg/m^2.

The estimate of σ was higher at 37.4% compared to the index set at 19.6%. The index set contained the data-rich Phase I patients, contributing 35% of the whole index data set. The Phase I dataset when merged with the validation set gave an estimate of σ of 18.3% closer to that of the index set.

Qualitative assessment included investigating whether validation data were consistent with the covariates entered in the population model; quantitative assessment included estimating the predictive performance of the population model and comparing it to that of the best naive predictor.

The firm stated the following:

"In the whole population of 267 patients, the performance (bias, precision) of the population model was good (8 % and 21 %, resp.) and similar to that of the naive predictor. However, the population model was much better than the naive predictor in predicting low clearance values (prediction improved in 78 % of the patients with CL < 20.7 l/h (10th quantile). Moreover, in most of the sub-populations of patients with extreme values of covariates (beyond the 10th and 90th quantiles), the population model does better than the naive predictor indicating that validation data are consistent with the dependence of clearance on covariate values estimated in the index set.

The performance of the population model is particularly improved in the sub-populations with the most prominent decrease in clearance (high AAG (> 2.27 g/l) and HEP12 = 1) and in elderly patients (AGE > 65 years), the bias is close to or less than 10 % (except for patients with high AAG : 24 %) and the precision is acceptable (typically between 20 - 30 %). Moreover, in those patients, the use of the population model markedly improves the prediction of clearance with 73 %, 71 % and 72 % of patients having smaller prediction errors using the index-set population model prediction."

POPULATION PK MODEL REFINEMENT

Data from the validation set also revealed that some patho-physiological covariates (AGE, BILI, ALB) not in the index set population model might have some additional influence on clearance. Therefore, the population model was re-evaluated with the whole population of 547 patients. In this reanalysis, docetaxel clearance was found to be related to albumin level (ALB) in addition to the other covariates previously in the model. There was a decrease in contribution of AGE to clearance. The following final model was therefore established (final population model)

$$\hat{}CL = BSA\ (\theta_1 + \theta_7\ AAG + \theta_8\ AGE + \theta_9\ ALB)\ (1-\theta_{14}\ HEP12)$$

ALB was normalized. Parameter estimates from the final model (also called model #5) were very

similar to those of the index set model. The intercept (θ_1) of the clearance regression model was modified under the effect of ALB but the estimation of clearance (calculated for mean covariate values) was very similar.

Table 9 : Docetaxel population PK analysis (Phase II studies) : Parameter estimates of index set model (280 patients) and final model (index + validation set i.e. 547 patients)

Model		Index Set		Final	
	θ_1	36.8	(8.0)	22.1	(26.9)
AAG	θ_7	-4.65	(21.9)	-3.55	(30.4)
AGE	θ_8	-0.139	(32.0)	-0.095	(49.4)
ALB	θ_9	-		0.225	(44.9)
HEP12	θ_{14}	0.418	(22.2)	0.334	(16.1)
	V_1 (l)	7.01	(6.3)	8.31	(8.8)
	K_{12} (h^{-1})	1.10	(13.3)	1.07	(21.8)
	K_{21} (h^{-1})	1.43	(9.7)	1.74	(8.5)
	K_{13} (h^{-1})	1.30	(8.8)	1.28	(8.9)
	K_{31} (h^{-1})	0.0793	(7.9)	0.0787	(6.4)
	ω_{CL} (%)	35.2	(17.9)	33.5	(13.0)
	σ_1 (%)	19.4	(18.0)	20.5	(22.4)
	CL^a (l/h)	39.6		36.7	
	$K_{10}{}^a$ (h^{-1})	5.65		4.42	
	Vss^a (l)	127		149	
	$t_{1/\alpha}{}^a$ (min)	5.0		5.8	
	$t_{1/\beta Y}{}^a$ (min)	34.5		29.7	
	$t_{1/2}$ (h)	10.8		11.4	

() CV of estimation

a computed for mean values of covariates

The effect (contribution) of the covariates on clearance was assessed one by one as the others were set to their means (see next table, Table 5). AAG, BSA and HEP contributed the most.

Table 5: Docetaxel population PK analysis (Phase II studies) : Predicted CL for theoretical patients with covariate values varying from 5th to 95th percentiles according to the final model and parameter estimates from 547 patients

Covariate	Quantiles		CL l/h	l/h/m^2	% change[a]
mean patient			36.7	20.6	-
AAG	5 %	0.8 (g/l)		23.3	+ 12
	95 %	2.6 (g/l)		16.6	- 19
AGE	5 %	39 (years)		22.2	+ 8.0
	95 %	71 (years)		19.2	- 6.7
ALB	5 %	31 (g/l)		18.6	- 9.8
	95 %	48 (g/l)		22.4	+ 8.1
BSA	5 %	1.47 (m^2)	30.3	-	- 17
	95 %	2.16 (m^2)	44.6	-	+ 21
HEP12[b]		1		13.7	- 33

[a] theoretical effect (% change with respect to the mean) of the covariate considered alone the other covariates being set to their mean values

[b] n = 18 patients

Clearance was found to decrease with increasing AGE and decreasing ALB levels, but the change is minimal. < 10 % change in clearance and probably not be of clinical significance. In considering elderly patients there was a 6.7 % decrease in clearance for patients 70 year old compared to the mean. The effect of body size (BSA) on patient CL was large: overall change of 38 % around the mean but this is already accounted for by adjusting the dose to BSA.

The most important covariate effects on docetaxel clearance were those of AAG and HEP. Increase in AAG levels greater than 2.6 g/l showed a 19 % decrease in clearance . This is consistent with pharmacokinetic theory with a drug that has

i) the extensive protein binding with a high affinity for AAG

ii) a rather low total clearance (36.7 l/h i.e. 1/3 of hepatic blood flow) which may therefore be affected by protein binding.

However, since the free fraction (fu) is also decreasing when AAG level increases, clearance of unbound drug and its plasma level should be little affected by AAG levels (if at all).

A 33 % decrease in clearance, 30 % and 50 % increases in peak and AUC respectively was shown

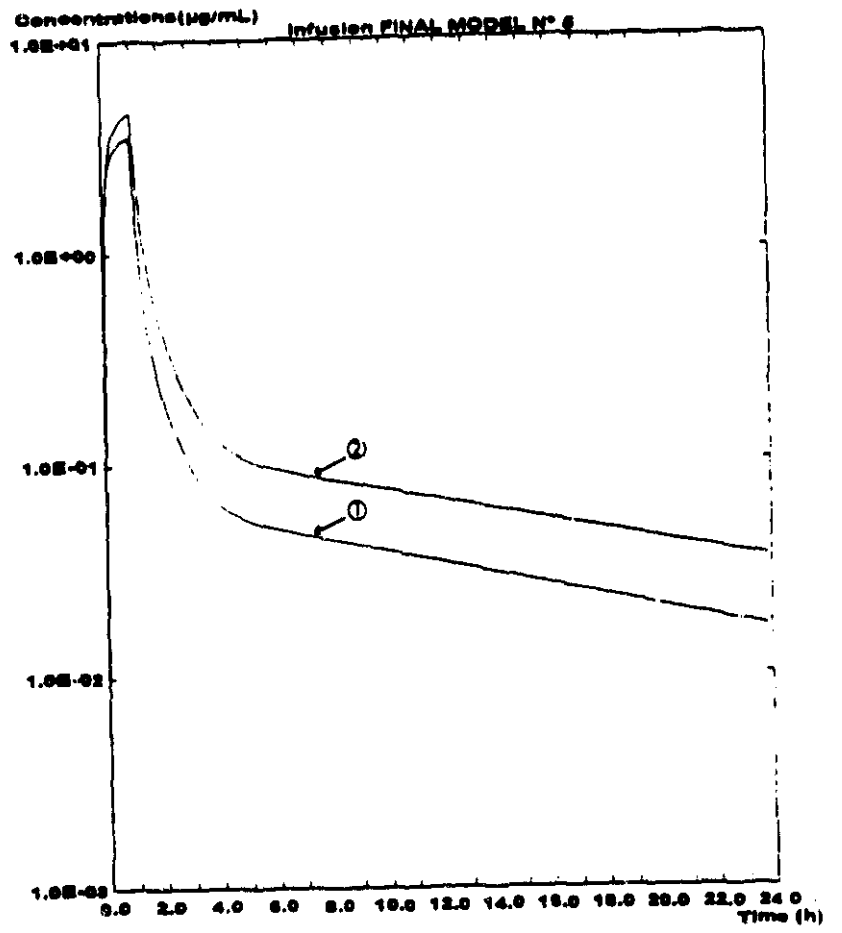
by hepatic dysfunction (defined in this analysis by (moderate) increase in either SGPT or SGOT levels (> 60 IU) and ALKPH levels (> 300 IU)). This will need to be monitored closely since only a small number of patients were in the database analyzed (18 patients out of 547 i.e. 3.3 % of the whole population). The presence of liver metastases per se was not found to alter clearance.

Gender effect:

Finally, clearance was not shown to be different between male and female patients.

The following figure shows simulated profiles of patients with normal or impaired liver function in terms of their docetaxel plasma levels.

Simulated profiles following dosing of 100 mg/m²



① patient with mean covariate values and normal liver function
② patient with impaired liver function

The firm did not study the affect of race, since the European studies did not record this information.

Internal Division of Biopharmaceutics Analyses (carried out by Dr. P. Zannikos):

The firm's estimates of mean systemic clearance and variability were confirmed with the outlying concentrations excluded from analysis. The effect of race and formulation did not affect the inter-patient variability in clearance to any great extent. The volume of distribution was also studied. BSA was included as a covariate. Improvement in the minimum objective function and reduction in the unexplained inter-patient variability resulted, but the change is probably not significant. The results of this analysis follows.

CONCLUSION:

The pharmacokinetic parameters estimated were similar to those obtained from the phase I studies.

Covariates important in docetaxel's clearance are BSA, age, AAG, albumin levels, and degree of hepatic impairment. The most significant effects are those of AAG and hepatic function.

Clearance was well predicted for most of the patients by the model.

Differences in pharmacokinetics due to gender, race or formulation were not detected.

Taxotere (docetaxel)
Submission Date: 07-22-94

Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Collegeville, PA 19426

Dear Dr. Kaus:

This report provides a brief summary of the population pharmacokinetic analyses performed by the sponsor. I have also included the results of additional analyses we performed using the data supplied by the sponsor.

1) The sponsor performed population pharmacokinetic analysis of docetaxel using nonlinear mixed effect modeling (NONMEM program, version III). A three-compartment structural kinetic model was used. Inter-patient variability was modelled on total body clearance according to an exponential error model. Residual variability was also modelled as proportional. The final analysis (refinement of the model) combined the index set (n = 280) with the validation set (n = 267) and included a total of 547 subjects. The sponsor considered model N°5* to be the most appropriate for explaining variability in the clearance of docetaxel (Taxotere).

   Systemic docetaxel clearance (computed for mean values of covariates) was reported to be 36.7 l/hr. Inter-patient variability in clearance and residual variability not explained by model N°5 were reported to be 33.5 % (coefficient of variation, CV) and 20.5 %, respectively (Table 9). These results contrast those obtained utilizing the basic model (involving no covariates) where interpatient variability was found to be much greater (50 % CV). Our attempts to reproduce the sponsor's estimates of mean systemic clearance and variability using these models and the submitted data were successful.

2) The sponsor omitted outliers (data points with weighted residuals greater than 5) from the data set early in their analysis. The influence of these data on final parameter estimates was therefore not reported. Following a request for this additional information, the outliers (14 concentration vs time points) were included in a NONMEM run utilizing the final model (N°5). Although a significant negative effect on the minimum objective function was found, estimates of mean docetaxel clearance, inter-patient variability in clearance and residual variability were comparable to those values obtained when outlying concentrations were omitted (Table 1).

3) Twenty-six subjects from the Phase I trials were included in the index data set. These data are expected to have a great influence on parameter estimates since multiple plasma samples were obtained over an extended period of time in these subjects. Of interest is the performance of the final model (N°5) without these "data-rich"

---

* $\hat{}Cl = BSA(\theta 1 + \theta 7\ AAG + \theta 8\ AGE + \theta 9\ ALB)(1-\theta 13\ HEP12)$ MODEL N°5

individuals (n = 521). The results, summarized in Table 1, are as follows: omission of the 26 subjects was found to significantly worsen the minimum objective function and increase the estimate of residual variability, whereas estimates of mean docetaxel clearance and inter-patient variability in clearance were essentially unchanged.

4) The sponsor reported that docetaxel clearance was not found to differ between male and female patients. Our analysis of the submitted data using model N°5 produced similar results. In addition, we found that inclusion of race or formulation provided little or no decrease in unexplained inter-patient variability in clearance.

Peter Zannikos

Peter N. Zannikos, Ph.D.
Pharmacokinetics Staff Fellow
October 5, 1994

Table 1. Docetaxel Population Analysis

	Model N°5[a] (n=547) (-)outliers	Model N°5 (n=547) (+)outliers	Model N°5 (n=521) (-)outliers
TVCl[b] (l/h)	36.3	35.9	35.1
TVVi (l)	8.31	7.06	9.55
ωCl(%)	33.2	37.4	29.8
ωV1(%)	56.6	-	-
σ1(%)	20.5	21.0	38.7
Objective Function	-3759.9	-2943.6	-2188.6

a Model N°5: $\hat{}Cl = BSA(\theta 1 + \theta 7\ AAG + \theta 8\ AGE + \theta 9\ ALB)(1-\theta 13\ HEP12)$

b computed for mean values of covariates

Table 9 : Docetaxel population PK analysis (Phase II studies) : Parameter estimates of index set model (280 patients) and final model (index + validation set i.e. 547 patients)

Model		Index Set		Final	
	θ_1	36.8	(8.0)	22.1	(26.9)
AAG	θ_7	-4.65	(21.9)	-3.55	(30.4)
AGE	θ_8	-0.139	(32.0)	-0.095	(49.4)
ALB	θ_9	-		0.225	(44.9)
HEP12	θ_{14}	0.418	(22.2)	0.334	(16.1)
	V_1 (l)	7.01	(6.3)	8.31	(6.8)
	K_{12} (h^{-1})	1.10	(13.3)	1.07	(21.8)
	K_{21} (h^{-1})	1.43	(9.7)	1.74	(8.5)
	K_{13} (h^{-1})	1.30	(8.8)	1.28	(8.9)
	K_{31} (h^{-1})	0.0793	(7.9)	0.0787	(6.4)
	ω_{CL} (%)	35.2	(17.9)	33.5	(13.0)
	σ_1 (%)	19.4	(18.0)	20.5	(22.4)
	CL^a_{st} (l/h)	39.6		36.7	
	K_{10a} (h^{-1})	5.65		4.42	
	Vss_a (l)	127		149	
	$t_{1/\alpha a}$ (min)	5.0		5.8	
	$t_{1/\beta Y}$ (min)	34.5		29.7	
	$t_{1/2}$ (h)	10.8		11.4	

() CV of estimation

a computed for mean values of covariates

Table 4 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Summary of patient characteristics - Index set (280 patients)

	Mean (SD)	median	Quantiles 5 %	95 %	Symbol
Demographics					
Age (years)	55.5 (9.8)	56	39	71	AGE
Weight (kg)	68.9 (14.8)	66	48	95	WT
Height (cm)	166 (8.9)	166	153	182	HT
Body surface Area (m^2)	1.76 (0.20)	1.73	1.47	2.13	BSA
Laboratory measurements					
Alanine Amino Transf. (IU)	28.5 (23.4)	22	8	72	SGOT
Aspartate Am. Transf. (IU)	27.5 (20.9)	22	7	71	SGPT
Alkaline phosphatase (IU)	148.3 (131)	108	49	401	ALKPH
Lysine deshydrogenase (IU)	454 (481)	335	150	1040	LDH
Bilirubin (µM)	9.0 (4.3)	8.6	3	17	BILI
Total protein (g/l)	71.4 (6.7)	71	60	83	TPROT
Albumin (g/l)	40.8 (5.6)	41	32	49	ALB
α1-acid glycoprotein (g/l)	1.42 (0.56)	1.30	0.75	2.58	AAG
Plasma creatinine (µM)	83.3 (18.3)	82	54.5	115	CREAT
Hepatic function indexes					
SGOT>60 or SGPT>60 (Yes)		25			HEP1
ALKPH>300 and BONE=0 (Yes)		24			HEP2
LDH>1000 (Yes)		38			HEP3
HEP1 and HEP2 (Yes)		11			HEP12
Other					
Sex (M/F)		114/166			SEX
Performance Status (0/1/2)		95/146/38 (1 missing)			PS
Hepatic Metastasis (Yes)		99			LIVER
Bone Metastasis (Yes)		42			BONE
Race (Caucasian/Hispanic/Black/Oriental)		79/14/5/2 (180 missing)[a]			RACE

[a] not recorded in European studies

Table 5 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Population PK model building - Summary of model selection

Run N°		Fit	ω_{CL} (%)	σ (%)	δ	p
Basic model (3 cpts, different Ω matrix structure)						
1	- ω_{CL}	-1403	48.7	54.2	-	-
2	- ω_{CL} (-outliers)	-2528	44.0	36.1	-	-
3	- Diag(6)	-2757	50.2	19.6	-	-
4	- Diag(5)	-2757[a]	50.2	19.6	-	-
5	- Block(5)	-2822	46.8	17.8	-65*	-
Screening CL =						
6	$\theta_1 + \theta_2$.AAG	-2903	39.4	19.3	-146	<0.0005
7	$\theta_1/(\theta_2 + AAG)$	-2889	41.2	19.2	-132	<0.0005
8	$\theta_1(1-\theta_2$ AAGc)[b]	-2866	41.8	20.3	-109	<0.0005
9	$\theta_1 + \theta_2$.ALKP	-2847	47.3	19.6	-90	<0.0005
10	$\theta_1(1 - \theta_2$.HEP2)	-2841	47.3	20.2	-84	<0.0005
11	$\theta_1 + \theta_2$.SGOT	-2814	49.5	19.7	-57	<0.0005
12	$\theta_1 + \theta_2$.SGPT	-2813	50.0	19.9	-56	<0.0005
13	$\theta_1(1 - \theta_2$.HEP1)	-2832	48.3	19.7	-75	<0.0005
14	$\theta_1 + \theta_2$.WGT	-2798	47.7	18.3	-41	<0.0005
15	$\theta_1 + \theta_2$.AGE	-2789	49.5	20.0	-32	<0.0005
16	$\theta_1 + \theta_2$.ALB	-2796	46.0	19.6	-39	<0.0005
17	$\theta_1 + \theta_2$.BSA	-2785	48.6	18.7	-28	<0.0005
18	$\theta_1(1 - \theta_2$.LIVER)	-2795	49.4	19.4	-38	<0.0005
19	$\theta_1 + \theta_2$.BILI	-2762	50.0	20.0	-5	NS <0.025
20	$\theta_1(1 - \theta_2$.SEX)	-2761	50.1	19.7	-4	NS =0.05
21	$\theta_1(1 - \theta_2$.PSS)[c]	-2757	50.3	19.6	0	NS
22	$\theta_1 - \theta_2$.TPROT	-2758	50.2	19.6	-1	NS
23	$\theta_1(1 - \theta_2$.DOS)[d]	-2757	50.2	19.6	0	NS
24	$\theta_1(1 - \theta_2$.HEP3)	-2758	50.2	19.5	-1	NS
25	$\theta_1 + \theta_2$.CREAT	-2761	50.2	19.8	-4	NS =0.05

* in comparison to diag(5)
[a] reference fit for the screening step
[b] AAGc = 1 when AAG > 2 g/l, 0 otherwise
[c] PSS = 1 when PS = 2, 0 otherwise
[d] DOS = 1 when DOSE > 90 mg/m^2, 0 otherwise
NS = p>0.05

Table 6 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Population PK model building - Summary of model selection (continued)

Run N°			Fit	ω_{CL}	σ (%)	δ	p
26	**Full model**		-3015[a]	35.9	18.9	[*-258*]	
27		($\theta_1 = 0$)	-2967	36.6	18.1	+48	<0.0005
28	- AAG	($\theta_7 = 0$)	-2925	42.2	19.2	+90	<0.0005
29	- AGE	($\theta_8 = 0$)	-3000	36.3	18.5	+15	<0.0005
30	- ALB	($\theta_9 = 0$)	-3010	35.5	18.9	+5	NS(=0.025)
31	- FSA	($\theta_{10} = 0$)	-2987	37.4	19.6	+28	<0.0005
32	- HEP2	($\theta_{11} = 0$)	-3010	36.1	18.9	+5	NS(=0.025)
33	- HEP1	($\theta_{12} = 0$)	-2986	37.1	19.3	+29	<0.0005
34	- LIVER	($\theta_{13} = 0$)	-3014	36.1	18.9	+1	NS
35	M 1	$\theta_9, \theta_{11}, \theta_{13} = 0$	-3005	35.6	18.9	+10	NS(<0.025)
36		WT instead of BSA	-3006	35.4	18.7	-1[b]	-
37	M 2	+ HEP12 (θ_{14})	-3020	35.1	19.3	-15[b]	<0.0005
38	M 3	-HEP1 ($\theta_{12} = 0$)	-3013	35.5	19.7	+7[c]	NS(<0.01)
39	M 4	BSA multiplicative	-3010	35.2	19.4	+3[d]	-
40		Mixed res. error	-3011	35.4	19.2	-1[e]	-
41		Block(5)	-3085	33.0	17.7	-75[e]	-

[a] reference fit for destruction of the full model
[b] in comparison to model 1 (M 1 - run N° 35)
[c] in comparison to model 2 (M 2 - run N° 38)
[d] in comparison to model 3 (M 3 - run N° 39)
[e] in comparison to model 4 (M 4 - run N° 40)
NS = p>0.005

75

Table 7 : RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Parameter estimates of alternative models and analysis of the index set of 280 patients

Model		N° 1 (run 35)	N° 2 (run 37)	N° 3 (run 38)	N° 4 (run 39)
Fit		-3005	-3020	-3013	-3010
	θ_1	41.2 (24.0)	40.8	39.1	36.8 (8.0)
AAG	θ_7	-8.23 (22.5)	-7.94	-7.72	-4.65 (21.9)
AGE	θ_8	-0.235 (31.7)	-0.238	-0.229	-0.139 (32.0)
BSA	θ_{10}	13.4 (37.0)	13.3	13.7	-
HEP1	θ_{12}	0.296 (25.0)	0.147	-	-
HEP12	θ_{14}	-	0.345	0.437	0.418 (22.2)
	V_1 (l)	7.01 (6.1)	6.99	6.93	7.01 (6.3)
	K_{12} (h^{-1})	1.10 (12.7)	1.09	1.10	1.10 (13.3)
	K_{21} (h^{-1})	1.44 (9.1)	1.41	1.42	1.43 (9.7)
	K_{13} (h^{-1})	1.31 (8.9)	1.30	1.30	1.30 (8.8)
	K_{31} (h^{-1})	0.0799 (8.2)	0.0789	0.0794	0.0793 (7.9)
	ω_{CL} (%)	35.6 (17.6)	35.1	35.5	35.2 (17.9)
	ω_{V1} (%)	55.0 (27.2)	54.9	54.2	54.8 (27.3)
	ω_{K21} (%)	115 (36.5)	108	106	108 (38.7)
	ω_{K13} (%)	38.5 (59.4)	41.1	40.9	41.0 (67.3)
	ω_{K31} (%)	38.7 (71.3)	38.3	37.9	35.4 (77.3)
	σ_1 (%)	18.9 (16.0)	19.3	19.7	19.4 (18.0)
	CL^a (l/h)	40.1	39.7	39.5	39.6
	K_{10}^a (h^{-1})	5.72	5.68	5.70	5.65
	Vss^a (l)	127	128	126	127
	α^a (h^{-1})	8.5	8.3	8.3	8.3
	β^a (h^{-1})	1.2	1.2	1.2	1.2
	γ^a (h^{-1})	0.065	0.064	0.064	0.064
	$t_{1/2\alpha}^a$ (min)	5.0	5.0	5.0	5.0
	$t_{1/2\beta}^a$ (min)	34.5	34.5	34.5	34.5
	$t_{1/2\gamma}^a$ (h)	10.7	10.8	10.8	10.8

( ) CV of estimation
[a] computed for mean covariates

Table 8 : RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Predicted docetaxel CL for theoretical patients with covariate values varying from the observed data 5th to 95th percentiles according to model N° 4 and parameter estimates from the index set of 280 patients

Covariate	Quantiles		CL l/h	l/h/m²	% change[a]
mean patient			39.2	22.3	-
AAG	5 %	0.75 (g/l)	-	25.5	+ 14
	95 %	2.58 (g/l)	-	16.7	- 25
AGE	5 %	39 (years)	-	24.6	+ 10
	95 %	71 (years)	-	20.1	- 9.7
BSA	5 %	1.47 (m^2)	32.8	-	- 16
	95 %	2.13 (m^2)	47.5	-	+ 21
HEP12[b]		1	-	13.6	- 39

[a] theoretical effect (% change with respect to the mean) of the covariate considered alone the other covariates being set to their mean values

[b] n = 11 patients

Table 9 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : Summary of patient characteristics - Validation Set (267 patients)

	Mean (SD)	median	Quantiles 5 %	95 %	missing	Symbol
Demographics						
Age (years)	56.5 (10.5)	58	37	71	0	AGE
Weight (kg)	69.8 (15.2)	67	49	95	1	WT
Height (cm)	169.1 (9.8)	170	154	185	1	HGT
Body surface Area (m^2)	1.79 (0.21)	1.77	1.49	2.18	0	BSA
Laboratory measurements						
Alanine Amino Transf. (IU)	24.9 (23.2)	20	8	57	16[a]	SGOT
Aspartate Am. Transf. (IU)	26.9 (23.9)	21	6	63	36[a]	SGPT
Alkaline phosphatase (IU)	137 (111)	102	56	334	0	ALKPH
Lysine deshydrogenase (IU)	422 (432)	272	141	1169	19	LDH
Bilirubin (µM)	8.4 (3.8)	7.0	3	15	0	BILI
Total protein (g/l)	70.6 (5.8)	71	60	79	0	TPROT
Albumin (g/l)	39.4 (5.0)	40	31	47	0	ALB
α1-acid glycoprotein (g/l)	1.50 (0.54)	1.41	0.81	2.62	0	AAG
Plasma creatinine (µM)	83.7 (19.1)	80	53	115	3	CREAT
Hepatic function indexes						
SGOT>60 or SGPT>60 (Yes)		18				HEP1
ALKPH>300 and BONE=0 (Yes)		17				HEP2
LDH>1000 (Yes)		30				HEP3
HEP12 (Yes)		7				HEP12
Other						
Sex (M/F)		139/128				SEX
Performance Status (0/1/2)		83/147/33 (4 missing)				PS
Hepatic Metastasis (Yes)		83				LIVER
Bone Metastasis (Yes)		25				BONE
Race (Caucasian/Hispanic/Black/Oriental)		121/9/9/3 (125 missing)[b]				RACE

[a] no patient with both SGOT and SGPT missing

[b] not recorded in European studies

Table 10 : RP 56976 (docetaxel) population PK analysis (Phase II studies) : NONMEM parameter estimates with basic model and different data sets

	Index Set	Validation Set	
			+ Ph I
Patients	280	267	293
Observations	1105 (4 / pt)	743 (2.8 / pt)	1132 (3.9 / pt)
Run N°	3	v1	v2
Fit Diag (6)	-2757	-885	-2496
Cl (l/h)	38.5	33.8	36.0
V_1 (l)	7.40	8.05	6.16
K_{12} (h^{-1})	1.06	2.16	1.98
K_{21} (h^{-1})	1.51	2.40	2.11
K_{13} (h^{-1})	1.26	1.41	1.56
K_{31} (h^{-1})	0.0840	0.0955	0.0924
ω_{CL} (%)	50.2	39.9	45.6
ω_{V1} (%)	60.2	0	51.6
ω_{K12} (%)	0	63.6	122.9
ω_{K21} (%)	126.5	50.6	101.0
ω_{K13} (%)	26.7	0	28.9
ω_{K31} (%)	40.4	0	44.4
σ (%)	19.6	37.4	18.3
K_{10} (h^{-1})	5.2	4.2	5.8
Vss (l)	124	134	116
$t_{1/2\alpha}$ (min)			
$t_{1/2\beta}$ (min)			
$t_{1/2\gamma}$ (h)			

Table 11 : RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Predictive performance of index set population model and naive predictor (mean clearance of the validation set patients : Mean(CL_j) = 38.3 l/h)

Data Set (n)	Predictor	Bias (mde) l/h (%)	Precision (mae) l/h (%)	Mean CL_j l/h	Patients[a] Improv %	Worse %
All pts (267)	Model	3.14 (8.2)	8.16 (21)	38.3	53	36
	Naive	2.29 (6.0)	10.0 (26)			
CL < 20.7 (27)	Model	15.0 (97)	15.0 (97)	15.5 (- 60 %)[b]	78	11
	Naive	22.0 (142)	22.0 (142)			
AAG > 2.27 (26)	Model	6 16 (24)	8 02 (32)	25 4 (- 34 %)[b]	73	23
	Naive	13 4 (53)	13 4 (53)			
AAG < 0 88 (26)	Model	2 17 (4 9)	9.24 (21)	44.7 (+ 17 %)[b]	42	50
	Naive	0.20 (0 4)	11.2 (25)			
Age > 69 (25)	Model	3 76 (11)	6 02 (18)	34.3 (-10%)[b]	72	20
	Naive	7 96 (23)	10 4 (30)			
BSA > 2.07 (26)	Model	2 80 (6 0)	11.6 (25)	46.6 (+ 22 %)[b]	69	27
	Naive	-7.74 (17)	14 9 (32)			
BSA < 1.54 (23)	Model	3.30 (10)	9.31 (28)	32.9 (- 14 %)[b]	61	39
	Naive	5.15 (16)	9.50 (29)			
HEP12 = 1 (7)	Model	-0.06 (0.3)	5.03 (22)	22.7 (- 41 %)[b]	71	14
	Naive	14.1 (62)	14.1 (62)			

[a] % of patients with improved (worsened) prediction by the population model as compared to the naive predictor
[b] % change relative to mean of the general population

Table 12 : RP 56976 (docetaxel) population PK analysis (Phase II studies)
Parameter estimates of alternative final models (index + validation set i.e. 547 patients)

Model		N° 4		N° 5	
		index set run 39	whole set run 42	whole set run 43	
Fit		-3010	-3728	- 3760 (δ=-32)[a]	
	θ_1	36.8 (8.0)	32.2 (9.9)	22.1 (26.9)	22·5
AAG	θ_7	-4.65 (21 9)	-4.52 (19.8)	-3.55 (30 4)	−3·69
AGE	θ_8	-0 139 (32 0)	-0 089 (52.8)	-0.095 (49 4)	−0·09
ALB	θ_9	-	-	0.225 (44.9)	+ 0·2
HEP12	θ_{14}	0.418 (22 2)	0.342 (16.7)	0.334 (16.1)	−0·3
	V_1 (l)	7.01 (6.3)	8.39 (10.3)	8.31 (8.8)	
	K_{12} (h^{-1})	1.10 (13 3)	1.10 (24.2)	1.07 (21 8)	
	K_{21} (h^{-1})	1 43 (9 7)	1.75 (9.0)	1.74 (8.5)	
	K_{13} (h^{-1})	1.30 (8 8)	1.26 (9 8)	1.28 (8 9)	
	K_{31} (h^{-1})	0 0793 (7 9)	0 0779 (7.2)	0 0787 (6 4)	
	ω_{CL} (%)	35.2 (17 9)	34 2 (13 7)	33.5 (13 0)	
	ω_{V1} (%)	54 8 (27 3)	56 4 (22.5)	56.1 (22.5)	
	ω_{K21} (%)	108 (38 7)	127 (40.9)	131 (38.1)	
	ω_{K13} (%)	41.0 (67.3)	46.9 (54.1)	47.7 (45.2)	
	ω_{K31} (%)	35 4 (77.3)	17.0 (130)	14.7 (152)	
	σ_1 (%)	19 4 (18.0)	20.5 (23 0)	20.5 (22 4)	
	CL^b (l/h)	39.6	36.7	36.7	
	$K_{10}{}^b$ (h^{-1})	5.65	4.37	4 42	
	Vss^b (l)	127	149	149	
	α^b (h^{-1})	8.3	7.1	7.1	
	β^b (h^{-1})	1.2	1.4	1 4	
	γ^b (h^{-1})	0.064	0 060	0.061	
	$t_{1/2\alpha}{}^b$ (min)	5.0	5.9	5.8	
	$t_{1/2\beta}{}^b$ (min)	34.5	29.7	29.7	
	$t_{1/2\gamma}{}^b$ (h)	10 8	11.6	11 4	

( ) CV of estimation
[a] compared to run 42
[b] computed for mean values of covariates

Table 13 : RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Predicted docetaxel CL for theoretical patients with covariate values varying from the observed data 5th to 95th percentiles according to model N° 5 and parameter estimates from 547 patients

Covariate	Quantiles		CL l/h	l/h/m²	% change[a]
mean patient			36.7	20.6	-
AAG	5 %	0.8 (g/l)		23.3	+ 12
	95 %	2.6 (g/l)		16.6	- 19
AGE	5 %	39 (years)		22.2	+ 8.0
	95 %	71 (years)		19.2	- 6.7
ALB	5 %	31 (g/l)		18.6	- 9.8
	95 %	48 (g/l)		22.4	+ 8.1
BSA	5 %	1.47 (m²)	30.3	-	- 17
	95 %	2.16 (m²)	44.6	-	+ 21
HEP12[b]		1		13.7	- 33

[a] theoretical effect (% change with respect to the mean) of the covariate considered alone the other covariates being set to their mean values

[b] n = 18 patients

Table 14 . RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Pharmacokinetic parameter estimates for PK/PD analysis (n = 577 patients)

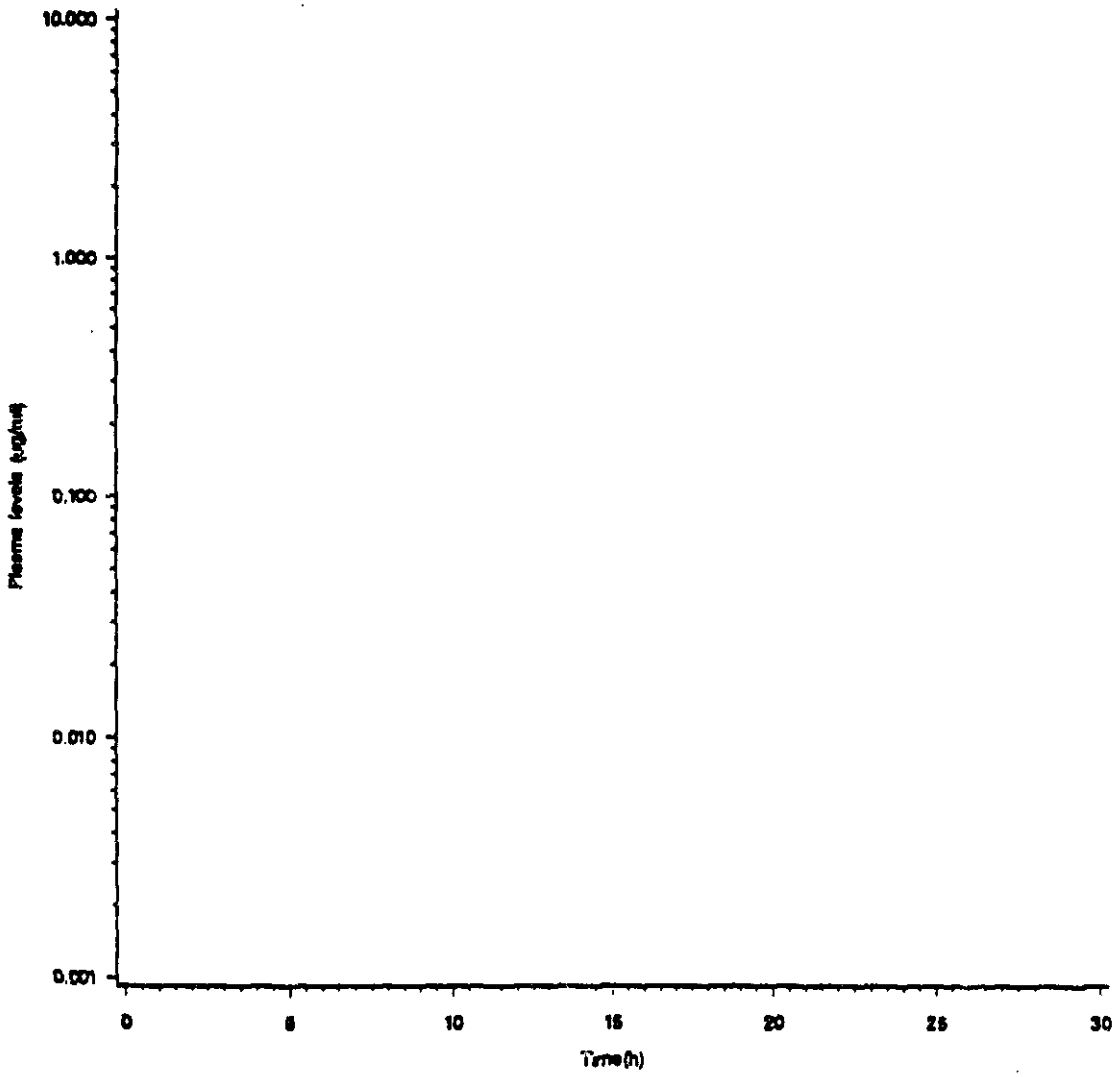
Estimates	Mean (SD)	Median	Quantiles 5 %	Quantiles 95 %
CL_j (l/h)	37.0 (12.3)	36.0	17.6	59.8
CLu_j (l/h)	660.0 (210.6)	637.4	351.1	1021.1
$\hat{}CL_j$ (l/h)	36.4 (7.0)	36.6	24.1	47.6
$\hat{}CL_j^*$ (l/h)	36.4 (5.5)	36.3	27.9	45.9
f_1	1.14 (0.49)	1.03	0.62	2.10
f_2	1.12 (0.43)	1.04	0.65	1.88
f_3	1.05 (0.26)	1.00	0.77	1.51
f_4	1.03 (0.17)	1.00	0.79	1.31
fu	0.056 (0.005)	0.056	0.046	0.064
AUC (µg h/ml)	5.37 (2.29)	4.81	2.93	9.56
AUC_{75}[a]	3.57 (2.00)	2.99	2.22	7.68
AUC_{100}[b]	5.47 (2.26)	4.89	3.22	9.56

[a] patients treated at 75 mg/m2 (n = 31)
[b] patients treated at 100 mg/m2 (n = 546)

Figure 1

Docetaxel – Phase II Studies

Index set n = 280



MASS BALANCE STUDY

TITLE: A Phase I study of RP56976- (Docetaxel) pharmacokinetics, excretion balance and metabolism achieved with ^{14}C radiolabeled RP56976 in cancer patients. (TAX016 Vol. 1.60 page 6-2-6)

OBJECTIVES:
1. To further determine the pharmacokinetics, excretion balance and metabolism of docetaxel (RP 56976) and docetaxel related products in cancer patients.
2. To further characterize the presence of docetaxel in easily accessible fluids. To further characterize the toxic effects of docetaxel in this group of patients.

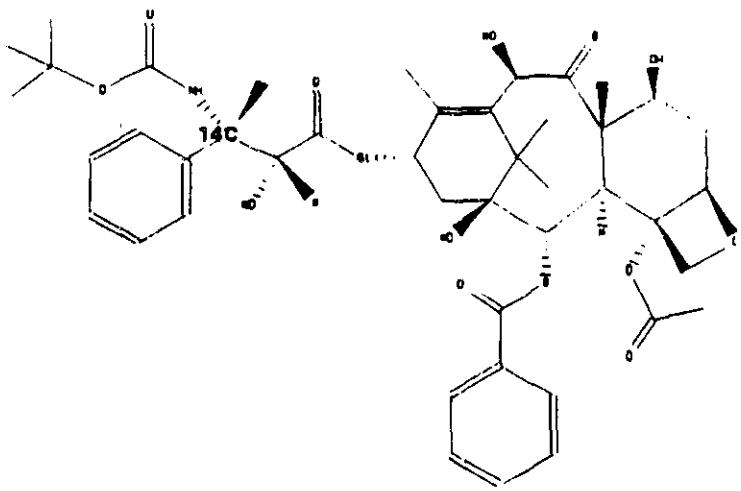
Clinical Investigator and Site:

Clinical Study Dates: June 23 1992 to September 15 1992.

Subject Demographics:
3 patients entered the study: 2 females (aged 26 and 53) and 1 male (aged 20 years). All had malignant solid tumors.

Drug Supplies:
Radiolabeled ^{14}C-docetaxel was prepared by the "Service des Molécules Marquées", CEA 91191Gif sur Yvette, France, labelled at the position [^{14}C-3-proprionate] corresponding to the structure given in figure 1.

Figure 1 : Docetaxel Structure



Specific activity of the tracer was 47 μCi/mmol or 1.73 GBq/mmol (batch number CMM 2035, lot 0392).
The metabolism study in man (TAX016) was conducted with ^{14}C-radiolabeled drug (formulation

N° 2) using the above tracer. Total radioactivity in the 2 ml vial was 30 μCi or 1.1 GBq (batch CB 5413).

STUDY DESIGN AND DOSAGE ADMINISTRATION:

A non-randomized open-label study was conducted:^{14}C radiolabeled RP56976 was infused IV for one hour at a dose of 100 mg/m^2 equivalent to 37.5μCi/m^2 of radioactivity. Samples were taken of blood, urine, feces, saliva and breath up to 7 days post infusion. Radioactivity was measured by means of liquid scintillation counting. Plasma levels were measured using HPLC with radioactive detection. Pharmacokinetic parameters were calculated and the metabolites were identified and quantified.

Biological Sampling: Blood samples (10 mL) were taken prior to infusion, 30 minutes after the start of infusion, at the end of infusion , 20, 30, 60, 90 minutes and 2, 4, 6, 12, 24, 36 and 48 hours post infusion. Then blood samples were taken once on day 3, 4, 5, 6 and 7. Additional 5 mL samples were taken 5 and 10 minutes and 8 hours post-infusion. Urine samples were taken prior to infusion, and at the following intervals; 0-6h, 6-12h, 12-18h, 18-24h post infusion. Fecal samples were collected over the 7 days as 24 hour pooled samples. Saliva samples were collected prior to infusion, at the end of infusion and 3 hours post-infusion. ^{14}C breath analysis was undertaken at 90 min, 4 and 24 hours after the end of infusion.

LOQ:For HPLC =15 ng/mL **Precision:**intra-and inter-run 1.7 to 23.4%

RESULTS:About 80% of the dose administered was recovered.

Table 6 : Excretion balance (% of administered dose) after 1 hour infusion of ^{14}C-docetaxel at 100 mg/m² (TAX016)

Patient	Urine	Feces	Total
	5.9%	74.8%	80.7%
	5.1%	73.4%	78.4%
	7.0%	NA*	NA*

NA : Incomplete feces collection*

The results were similar to those from preclinical studies where in four species (mouse, rat, rabbit and dog) the average percentage of dose in feces and in urine ranged from 83 to 92% and from 3 to 9%, respectively. In subjects 501 and 502 most of the fecal excretion occurred during the first 2 days.

Again the metabolic profiles determined in urine and feces showed that the human metabolic pathways were similar to those observed in animal studies. The majority of a dose of docetaxel is almost completely eliminated by metabolism. Although AUC of parent drug represent 72 % of that of total radioactivity, no circulating metabolites could be detected in plasma. No radioactivity was detected in the breath.

From the firm's review: "The main metabolic pathway for docetaxel metabolism in humans consists of successive oxidations (alcohol, aldehyde, acid) of the tert-butyl ester group on the side chain. The alcohol derivative is identified as metabolite VI or RPR 104952. The next step of oxidation leads to a putative aldehyde derivative which gives, by cyclisation, two diastereoisomeric hydroxy-oxazolidinedione metabolites, V (RPR 111026) and VII (RPR 111059). Oxidation of the aldehyde intermediate gives the unstable acid derivative (IV), which yields, after cyclisation, the oxazolidinedione derivative identified as metabolite XVI or RPR 104943. A scheme of these biotransformations is presented in figure 1." RPR 104943 accounts for about 23% of the administered dose. RPR 104952, metabolites V and VII, each account for about 6-7% of the administered dose. These metabolites are 30 and 140-fold less active in vitro respectively, than the parent.

Protein binding: These results were not used by the firm as the main study on protein binding. This information was found within the investigator's report and not the report written by RPR.Protein binding was measured by ultrafiltration method. The results show that docetaxel was about 97% bound at the end of infusion (and at concentrations around 2 μg/mL). The binding protein was not characterized.

Pharmacokinetic modeling: Plasma HPLC and radioactivity data were modeled using ADAPT. The pharmacokinetic parameters are summarized:

Pt #	Method	Dose mg	Cpeak ng/ml	ratio*	Vss L/m2	Vc L/m2	TBC L/hr/m2	T1/2 α min	T1/2 β min	T1/2 γ hr	AUC 0-8hrs ng/mlxhr	ratio*	AUC 0-168hrs ng/mlxhr	ratio*
	HPLC	126.9	2266	0.84	43.8	2.3	28.0				2692	0.79	2880	0.74
	RA		2709		60.5	2.2	20.6				3425		3918	
	HPLC	163.5	2292	0.73	53.8	3.0	33.5				2577	0.66	2782	0.63
	RA		3132		48.4	2.7	21.2				3919		4354	
	HPLC	157.9	2117	0.73	17.3	4.2	41.0				2167	0.71	2178	0.31
	RA		2895		97.1	3.6	10.2				3061		6980	

RA, Radioactivity; Vss and Vc, Volumes of steady-state and of central compartment; TBC, Total body clearance.
*, Ratio between HPLC and RA determinations

COMMENTS:

1. The firm have adequately characterized the mass balance of docetaxel.

2. The protein binding study was not in sufficient detail to critique. No characterization of the binding protein was undertaken. This was not considered the main protein binding study by RPR. In **Report RP 56976 Vol. 1.95 page 6-37-155**, the % bound was found to be around 94% in the concentration range of μg/mL.

3. The pharmacokinetic parameters are lower than the mean parameters calculated for TAX006 for the same infusion time and dose. However they are within the range of the individuals for TAX006.

CONCLUSIONS:

The study is adequate for describing the mass balance of docetaxel for the purpose of labeling.

Page 87 deleted

LIVER MICROSOMAL AND HEPATIC CELL METABOLISM STUDIES:

TITLE: 1. Preliminary characterization of Taxotere™ metabolism using human liver microsomal fractions. 2. *In vitro* metabolism of Taxotere™ by human hepatic cells and microsomes: involvement of CYP3A subfamily.

This information was provided in the form of abstracts from meetings/conferences in the Pharmacology Section of the submission **(Vol. 1.56, page 5-35-283)**. These investigators were supported by RPR-Rorer.

The firm have been requested to send a more full report if available and not just in abstract form.

STUDY DESIGN :
Abstract 1. "Preliminary Characterization of Taxotere™ Metabolism using Human Liver Microsomal Fractions, Zhou-Pan XR, Marre F, Zhou XJ et al. Second Interface of Clinical and Laboratory Responses to Anticancer Drugs: Drugs and Microtubules, Marseille, France, April 2-4, 1992 Abstracts".

A bank of human liver microsomes was used (N=29).
The drug was incubated with human microsomal fractions.
Four more polar metabolites named M1, M2, M3 and M4 were formed.
Taxotere™ had a wide inter-individual variability with metabolizing rates ranging from 6.9 to 164.7 pmol/min/mg.
Formation of M2 and M4 significantly correlated with erythromycin N-demethylase activity known to be supported by cP450IIIA.
Inhibitors of P450IIIA such as troleandomycin, nifedipine and ketoconazole significantly reduced the metabolism of Taxotere™.

A translation of this was sent by the firm to the Agency 11/7/94. These are additional comments from a review of this new information:

Mean K_i (inhibition by ketoconazole) was 1.35μM ± 0.25.

Comments:
1. It would have been useful to have characterized the metabolites, especially the predominate metabolites M2, M3 and M4.

2. The authors chose the most appropriate microsome batches for their work on the determination of inhibition constants, K_i.

3. The Dixon plots for determination of K_i's needed sampling between 5 and 10 μM ketoconazole (microsome batches HL 15 and HL 23) or between 2.5 and 10 μM for more accurate determination of linear regression.

4. The authors suggest that there was a high correlation of M1, M2 and M4 with erythromycin N-demethylase activity. Correlations need to be more appropriately expressed in terms of r^2 rather than r values. The correlation with total metabolites r=0.7698 then becomes r^2 =0.5926 and the highest r value for the correlation of activity with M2 where r=0.8330, becomes r^2=0.6939. At these values the correlations may not be definitive and further evaluation with for instance expressed s' stems is suggested.

5. There is a need for further work using 3A expressed systems and anti-P450 3A for definitive conclusions to be made.

6. The histogram of microsome number vs. total metabolites in (pmol/min/mg P) shows values ranging from about pmol/min/mg not pmol/min/mg as described in the abstract. This does not seem to suggest high variability as stated by the authors.

Abstract 2. "*In vitro* metabolism of Taxotere™ by human hepatic cells and microsomes: involvement of CYP3A subfamily, Marre F, de Sousa G, Placidi M and Rahmani R. Proceedings ISSX Volume 3. 5th European ISSX Meeting Tours, France, September 29, 1993.

Specific cP450 was induced by treating hepatocytes with
β-naphthoflavone (β-NF)
3-methylcholanthrene (3MC)
phenobarbital (PB)
rifampicin (RIF)

Specific inhibitors or substrates of P450 subfamilies were used to study inhibition of Taxotere™'s metabolism:
benzopyrene (BP)
theophylline (TP)
hexobarbital (HB)
debrisoquine (DBQ)
sparteine (SPA)
propranolol (PRO)
aniline (ANI)
erythromycin (ERY)
ketoconozole (KETO)
nifedipine (NF)
midazolam (MDZ)
quinidine (QUI)
cimetidine (CIME)
SKF 525A

Results:

Substrate of CYP3A	% reduction in Taxotere™ metabolism
ERY	385
KETO	95%
NF	90%
MDZ	77%
QUI	44%

Microsomal work showed Taxotere was inhibited by ERY, KETO, NF, MDZ and QUI.

Taxotere's metabolism was strongly induced by RIF (144% of control) by hepatocytes in culture. PB, 3MC and β-NF had less effect.

Biotransformation rate of Taxotere was strongly correlated to erythromycin N-demethylase activity.

3. Docetaxel metabolizing enzymes and metabolic drug-drug interactions *in vitro* was reported in Vol. 1.59 page 6-1-63 as Biodyn # 1728 study and was also presented by RPR. at the Fifth European ISSX Meeting Sept., 1993.

Rat, mouse, dog and human microsomes were used to study the metabolism of docetaxel. The study confirmed the inhibitors of docetaxel shown in the previous studies (IC50 values were given for these inhibitors). Biotransformation rates were higher in the animal species with the mouse being the highest. Enzyme kinetic constants for human microsomes were Vmax=9.2 pmol/min/mg, Km(app)=1.1 μM and CLint = 8.2 mL/min/g. The mean docetaxel biotransformation rate in these liver microsomes from five human subjects was 25±6 pmol/min/mg.

Assay:
The assay method for this study used a different type of HPLC column from that used in the assay for the PK studies. Both used the same mobile phase and UV detection wavelength. The chromatograms show different retention times to those in the PK studies being much longer. The peak appearing after 15 minutes was not identified and its impact on the assay concentration of docetaxel was not described, if it is say the 7-epimer of docetaxel.

No rationale was given for the incubation time of 60 minutes, this seems rather long. No rationale was given for using substrate disappearance assay for incubates with liver microsomes rather than product formation method.

CONCLUSIONS:
Taxotere is metabolized by cP4503A subfamily.

COMMENTS:

7. The following was noted from the report on study Biodyn 31728: the peak appearing after 15 minutes was not identified and its impact on the assay concentration of docetaxel was not described, if it is say the 7-epimer of docetaxel.

8. From study Biodyn # 1728: no rationale was given for the incubation time of 60 minutes, this seems rather long. No rationale was given for using substrate disappearance assay for incubates with liver microsomes rather than product formation method.

9. The effect of anicancer drugs on docetaxel biotransformation was studied in Biodyn #1728 Exp # 27. The impact of the results would have been put into better perspective if there was an additional control substance such as ketoconozole for comparison.

Comment # 1 and Comments # 3 to 9 need to be conveyed to the firm.

IN VITRO PROTEIN BINDING STUDY

TITLE:
In vitro protein binding of docetaxel in human blood and study of drug interaction **(Report RP 56976 Vol. 1.95 page 6-37-155)**

OBJECTIVES:
To measure the binding of docetaxel to plasma proteins, platelets, lymphocytes and erythrocytes in human blood.
To measure the effect of drugs (cisplatin, doxorubicin, etoposide, vinblastine or dexamethasone) on docetaxel plasma binding.

Investigator and Site:

Dates; Aug. 3 1993 to Nov. 18 1993.
Drug Supplies:
Labeled ^{14}C-docetaxel 47 mCi/mmol or 1.73 GBq/mmol. Radiochemical purity =96.7%.

METHODOLOGY:
Blood supply was from healthy subjects collected in tubes containing EDTA (15mg/10 mL of blood). **Plasma** was separated from erythrocytes by centrifugation at 2000 g during 10 min. **Erythrocytes** were washed twice with NaCl 9 g/l before use. **Platelet-rich plasma** was obtained from the supernatant after blood was centrifuged for 10 min at 130 g. Lymphocytes were also isolated.

A serum pool was used in the protein binding experiments. This had an HSA concentration of 696μM and an AAG concentration of 17.5 μM. Lactic acid was used to adjust the serum/plasma pH to 7.35 to 7.40.

Binding Assay:
Binding was determined by ultrafiltration method. **Polysorbate 80 was used in all experiments at a concentration of 100 μg/mL.** Total drug concentration was obtained before centrifugation and then after centrifugation at 1000-2000 g for 5-10 min at 37°C.
The final docetaxel concentration was 3 μg/mL in these studies. Comment: Cmax in the pharmacokinetic studies was around 2 to 3μg/mL for 100 mg/m^2 dose.

Drug interactions:
Cisplatin 50 μg/mL, dexamethasone 50 ng/mL, doxorubicin 500 ng/mL, etoposide 10 μg/mL and vinblastine 300 ng/mL were investigated for the effect on docetaxel serum binding.

RESULTS:
Docetaxel binds to HSA, AAG and lipoproteins such as HDL and LDL.

Mean % Serum Binding ± SD (N=5 per measurement):

	Docetaxel μg/mL			
Polysorbate 80 μg/mL	**0.1**	**1.0**	**3.0**	**5.0**
10	77.13±1.25	92.96±0.34	93.77±0.25	93.79±0.51
100	86.65±0.53	93.02±0.44	93.39±0.36	93.24±0.15
200	86.91±2.28	92.73±1.55	93.45±0.15	93.20±0.16

There was a significant statistical difference between % bound at 0.1 μg/mL and the other concentrations of docetaxel. The firm believes that this discrepancy is due to the low dpm's at this concentration of the radiolabeled docetaxel. This however was not present to confirm in the Appendix 2 as cited by the firm.

Mean % bound Docetaxel (1μg/mL) in Presence of Other Drugs:

Serum	**% Bound Docetaxel Mean±SD (N=5)**
Control	94.12±0.59
Cisplatin 50μg/mL	92.14±1.88
Dexamethasone 50 ng/mL	93.11±0.49
Doxorubicin 500 ng/mL	93.86±0.30
Etoposide 10μg/mL	92.94±0.65
Vinblastine 300 ng/mL	93.49±0.23

These were not significantly different from the control % bound.

The table shows the mean binding parameters ± SD for these proteins:

Protein	n	K, mM^{-1}	nK, mM^{-1}
albumin	0.82 ± 0.01	8.37 ± 1.25	
AAG	1.27± 0.23	114 ± 44	
γ-globulin			4.51 ± 0.16
HDL			538 ± 49
LDL			1714 ± 118
VLDL			3011 ± 114

HDL : High density lipo-proteins.

LDL : Low density lipo-proteins.

VLDL : Very low density lipo-proteins.

These were estimated using the programMicropharm.

In serum, docetaxel is 93-94 % bound (at concentrations of 1-5 μg/ml), mainly to human serum albumin, 1-acid glycoprotein and lipoproteins. The binding to γ-globulins is very weak. Docetaxel is 8-19 % bound to erythrocytes resuspended in plasma (40 % hematocrit).

Polysorbate 80 in the range 10 to 200 μg/ml did not significantly influence the serum binding.

The global constant of association (n.K), and, in the case of saturable binding, the number of sites (n) and the association constant (K) could be estimated from the individual serum protein binding studies.

Simulation of docetaxel plasma protein binding in healthy patient using the above parameters shows a binding of 93.8 % (fraction unbound fu : 6.2 %), consistent with the observed values.

Simulation in cancer patient with severe biological syndrome of inflammation (1-acid glycoprotein = 60 μM (2.4 g/l) and albumin = 500 μM (33 g/l)) indicated a small increase in docetaxel plasma

binding to 95.1 % (decrease of fu to 4.9 % i.e. a 21 % decrease).

Based on this data estimations were made for the PK/toxicity data analysis in Vol.1.99

The free docetaxel fraction was also determined by ultrafiltration of plasma samples collected at the end of infusion and at different times post-infusion during study TAX016. Docetaxel levels in ultrafiltrate were measurable for all three patients at the end of infusion, but were undetectable at later times, except for one patient, for whom levels could be determined at 20 minutes post infusion.

The end of infusion samples showed 97.8 ± 0.8 % protein binding.

Further results in the form of a table were sent by the firm 11/7/94 to show that docetaxel at a concentration of 1.5 μg/mL was around bound in the absence of Polysorbate 80.

PKPD Analysis:

TITLE: Study of the relationship between the pharmacokinetics and the pharmacodynamics of Taxotere ™ (RP56976, docetaxel) in cancer patients **(Vol. 1.97 page 6-39-43 and Vol. 1.99 page 6-41-7).**

OBJECTIVES:
1. To explore whether the interpatient variability in pharmacokinetics, as predicted by the population pharmacokinetics model translates into different pharmacodynamic effects.

2. To assess the prognostic importance of patients clinical features and pharmacokinetic parameters (clearance, estimated during cycle 1) in determining the chance of response, and the risk of developing some toxicities, namely grade IV neutropenia and fluid retention.

Subject Demographics:
A total of 847 patients were entered into the database. 577 of these ie 68.1% had PK data. 2705 observations were available in terms of patients having PK by number of cycles received.

Diagnosis	Patients with PK data
Breast cancer	
NSCL	
Other tumors	

There were 17 patients in the breast cancer trials, 22 patients in the NSCL trials and 17 patients in the other cancer trials that were not included in the original population PK modeling **adding a total of 56 patients**. The 577 patients in this database **do not include the Phase I patients.**

STUDY DESIGN
Several different patient populations all in Phase II trials were included. A total of 10 different tumor types were in the database. The analysis of response (ie tumor regression) used the breast cancer and non small cell lung patients alone. These were also subgrouped. The analysis of safety included all patients and all tumor types.

The analysis of PK/response relationship used the patients in the response dataset alone. The analysis of the PK/neutropenia used patients evaluable for neutropenia. The analysis of PK/fluid retention used all patients in the database.

The "core" model consisted of clinical covariates in relation to outcome. The second step involved assessing the additional influence of PK parameters using their estimates from the Population PK model. The pharmacokinetic parameters were estimated either by Bayesian estimation or by prediction.

GENERATION OF INDIVIDUAL PHARMACOKINETIC PARAMETER ESTIMATES FOR PK/PD ANALYSIS

Individual PK estimates (predictions) of clearance were generated using the final model for all the Phase II patients available for population PK/PD (n = 577, index set + validation set + additional patients).

Two sets of estimates were considered : Bayesian estimates using parameter estimates from the final population model as priors and individual concentrations designated as CLj

Predictions by the final population model, using only individual covariates (BSA, ALB, AGE, HEP12, AAG) designated as ^CLj

The major contribution of AAG to the population model and its possible influence clinically in terms of protein binding was investigated by generating these estimates:

- Clearance of unbound drug : CLu_j.

$$CLu_j = CL_j / fu_j$$

where fu, the fraction of drug unbound to plasma proteins was based on binding constants estimated *in vitro* (see review of Protein binding studies page 91) and actual protein levels (ALB and AAG) measured in patient's plasma. The plasma levels of other proteins were assumed to be normal that might contribute to docetaxel binding. So

$$fu = 1/(1 + \Sigma nP_iK_i)$$

where n is the number of binding sites on a given protein i and P_i is the protein concentration in μM and K_i is the association constant in μM^{-1}.

The Clearance prediction by the population model without the effect of AAG (i.e. AAG set to the mean) was designated: ^CLj*.

The following factors were developed from the clearance estimates defined above.

f_1 = (mean CL)/ CL_j
f_2 = (mean CLu)/ CLu_j
f_3 = (mean ^CL/ ^CL_j
f_4 =(mean ^CL*/ ^CL_j*

Pharmacokinetic variability can be predicted by estimates from f_1,f_2 or f_3 ,f_4. On the other hand comparison of f_1,f_2 to f_3 ,f_4 predictors allows conclusions to be drawn as to the value of measured drug levels and the value of the population model. The significance of AAG and hence protein binding in relation to pharmacodynamics, was assessed by comparison of f_1 vs. f_2 and f_3 vs. f_4.

The Appendix to this report shows the manner in which the values for AAG and the factors were

categorized for the purpose of univariate analysis.
Patients were also considered by grouping into treated vs. untreated previously. Those patients treated with **adjuvant** chemotherapy were grouped as untreated.

The analysis also compared the patients with pharmacokinetic data available (N=577) to those without PK data (N=270) in terms of demographics and clinical covariates by means of chi-square test. Covariates such as performance status, age, number of organs affected, visceral organs involved, baseline liver metastases and baseline bone metastases tested not significant. A significantly different (p=0.013) number of patients with pharmacokinetic data had been previously treated (28% vs. 36%).

An estimation of actual drug exposure (AUC) was also described by the expression :

$$AUC_j = \frac{Dose}{CL_j}$$

The statistical methods used were multivariate analysis consisting of logistic regression and Cox (hazard) Model.

Efficacy Analysis:
This was carried out for the breast and NSCL patients alone. The core model consisted of the population final model and the covariates to which AAG level, the "f" PK factors and the initial dose multiplied by the "f" PK factors were added independently. Called PK factors for the rest of the text.

A logistic regression model was used in this analysis.

Safety Analysis:
Fluid retention and neutropenia were evaluated in this analysis. Evaluable patients for neutropenia analysis were defined as those patients with at least one blood count between Day 2 and Day 19 with no G-CSF given in the cycle. The first cycle alone was considered since PK parameters were from this cycle.

Logistic regression again was used as a multivariate analysis method, where the response probability $p = Pr(Y=1|X)$ and $\text{logit}(p) = \alpha + \beta' X + \epsilon$.

Cox regression with time dependent covariates was used to model the risk of developing fluid retention ie the hazard function, $h(t,z) = h_0(t)\exp(z'\beta)$. Pre-medication was an additional covariate in the analysis. This was grouped into reference group (no premedication), premedicated group (corticosteroids at cycle one) or mixed group (antihistamines cycle one, or no pre-med cycle one, but pre-med at some time during the study). This was a step-wise method

with a 10% level of significance.

The time dependent covariate was cumulative dose at each cycle.

RESULTS:

Response - Breast

A core model was obtained from logistic regression of the Integrated Summary of Efficacy. So covariates used in this analysis for the statistical section were also used here. This model was applied to the evaluable population where there were 146 patients with PK data. The core model showed that each additional organ affected (N_ORG) decreases the odds of response by 45%. PK factors as described previously and dose multiplied by PK factors were added to the model one at a time. The individual models were compared using the log likelihood statistic

AAG plasma level proved to be significant as a predictor of response (p=0.02) and when it was part of the core model (0.054). The odds of response decreased by 52% for each mg/L increase in AAG plasma level.

Addition of the PK factors did not improve the model.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	2.3680	0.6650	12.6809	0.0004	.	10.676
N_ORG	1	-0.5584	0.1704	10.7328	0.0011	-0.356383	0.572
PR_HORMO	1	0.5454	0.3655	2.2264	0.1357	0.150869	1.725
AAG	1	-0.7432	0.4033	3.3949	0.0654	-0.201269	0.476

See appendix for summary Table.

Response - Lung

A core model was obtained from logistic regression of the Integrated Summary of Efficacy. So covariates used in this analysis for the statistical section were also used here. This model was applied to the evaluable population where there were 151 patients with PK data. The core model showed covariates of age, baseline bone metastases and baseline liver metastases. Age alone is significant in the core model (p=0.188); the odds of response increased by 4.5 % for each year of age. PK factors as described previously and dose multiplied by PK factors were added to the model one at a time. The individual models were compared using the log likelihood statistic.

AAG plasma level proved to be significant as a predictor of response ($p<0.01$) and when it was part of the core model ($p<0.02$). The odds of response decreased by 64% for each mg/L increase in AAG plasma level.

Addition of the PK factors did not improve the model with the exception of factor f3 having borderline significance ($p=0.10$) without the presence of AAG in the model. However f3 was found to be strongly correlated to AAG ($r=0.66$).

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-1.8064	1.5222	1.4082	0.2353	.	0.164
AGE	1	0.0437	0.0225	3.7810	0.0518	0.219690	1.045
BL_BONEM	1	-0.7063	0.5982	1.3939	0.2378	-0.147502	0.493
BL_LIVEM	1	-0.5566	0.5541	1.0091	0.3151	-0.121276	0.573
AAG	1	-1.0304	0.4259	5.8533	0.0155	-0.315926	0.357

Safety - Neutropenia (first course)

The core model had significant covariates of baseline neutrophils and prior chemotherapy (obtained from the Integrated Summary of Safety). 534 patients were included of which the overall incidence of neutropenia (grade IV) was 61.6% 34 patients were excluded because of missing baseline values.

PK factors as described previously and dose multiplied by PK factors were added to the model one at a time. Also HEP12 (hepatic impairment indicator) and HEP12B (hepatic impairment indicator with no baseline metastasis) were included as covariates. The individual models were compared using the log likelihood statistic.

AAG was a strong predictor of neutropenia alone or added to the core model ($p<0.0001$). PK factors f1 and f2 improved the model being strongest when AAG is present in the model. So an increase in AAG levels decreases the probablility of neutropenia. An increase in the PK factors (interpreted as a decrease in clearance of docetaxel) increase the likelihood of toxicity. HEP12 did not have a significant effect. However an improvement in the model was seen with the addition of HEP12B but the effect was diluted out with the addition of f1, this implied that the effect of HEP12B was due to the changed PK in this population group (previously predicted to have a 30% decrease in docetaxel clearance).

The odds of Grade IV neutropenia:
decreased by 16% when baseline neutrophils increased by 1 X 10^9 /L,
decreased by 85% for each mg/L increase in AAG
increased by 90% for patients with prior chemotherapy
increased by 4X for each unit increase of f1 which means that clearance decreased two fold.

Safety - Fluid Retention

There were 575 patients with 10 different tumor types. The incidence of fluid retention was 49%.

The core model included the covariates sex, baseline protein level, number of organs involved and a covariate reflecting premedication. Premedication consisted of antihistamines and/or steroids. The reference group were those patients who received no premedication. In the Integrated Safety report the premedication was divided into 3 groups for statistical evaluation:

Type 1 Antihistamines alone
Type 2 Short administration of corticosteroids This also included patients on antihistamines at Day 1 and/or Day minus 1
Type 3 Long administration of corticosteroids This also included patients on antihistamines during at least 2 days from Day minus 1.

Based on safety data from this report Type 3 premedication ie long term corticosteroids was recommended. Type 1 premedication seemed to worsen fluid retention.

With this analysis, there were two indicator variables STER1 and MIX. STER1 represented patients who received corticosteroids in cycle 1 and MIX represented those patients who received antihistamines in cycle 1 or no premedication in cycle 1 but some premedication whilst in the study.

AAG was a strong predictor of fluid retention alone ($p<0.01$) or in addition to the core model ($p<0.02$). Both AAG and PK factors together in the model show an improved model. Without AAG, the PK factor f2, f3 and f4 have an impact. The best model was one that included the clinical covariates and AAG with cumulative dose (in relation to f1).

See appendix for Summary Table
The risk of fluid retention was
increased 1.6X for female patients
decreased 33% with 1g/L increase in AAG
decreased by 25% when protein levels increased by 10 g/L
decreased by 35% when steroids were included in the premedication
increased by 20% for unit increase in f1 implying a two fold decrease in clearance or this can also be interpreted as an increased risk of 10% for each additional 100mg/m^2 course.
decreased by 13% with each additional organ involved

COMMENTS:
Assumptions made were that protein levels were normal and that fu could be calculated from actual values of ALB and AAG. This assumption seems reasonable since the predominate proteins involved in binding were shown to be albumin and AAG both of which were measured.

Covariates were categorized according to clinical significance or into quartiles. Categories based on a different method other than quartiles might have produced a different result.

These were not randomized control studies.

The combination of the studies in the safety analysis with different response rates is probably acceptable.

It is assumed that there is no nonlinearity in the pharmacokinetics and hence cumulative exposure can be estimated since data is available for cycle 1 alone. This assumption would not hold for toxic side-reactions or drug/metabolites remaining in sites other than the central compartment.

Neutropenia was only studies for the first course. It would have been interesting to see the relationship for neutropenia over a series of courses.

The acceptable level of significance was set at 10% but no statistical justification was given for this.

The firm looked at evaluable not intent to treat patients.

CONCLUSIONS:

The strong trend in AAG plasma levels as a predictor to toxicity in terms of fluid retention and Grade IV neutropenia is noted and needs further investigation.

The implication of steroids being of benefit is muddied by the various premedication schedules used and needs to be clarified in some way.

STER1 still contains some patients on antihistamines.

The firm have not addressed the mechanism behind the high incidence of fluid retention and AAG levels and the paradoxical relationship of clearance. The drug is highly bound and has a relatively low clearance (restrictive), so the expectation is as the protein levels rise, clearance decreases since the fraction unbound decreases. Therefore, greater exposure means the expectation of higher incidence of neutropenia. However, here neutropenia incidence is lower, the higher AAG. Response is a difficult measure to relate to pharmacokinetics with many chemotherapeutic agents, more success has been met with the relations established between the pharmacokinetics of a drug and its toxicity.

TABLE 1
SUMMARY OF LOGISTIC REGRESSION MODELS - BREAST

MODEL	-2 LOG L	Model Compared to:	Difference in -2 LOG L	p-value
intercept	198.436			
AAG alone	192.214	intercept	6.222	0.013
CORE	182.723	intercept	15.712	<0.001
CORE + F1*DOSE	179.484	core	3.239	0.072
CORE + F1	178.937	core	3.786	0.052
CORE + F2*DOSE	180.639	core	2.084	0.149
CORE + F2	180.148	core	2.575	0.109
CORE + F3*DOSE	181.421	core	1.302	0.254
CORE + F3	180.506	core	2.217	0.136
CORE + F4*DOSE	182.720	core	0.003	0.956
CORE + F4	182.529	core	0.194	0.660
CORE + AAG	179.006	core	3.717	0.054
CORE + AAG + F1*DOSE	177.024	core + AAG	1.982	0.159
CORE + AAG + F1	176.527	core + AAG	2.479	0.115
CORE + AAG + F2*DOSE	176.949	core + AAG	2.057	0.152
CORE + AAG + F2	176.460	core + AAG	2.546	0.111
CORE + AAG + F3*DOSE	178.999	core + AAG	0.007	0.933
CORE + AAG + F3	178.866	core + AAG	0.140	0.708
CORE + AAG + F4*DOSE	178.999	core + AAG	0.007	0.933
CORE + AAG + F4	178.958	core + AAG	0.048	0.827

TABLE 2
SUMMARY OF LOGISTIC REGRESSION MODELS - LUNG

MODEL	-2 LOG L	Model compared to:	Difference in -2 LOG L	p-value
Intercept	180.415			
AAG alone	169.492	Intercept	10.923	<0.001
CORE	169.329	Intercept	11.086	0.011
CORE + F1*DOSE	169.316	core	0.013	0.909
CORE + F1	169.327	core	0.002	0.964
CORE + F2*DOSE	166.863	core	0.466	0.495
CORE + F2	166.938	core	0.391	0.532
CORE + F3*DOSE	167.332	core	1.997	0.158
CORE + F3	166.313	core	3.016	0.082
CORE + F4*DOSE	169.125	core	0.204	0.652
CORE + F4	166.842	core	0.687	0.407
CORE + AAG	162.817	core	6.512	0.011
CORE + AAG + F1*DOSE	161.144	core + AAG	1.673	0.196
CORE + AAG + F1	161.190	core + AAG	1.627	0.202
CORE + AAG + F2*DOSE	161.385	core + AAG	1.432	0.231
CORE + AAG + F2	161.426	core + AAG	1.391	0.238
CORE + AAG + F3*DOSE	162.766	core + AAG	0.051	0.821
CORE + AAG + F3	162.817	core + AAG	0.000	1.000
CORE + AAG + F4*DOSE	162.817	core + AAG	0.000	1.000
CORE + AAG + F4	162.761	core + AAG	0.056	0.813

TABLE 3
Summary of Logistic Regression Models - Neutropenia

MODEL	-2 LOG L	Model compared to:	Difference in -2 LOG L	p-value
intercept alone	683.077			
AAG alone	588.454	intercept	74.623	<0.001
CORE	585.554	intercept	77.522	<0.001
CORE + F1*DOSE	580.695	core	4.859	0.028
CORE + F1	579.948	core	5.606	0.018
CORE + F2*DOSE	575.101	core	10.453	0.001
CORE + F2	573.633	core	11.921	0.001
CORE + F3*DOSE	584.105	core	1.449	0.229
CORE + F3	584.179	core	1.375	0.241
CORE + F4*DOSE	585.543	core	0.011	0.916
CORE + F4	585.479	core	0.075	0.784
CORE + AAG	560.452	core	25.102	<0.001
CORE + AAG + F1*DOSE	535.947	core + AAG	24.505	<0.001
CORE + AAG + F1	533.801	core + AAG	26.651	<0.001
CORE + AAG + F2*DOSE	539.462	core + AAG	20.99	<0.001
CORE + AAG + F2	537.313	core + AAG	23.139	<0.001
CORE + AAG + F3*DOSE	555.392	core + AAG	5.060	0.024
CORE + AAG + F3	554.375	core + AAG	6.077	0.014
CORE + AAG + F4*DOSE	558.801	core + AAG	1.651	0.199
CORE + AAG + F4	558.082	core + AAG	2.370	0.124
CORE + AAG + HEP12	559.118	core + AAG	1.334	0.248
CORE + AAG + HEP12 + F1	533.594	core + AAG + HEP12	25.524	<0.001
CORE + AAG + HEP12B	555.068	core + AAG	5.384	0.020
CORE + AAG + HEP12B + F1	532.885	core + AAG + HEP12B	22.183	<0.001

HEP12 =1 for pasents with hepatic impairment: SGOT or SGPT > 60 IU and ALKPH > 300 IU.
HEP12B=1 for pasents with hepatic impairment: SGOT or SGPT > 60 IU and ALKPH > 300 IU and no baseline bone metastases

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	2.3804	0.3845	38.3279	0.0001	.	10.809
BASENEUT	1	-0.1804	0.0495	13.3027	0.0003	-0.280243	0.835
PR_CHEMO	1	0.6602	0.2275	8.4246	0.0037	0.178343	1.935
AAG	1	-1.7777	0.2849	38.9439	0.0001	-0.538619	0.169
F1	1	1.4040	0.2957	22.5486	0.0001	0.377929	4.072

the odds of neutropenia Grade IV :

TABLE 4
SUMMARY OF COX MODELS - FLUID RETENTION

MODEL	-2 LOG L	Model compared to:	Difference in -2 LOG L	p value
null	3048.450			
AAG alone	3035.138	null	11.312	<0.001
CORE	3007.403	null	39.047	<0.001
CORE + F1*CUM. DOSE	3005.462	core	1.941	0.164
CORE + F1	3007.402	core	0.001	0.975
CORE + F1 + CUM. DOSE	2987.824			
CORE + F2*CUM. DOSE	3003.447	core	3.956	0.047
CORE + F2	3006.992	core	0.411	0.521
CORE + F2 + CUM. DOSE	2996.691			
CORE + F3*CUM. DOSE	3007.271	core	0.132	0.716
CORE + F3	3003.185	core	4.218	0.040
CORE + F3 + CUM. DOSE	2992.972			
CORE + F4*CUM.DOSE	3005.531	core	1.672	0.171
CORE + F4	3005.700	core	1.703	0.192
CORE + F4 + CUM. DOSE	2996.077			
CORE + AAG	3000.995	core	6.408	0.011
CORE + AAG + F1*CUM. DOSE	2995.578	core + AAG	5.417	0.020
CORE + AAG + F1	3000.076	core + AAG	0.919	0.338
CPRE + AAG+ F1 + CUM.DOSE	2987.939			
CORE + AAG + F2*CUM.DOSE	2996.038	core + AAG	4.959	0.026
CORE + AAG + F2	3000.100	core + AAG	0.895	0.344
CORE + AAG + F2 + CUM. DOSE	2988.092			
CORE + AAG + F3*CUM. DOSE	2997.713	core + AAG	3.282	0.070
CORE + AAG + F3	3000.847	core + AAG	0.148	0.700
CORE + AAG + F3 + CUM. DOSE	2990.152			
CORE + AAG + F4*DOSE	2997.726	core + AAG	3.269	0.071
CORE + AAG + F4	3000.348	core + AAG	0.647	0.421
CORE + AAG + F4 + CUM. DOSE	2989.649			

The best model is that involving AAG and f_1 scaling the cumulative dose, as seen below:

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
MIX	1	0.229069	0.12825	3.19035	0.0741	1.257
STER1	1	-0.423329	0.24078	3.09104	0.0787	0.655
SEX	1	0.446126	0.12961	11.84764	0.0006	1.562
N_ORG	1	-0.138451	0.05542	6.24046	0.0125	0.871
BL_TPROT	1	-0.027910	0.00929	9.02745	0.0027	0.972
AAG	1	-0.395096	0.12904	9.37443	0.0022	0.674
CUMDOSE*F1	1	0.000949	0.0003880	5.97986	0.0145	1.001

4.4. OTHER INDICATIONS

					PTS. WITH PK DATA		
INDICATION	STUDY	Previous Treatment†	Pre-Medication	PTS. REGISTERED	N	TOTAL NO. OF CYCLES	DOSE
Colorectal	220	Untreated	no	40	32	91	100 mg/m^2
	230	Untreated	yes‡	18	18	50	100 mg/m^2
	257	Untreated	yes‡	19	9	18	100 mg/m^2
Melanoma	222	Untreated	no	36	29	136	100 mg/m^2
SCLC	224	Previously Treated	no	34	26	89	100 mg/m^2
Renal	226	Untreated	no	33	21	71	100 mg/m^2
Head & Neck	227	Untreated	no	43	28	128	100 mg/m^2
Gastric	236	Untreated	no	42	31	129	100 mg/m^2
Soft tissue / Sarcoma	245	Previously Treated	no	31	16	74	100 mg/m^2
Ovarian	252	Previously Treated	yes‡	47	10	54	100 mg/m^2
OVERALL - OTHER IND.		[illegible]	[illegible]	345	220 (63.8% of reg.)	840	[illegible]
OVERALL - PHASE II		[illegible]	[illegible]	847	577 (68.1% of reg.)	2705	[illegible]

†for advanced disease
‡Not all patients received premedication

Not 2.56 Canada
Renal

4.3. LUNG

						PTS. WITH PK DATA			
INDICATION	STUDY	Previous Treatment	Population	Pre-Medication	PTS. REGISTERED	N	EVAL. FOR EFFIC.	TOTAL NO. OF CYCLES	SCHEDULED DOSE
NSCLC	270	Previously Treated	platinum resistant	yes†	44	22	19	135	100 mg/m^2
	271		platinum resistant	yes†	44	30	26	149	100 mg/m^2
	231	Untreated		yes†	49	39	27	178	100‡ mg/m^2
	232			yes†	41	31	25	143	100 mg/m^2
	223			no	43	37	30	182	100 mg/m^2
	269			yes†	46	31	25	145	100 mg/m^2
OVERALL LUNG					269	189 (70.3% of reg.)	151 (56.1%) of reg.)	912	
OVERALL for EFFICACY					502	357 (71.1% of reg.)	297 (59.1% of reg.)	1665	

†Not all patients received premedication
‡75 mg/m^2 for patient nos.

4.2. BREAST

						PATIENTS WITH PK DATA			
INDICATION	STUDY	Previous Treatment	Population	Pre-Medi-cation	PTS REGIS-TERED	N	EVAL. FOR EFFIC.	TOTAL NO. OF CYCLES	SCHED-ULED DOSE
Breast	221	Previously Treated		no	39	26	22	134	100 mg/m^2
	233		anthracycline resistant	yes†	41	31	27	185	100 mg/m^2
	267		anthracycline resistant	yes†	42	27	22	165	100 mg/m^2
	237	Previously Untreated		no	35	27	24	128	100 mg/m^2
	266			yes†	37	35	33	209	100 mg/m^2
	280			no	39‡	22	18	132	75 mg/m^2
OVERALL BREAST					233	168 (72.1% of reg.)	146 (62.7% of reg.)	953	

†Not all patients received premedication
‡Patient no. was registered but not included in the database.

SUMMARY OF PARAMETERS FROM PK ANALYSIS

PARAMETER	VALUES	CATEGORIES FOR UNIVARIATE ANALYSIS
• AAG	range of g/l	<1.0; 1.0 - 1.3; 1.3 - 1.6; ≥1.6
• Factor 1	range of	>0.85; 0.85 - 1.00; 1.00 - 1.15; ≥1.15
• Factor 2	range of	>0.85; 0.85 - 1.00; 1.00 - 1.15; ≥1.15
• Factor 3	range of	>0.85; 0.85 - 1.00; 1.00 - 1.15; ≥1.15
• Factor 4	range of	>0.85; 0.85 - 1.00; 1.00 - 1.15; ≥1.15

PARAMETER	VALUES	CATEGORIES FOR UNIVARIATE ANALYSIS
• Tumor characteristics:		
• visceral/not visceral	yes/no	yes/no
• no. of organs involved	1,2,3,4,5,6	≤2; >2
• baseline bone metastasis	yes/no	yes/no
• baseline liver metastasis	yes/no	yes/no
• Prior therapy		
• chemotherapy	yes/no	yes/no
• number of regimens	0,1,2,3	≤1; ≥2
• hormonal therapy	yes/no	yes/no
• anthracycline resistant (breast only)	yes/no	yes/no
• cisplatinum resistant (lung only)	yes/no	yes/no

5. COVARIATES

5.1. CLINICAL COVARIATES

Possible prognostic clinical covariates in the analyses include:

PARAMETER	VALUES	CATEGORIES FOR UNIVARIATE ANALYSIS
• patient characteristics		
• performance status (WHO)	0,1,2,3	0-1; ≥2
• age	range 27-73 years	<50; ≥50
• sex	1=male 2=female	
• baseline neutrophils	range	>1.3;1.3-3.7; 3.7-4.9;≥4.9
• baseline total protein (fluid retention analysis only)	range g/l	N/A
• Hepatic impairment† (neutropenia analysis only)	yes/no	yes/no
• Hepatic impairment and no baseline bone metastasis‡ (neutropenia analysis only)	yes/no	yes/no
• drug delivery		
• premedication	none, antihistamines or corticosteroids	N/A
• initial dose	mg/m^2	75; 100
• initial actual dose	mg/m^2	
• cumulative dose (by cycle)	time-dependent	N/A

†Hepatic impairment is defined by: SGOT or SGPT > 60 IU and ALKPH > 300 IU

‡Hepatic impairment with no baseline bone metastases is defined by: SGOT or SGPT > 60 IU and ALKPH > 300 IU and no baseline bone metastases.

ASSAY VALIDATION - Vol. 1.59 page 6-1-240

ANALYTICAL METHODOLOGIES:

Docetaxel was measured by high performance liquid chromatography (HPLC) with ultraviolet (UV) detection at 225 nm. The method developed at RPR Antony was taken as the reference by the different pharmacokinetic investigators. The method involves a solid-phase extraction step (ethyl C2 micro-columns) using an Advanced Automated Sample Processor (AASP Varian) followed by a reverse phase HPLC. A back-flush procedure is used to speed up the assay. The calibration range of this method is 10-5000 ng/ml in plasma and in urine with coefficients of variation less than 11% and 9 % respectively for plasma and urine, using 0.5 to 1 ml sample. Higher levels can be measured after sample dilution.

Mobile Phase: Methanol 0.3%: Orthophosphoric acid (67.5:32.5 v:v)
Flow rate: 1 mL/min
Column: Spherosil C18, 5μm (250X4.6 mm ID)

1 mL of water/acetonitrile (70/30, v/v) is added during the solid phase extraction procedure. The RPR method is often referred to by the developers i.e. Verginol, Bruno etc. RP 56976.
A manual extraction method was used by external Phase I investigators and for samples drawn in the US Phase II studies. In all cases cross-validation of the method used by each investigator was performed by comparative analysis of selected plasma controls and patient samples at RPR

Specificity: The validation report showed chromatograms of blank plasma and those with docetaxel and the internal standard paclitaxel.

Linearity: Range 10 to 5000 ng/mL : $r^2 \geq 0.996$

LOQ: 10 ng/mL

Accuracy and Precision: Within-day reproducibility in plasma 1.9 %CV (100 ng/mL) to 12.1 %CV (25 ng/mL) N=6 runs. The within-day %CV in urine as 2.1% (500 ng/mL) to 8.2% (250 ng/mL).

Recovery: The recovery of docetaxel from plasma was 81.6%±7.3% (at 25 ng/mL, N=6) and 94.7% ±1.8 % (at 2500 ng/mL, N=6). The recovery of paclitaxel from plasma was 100.6%±3.9%(at 250 ng/mL, N=12). The recovery of docetaxel from urine was 90.3%±7.0%(at 25 ng/mL,N=6) and 90.9% ±2.2 % (at 2500 ng/mL, N=6). The recovery of paclitaxel from urine was 93.8%±2.5%(at 150 ng/mL, N=12).

Stability: Docetaxel is stable in plasma/urine for 8 hours at 21°C. Post-extraction and stability on micro-columns was found to be good for 48 hours.

Pharmacokinetic studies were conducted under the responsibility of both RPR and external investigators as summarized in table 1.

Table 1 : Analytical methods used for docetaxel determination in Phase I and II studies.

Study code	Investigator name or study director	Location	Limit of Quantif. ng/ml
TAX001	R. Bruno	RPR, Antony (F)	10
TAX002	M.A. Graham	Glasgow (UK)	15
TAX003	R.A. Newman	Houston, TX (USA)	15
TAX004	J.G. Kuhn	San Antonio, TX (USA)	15
TAX005	D. de Valeriola	Bruxelles (B)	15
TAX006	R. Bruno	RPR, Antony (F)	10
TAX016	D de Valeriola	Bruxelles (B)	15
Phase II	R. Bruno	RPR, Antony (F)	10
	J.M. Wilkinson	Pharmaco-LSR Richmond, VA (USA).	10-25
	S.L. DePhilipps	RPR, Collegeville, PA(USA)	

The RPR France method was adapted by A report was submitted to outline the validation of the method (**Vol. 1.59 page 6-1-345**). This method was then cross-validated with the previously developed RPR method. The following summarizes this information:

Specificity:Shown from representative chromatograms; no interference from diphenhydramine nor dexamethasone.

Linearity:

10 to 2500 ng/mL Mean correlation coefficient of 0.9993.

LOQ:10 ng/mL

Precision: Within-day %CV from 2.57 to 7.49%. Inter-day %CV from 4.1 to 6.6%

Recovery:%recovery ranged from 69.7 to 80.2% over three control levels.

Accuracy:% Difference from nominal for the 4 QC standards ranged from -0.412 to 9.56 (N=6, within-day) and 0.917 to 10.2 (N=11, between-day).

Cross-validation: The clinical samples and calibration standards gave significantly different results between the two sites, however QC standards prepared by and sent to RPR France did not give significantly different results between the two methods.

APPENDIX

Pharmacokinetics in the Japanese population: Vol. 135 page 8-36-249
TAX 015 was a Phase 1 dose escalation study conducted in Japan. Plasma samples were only collected up to 5 hours post administration of the drug, so the design was not too good in terms of number of samples taken etc. The following was stated in the submission "No difference was observed in the pharmacokinetics of docetaxel between Caucasian and Asian patients". The pharmacokinetic data was provided as mean parameters in a summary table :

Dose mg/m²	AUC[1] μg.h/mL	Elimination half-life h
10 (N=1)	0.35	2.7
20 (N=3)	1.38 ± 1.06	3.2 ± 1.7
50 (N=4)	2.08 ± 0.4	5.4 ± 3.4
60 (N=6)	2.44 ± 0.83	7.5 ± 6.3
70 (N=6)	3.77 ± 1.19	6.1 ± 3.6
90 (N=3)	4.37 ± 0.61	4.2 ± 0.5

[1] AUC = area under the plasma concentration time curve.

It is not clear what premedication (if any) or concomitant medication was given to these patients. The clearances are within the range of those found in the Phase 1 studies conducted in US/Europe.

Table 5

Taxotere (docetaxel) for Injection Concentrate-Quantitative Compos

Component	Per 20 mg Vial	Per 80 mg Vial
Docetaxel	20 mg[1]	80 mg[1]
Polysorbate 80 DF (Dioxane Free)	q.s. 0.5 mL	q.s 2.0 mL
Dehydrated Alcohol	NMT 2.0%w/v	NMT 2.0%w/v
Nitrogen*	n/a	n/a

[1]This quantity is the theoretical quantity of docetaxel expressed as the anhydrous form. The actual quantity of docetaxel trihydrate used (Wd) calculated using the following formula:

Wd = (Wt/Td) x 100, where Wt = theoretical quantity of docetaxel anhydrous, and
Td = potency of docetaxel trihydrate

*Nitrogen is used as a purging agent during the manufacturing process, a described in Item 3.5(e) of this submission.

IN-VIVO STUDY DATA SUMMARY

Study Number	Piv(Sup) Yes/No	No. Pts Mal/Fem	Dose mg	Cmax µg/ml	AUC h.µg/ml	CL l/h/m²	Vss l/m²	Comments	Report Location (Volume /Page)
Tax 001	y	1/0	5	0.1	-	-	-	Inf. Dur.	6-3-6
		1/0	10	0.1	-	-	-	1-2 h	
		0/1	20	0.8	1.0	20.8	16		
		0/3	30	0.6	1.3	24.9	81		
				(0.5)	(0.3)	(6.3)	(61)		
		0/1	40	0.4	0.7	54.0	190		
		0/3	55	0.8	1.4	40.0	39		
				(0.4)	(0.4)	(10.5)	(34)		
		0/3	70	1.9	2.8	26.7	16		
				(0.3)	(0.9)	(8.2)	(5)		
		1/5	85	2.4	4.1	22.6	72		
				(0.9)	(1.3)	(7.7)	(24)		
		3/1	100	2.4	5.9	17.0	95		
				(0.4)	(0.5)	(1.5)	(62)		
		0/4	115	2.7	5.2	22.2	53		
				(0.9)	(0.2)	(0.7)	(39)		
Tax 002	n	0/1	20	0.1	0.9	21.7	-	Inf. Dur.	6-11-6
		1/2	40	0.1	2.2	18.5	-	= 24h	
				(0.04)	(0.1)	(0.2)	-	Cmax =	
		1/3	55	0.1	2.6	25.3	-	end of	
				(0.1)	(0.9)	(14.0)	-	infusion	
		2/1	70	0.2	3.5	21.0	-	conc.	
				(0.1)	(0.9)	(4.8)	-	Vss not	
		3/2	90	0.5	7.8	12.0	-	reported	
				(0.1)	(1.7)	(2.6)	-		

Parameters are espressed as mean (SD).

IN-VIVO STUDY DATA SUMMARY

Study Number	Piv(Sup) Yes/No	No. Pts Mal/Fem	Dose mg	Cmax µg/ml	AUC h.µg/ml	CL l/h/m²	Vss l/m²	Comments	Report Location (Volume /Page)
Tax 003	n	0/3	12	0.06-0.27	0.57 (0.41)	52.3 (64.5)	311 (118)	1 h Inf. Day 1. Cmax range.	6-14-6
		0/3	14	0.22-0.52	0.39 (0.15)	39.9 (16.7)	11 (6)		
		3/3	16	0.12-0.63	0.49 (0.40)	43.5 (22)	133 (125)		
Tax 004	n	1/2	5 /6h	0.11 (0.05)	- -	- -	- -	Dose /infusion duration	6-19-6
		1/1	10 /6h	0.86 (0.36)	- -	- -	- -		
		1/0	20 /6h	0.18	-	-	-		
		1/1	40 /6h	0.31 (0.15)	1.9 (0.2)	21.0 (1.9)	246 (304)		
		0/2	60 /6h	0.90 (0.36)	3.7 (0.4)	16.5 (1.9)	29 (11)		
		2/7	80 /6h	0.87 (0.30)	3.9 (1.6)	23.2 (8.0)	38 (21)		
		2/4	100 /6h	1.04 (0.39)	6.8 (2.3)	16.0 (4.9)	108 (101)		
		2/3	100 /3h	1.77 (0.65)	4.5 (1.1)	23.4 (6.4)	93 (99)		
		1/0	80 /2h	1.49	2.7	29.3	19		
		4/10	100 /2h	2.47 (1.09)	4.4 (1.4)	24.5 (7.4)	76 (43)		
		3/0	115 /2h	2.48 (0.71)	5.8 (1.8)	21.0 (6.1)	112 (74)		
Tax 005	n	5/7	10 to 65	0.28-2.7	0.3-4.2	28.8 (28.2)	79 (100)		6-31-6

Parameters are espressed as mean (SD).

DRUG FORMULATION DEVELOPMENT SUMMARY

a) Phase I studies with pharmacokinetics determination

STUDY NUMBER	BATCH N°	DOSAGE FORM(S) AND STRENGTH	BATCH SIZE	REPORT LOCATION (Volume/Page)
TAX 001	CB 4445 CB 4587 CB 5327 CB 4579 CB 4993 CB 5545 CB 5363	Concentrate for infusion F1/F2	1600 2700 3000 4200 3100 6000 3000	6-3-6 (Volumes 6-3 to 6-8)
TAX 002	CB 4445 CB 4587 CB4579	Concentrate for infusion F1	1600 2700 4200	6-11-6 (Volumes 6-11 to 6-13)
TAX 003	CB 4579 CB 4587 CB 5140 CB 5327	Concentrate for infusion F1	4200 2700 2950 3000	6-14-6 (Volumes 6-14 to 6-18)
TAX 004	CB 4579 CB 4587 CB 5140 CB 5327 CB 5363 CB 5545	Concentrate for infusion F1/F2	4200 2700 2950 3000 3000 6000	6-19-6 (Volumes 6-19 to 6-30)
TAX 005	CB 4445 CB 4579 CB 4587 CB 4993	Concentrate for infusion F1	1600 4200 2700 3100	6-31-6 (Volumes 6-31 to 6-36)
TAX 006	CB 4993 CB 5545	Concentrate for infusion F2	3100 6000	6-9-6 (Volumes 6-9 and 6-10)
TAX 016	CB 5327 CB 5413 CB 5363	Concentrate for infusion F2	3000 3000	6-2-6 (Volume 6-2)

- Formulation 1 : 15 mg/ml docetaxel, alcool 50%, polysorbate 80 , 50% (1 ml)
- Formulation 2 : 40 mg/ml docetaxel in polysorbate 80 (2ml)

DRUG FORMULATION DEVELOPMENT SUMMARY

b) Phase II studies involved in the population pharmacokinetic/pharmacodynamic analysis

STUDY NUMBER	BATCH N°	DOSAGE FORM(S) AND STRENGTH	BATCH SIZE	REPORT LOCATION (Volume/Page)
TAX 233	CB 5140 CB 5437 CB 5486 CB 5545 CB 5546	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000 6000 6000	6-37-6
TAX 267	CB 5140 CB 5545 CB 5437 CB 5546	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 6000 3000 6000	6-37-13
TAX 221	CB 5240 CB 5364 CB 5437 CB 5363 CB 5436 CB 5530 CB 5546 CB 5545 CB 5583	Concentrate for infusion 40 mg/ml (2ml) formulation 2	3000 3000 3000 3000 3000 3000 6000 6000 6000	6-37-20
TAX 266	CB 5140 CB 5364 CB 5545 CB 5327 CB 5437	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 6000 3000 3000	6-37-28
TAX 237	CB 5140 CB 5436 CB 5545 CB 5240 CB 5437 CB 5546 CB 5637	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 6000 3000 3000 6000 6000	6-37-35
TAX 280	CB 5546 CB 5637	Concentrate for infusion 40 mg/ml (2ml) formulation 2	6000 6000	6-37-44
TAX 270	CB 5140 CB 5364 CB 5486 CB 5327 CB 5437 CB 5545	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000 3000 3000 6000	6-37-51
TAX 271	CB 5140 CB 5364 CB 5546 CB 5327 CB 5545	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 6000 3000 6000	6-37-58
TAX 231	CB 5140 CB 5364 CB 5546 CB 5327 CB 5545	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 6000 3000 6000	6-37-60
TAX 232	CB 5140 CB 5364 CB 5486 CB 5327 CB 5437 CB 5545	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000 3000 3000 6000	6-37-62

DRUG FORMULATION DEVELOPMENT SUMMARY

b) Phase II studies involved in the population pharmacokinetic/pharmacodynamic analysis

STUDY NUMBER	BATCH N°	DOSAGE FORM(S) AND STRENGTH	BATCH SIZE	REPORT LOCATION (Volume/Page)
TAX 269	CB 5140 CB 5437 CB 5546 CB 5327 CB 5545 CB 5364	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 6000 3000 6000 3000	6-37-69
TAX 223	CB 5240 CB 5364 CB 5437 CB 5363 CB 5436 CB 5530 CB 5546 CB 5545 CB 5583	Concentrate for infusion 40 mg/ml (2ml) formulation 2	3000 3000 3000 3000 3000 3000 5546 6000 6000	6-37-71
TAX 252	CB 5140 CB 5364 CB 5437 CB 5486 CB 5545	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000 3000 6000	6-37-78
TAX 230	CB 5140 CB 5364 CB 5486	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000	6-37-85
TAX 257	CB 5140 CB 5437 CB 5486	Concentrate for infusion 40 mg/ml (2ml) formulation 2	2950 3000 3000	6-37-92
TAX 220	CB 5240 CB 5363 CB 5364 CB 5436 CB 5437 CB 5530 CB 5545 CB 5546 CB 5583	Concentrate for infusion 40 mg/ml (2ml) formulation 2	3000 3000 3000 3000 3000 3000 6000 6000 6000	6-37-100
TAX 222	CB 5240 CB 5363 CB 5364 CB 5436 CB 5437 CB 5530 CB 5545 CB 5546 CB 5583	Concentrate for infusion 40 mg/ml (2ml) formulation 2	3000 3000 3000 3000 3000 3000 6000 6000 6000	6-37-108
TAX 224	CB 5240 CB 5363 CB 5364 CB 5436 CB 5437 CB 5530 CB 5545 CB 5546 CB 5583	Concentrate for infusion 40 mg/ml (2ml) formulation 2	3000 3000 3000 3000 3000 3000 6000 6000 6000	6-37-115

IN-VIVO STUDY DATA SUMMARY

Phase I studies with pharmacokinetics determinations

Study Number	Piv(Sup) Yes/No	No. Pts Mal/Fem	Dose mg	Cmax µg/ml	AUC h.µg/ml	CL l/h/m²	Vss l/m²	Comments	Report Location
Tax 006	y	2/1	70	2.6 (0.6)	3.5 (1.1)	24.3 (8.2)	47 (13)		6-9-6
		3/4	100	3.6 (0.9)	4.6 (0.8)	22.4 (4.1)	149 (138)		
Tax 016	y	1/2	100	2.1-2.2	2.2-2.9	28-41	17-53	metabol.	6-2-6

Parameters are expressed as mean (SD).

Phase II studies involved in the population pharmacokinetic/pharmacodynamic analysis

n=577

Study Number	Piv(Sup) Yes/No	No. Pts for PK analysis	Dose mg/m²	AUC h.µg/ml	CL l/h/m²	Fu	Comments	Report Location
Tax 233	p	31	100					
Tax 267	p	27	100					
Tax 221	p	26	100					
Tax 266	s	35	100					
Tax 237	s	27	100					
Tax 280	s	22	75					
Tax 270	p	22	100					
Tax 271	p	30	100				Population	
Tax 231	p	38	75/100	5.37	37.0	0.056		Report
Tax 232	p	31	100				pharmacokinetics	No. 1835
Tax 269	p	31	100	(2.29)	(12.3)	(0.005)		6-39-6
Tax 223	p	37	100				Analysis	and
Tax 252	ss	10	100					6-40-6
Tax 230	ss	18	100					
Tax 257	ss	9	100					
Tax 220	ss	32	100					
Tax 222	ss	29	100					
Tax 224	ss	26	100					
Tax 225	ss	21	100					
Tax 227	ss	28	100					
Tax 236	ss	31	100					
Tax 245	ss	16	100					

p : pivotal

s : supportive

ss : safety

Parameters are expressed as mean (SD).

DRUG FORMULATION DEVELOPMENT SUMMARY

b) Phase II studies involved in the population pharmacokinetic/pharmacodynamic analysis

STUDY NUMBER	BATCH N°	DOSAGE FORM(S) AND STRENGTH	BATCH SIZE	REPORT LOCATION (Volume/Page)
TAX 223	CB 5240	Concentrate for	3000	6-37-124
	CB 5363	infusion 40 mg/ml	3000	
	CB 5364	(2ml)	3000	
	CB 5436	formulation 2	3000	
	CB 5437		3000	
	CB 5530		3000	
	CB 5545		6000	
	CB 5546		6000	
	CB 5583		6000	
TAX 227	CB 5240	Concentrate for	3000	6-37-132
	CB 5363	infusion 40 mg/ml	3000	
	CB 5364	(2ml)	3000	
	CB 5436	formulation 2	3000	
	CB 5437		3000	
	CB 5530		3000	
	CB 5545		6000	
	CB 5546		6000	
	CB 5583		6000	
TAX 236	CB 5240	Concentrate for	3000	6-37-139
	CB 5363	infusion 40 mg/ml	3000	
	CB 5364	(2ml)	3000	
	CB 5436	formulation 2	3000	
	CB 5437		3000	
	CB 5530		3000	
	CB 5545		6000	
	CB 5546		6000	
	CB 5583		6000	
TAX 245	CB 5437	Concentrate for	3000	6-37-147
	CB 5363	infusion 40 mg/ml	3000	
	CB 5583	(2ml)	6000	
	CB 5530	formulation 2	3000	
	CB 5545		6000	
	CB 5436		3000	
	CB 5546		6000	

JUL 6 1995

NDA 20-449
Taxotere Injection
40 mg/mL -2mL or 0.5 mL vial
Rhone -Poulenc Rorer

Submission Date: May 22, 1995

Reviewer: Lydia C. Kaus, M.S., Ph.D.

Type of Submission: NME IP **BB Amendment**

Synopsis:
The sponsors have submitted information to the NDA in response to FDA letter dated May 11th, 1995 and a FAX dated May 10th, 1995.

1. FDA Request:
Forward copies of example NONMEM control files from the new look at the data, and the datasets that include HEP10, HEP20, HEP10N, HEP20N and HEP12N. The summary results were sent to the Agency 5/5/95 in Appendix II.

Sponsors' response:
A diskette and hard copy was sent to the Agency as per the above request.

Comment:
The results were confirmed within the Agency by running the NONMEM control file.

FDA Requests :
2. In report IBP/Biodyn #1728, Vol. .56 page 5-23-70 of the NDA submission, it was noted in rats that dexamethasone was an inducer of the metabolism of taxotere *in vitro*. Does the sponsor have any *in vitro* data in human hepatocyte system, where dexamethasone, prednisolone, methylprednisolone were tested on docetaxel biotransformation?

3. Does the sponsor have any *in vivo* data on the effect of dexamethasone on the pharmacokinetics of docetaxel?

Sponsors' response to 2 & 3:
"in vitro data
In cultured hepatocytes preincubated with dexamethasone (50μM), the metabolism of docetaxel was induced by 41%. Those data are described in the paper by Marre et al submitted for publication to Cancer Res. "

Comment:
The sponsors provided a copy of the journal article by Marre. Induction of docetaxel by dexamethasone was shown. The sponsors also submitted a summary table of data in which the influence of dexamethasone on docetaxel was studied in tumor bearing mice. This information

had not been submitted as part of the original NDA. The sponsors were requested to submit the full study to the Pharmacologists at the Agency. The PK-PD database was also analyzed further to see the effect of dexamethasone on d ·:etaxel clearance. A Figure was submitted to illustrate this information. The sponsors were requested to identify the individual patients on dexamethasone used from the population PK database in this analysis.

FDA Request:
4. Forward the individual pharmacokinetic data from TAX 015 study, Vol. 1.135

Sponsors' response to 4:

A table showing individual data from this study was submitted.

Comment:
Previously, the sponsors had submitted Pharmacokinetics in the Japanese population: Vol. 135 page 8-36-249. TAX 015 was a Phase 1 dose escalation study conducted in Japan. Plasma samples were only collected up to 5 hours post administration of the drug, so the design was not too good in terms of number of samples taken etc. The following was stated in the submission "No difference was observed in the pharmacokinetics of docetaxel between Caucasian and Asian patients". The pharmacokinetic data was provided as mean parameters in a summary table :

Dose mg/m²	AUC[1] µg.h/mL	Elimination half-life h
10 (N=1)	0.35	2.7
20 (N=3)	1.38 ± 1.06	3.2 ± 1.7
50 (N=4)	2.08 ± 0.4	5.4 ± 3.4
60 (N=6)	2.44 ± 0.83	7.5 ± 6.3
70 (N=6)	3.77 ± 1.19	6.1 ± 3.6
90 (N=3)	4.37 ± 0.61	4.2 ± 0.5

[1] AUC = area under the plasma concentration time curve.

The clearances are within the range of those found in the Phase 1 studies conducted in US/Europe. The individual data are in keeping with the previous statement. (See attached Table).

Comment to send to sponsors:
The Division of Biopharmaceutics awaits the individual patient identification of the group of patients used in the analysis of the influence, if any, of dexamethasone on docetaxel clearance submitted in the present amendment. This request was made at the 5/26/95 meeting with the sponsors.

6/23/95

Lydia C. Kaus, M.S., Ph.D.
Pharmacokinetics Evaluation Branch

FT 6/6/95
Mehul Mehta, Ph.D., Section Head.

cc file NDA 20-449
HFD-150:Pease
HFD-150: Div. File
HFD-150:Beitz
HFD-150:DeGeorge
HFD-426:Biopharm/Drug File
HFD-426: Biopharm/Mehta
HFD-426: Biopharm/Fleischer
HFD-426: Biopharm/ChenL
HFD-340: Viswanathan

Appendix III - Evaluation of the effect of dexamethasone co-administration on the pharmacokinetics of docetaxel

1 - Methods

1.1 - Patients

We considered in this analysis the patients evaluable for PK/PD presented previously (n = 577 from 22 Phase II studies, see Table 1 of reference 1). Dexamethasone was given to 55 patients at first cycle. Typical dosage regimen involved short term oral administration of 8 mg b.i.d. for 3 to 5 days, starting the day, or the day before, docetaxel administration.

1.2 - Data analysis

The potential influence of administration of dexamethasone on docetaxel CL was evaluated using the population model prediction error which allows assessment of the influence of covariates on clearance after adjustment for the effects of the other covariates in the model. This approach was previously used as a diagnostic tool during model building in the population PK analysis (1).

The clearance prediction error ($\hat{pe}_j$) was computed as follows :

$$\hat{pe}_j\ (\%) = (\hat{CL}_j - CL_j) / \hat{CL}_j \times 100$$

where j refers to a particular patient, $\hat{CL}_j$ denotes the population model predicted clearance using actual values of patient j covariates (BSA, ALB, AGE, HEP12, AAG) and CL_j is a posterior Bayes estimate of clearance based on actual concentration measurements for patient j and parameter estimates of the final population model (model of reference 1) as priors. Those parameters values are those previously generated for the PK/PD analysis (chapter 3.5.2 of reference 1).

2 - Results

The mean of CL estimates for the 55 patients who were co-administered dexamethasone was 37.1 l/h (SD : 13.6 l/h) i.e. very close that of the general population of 37.0 l/h (SD : 12.3 l/h, n = 577, see table 14 of reference 1). Mean $\hat{pe}$ was - 1.1 % (SD : 28.4 %), similar to that of other patients as illustrated in the enclosed Figure.

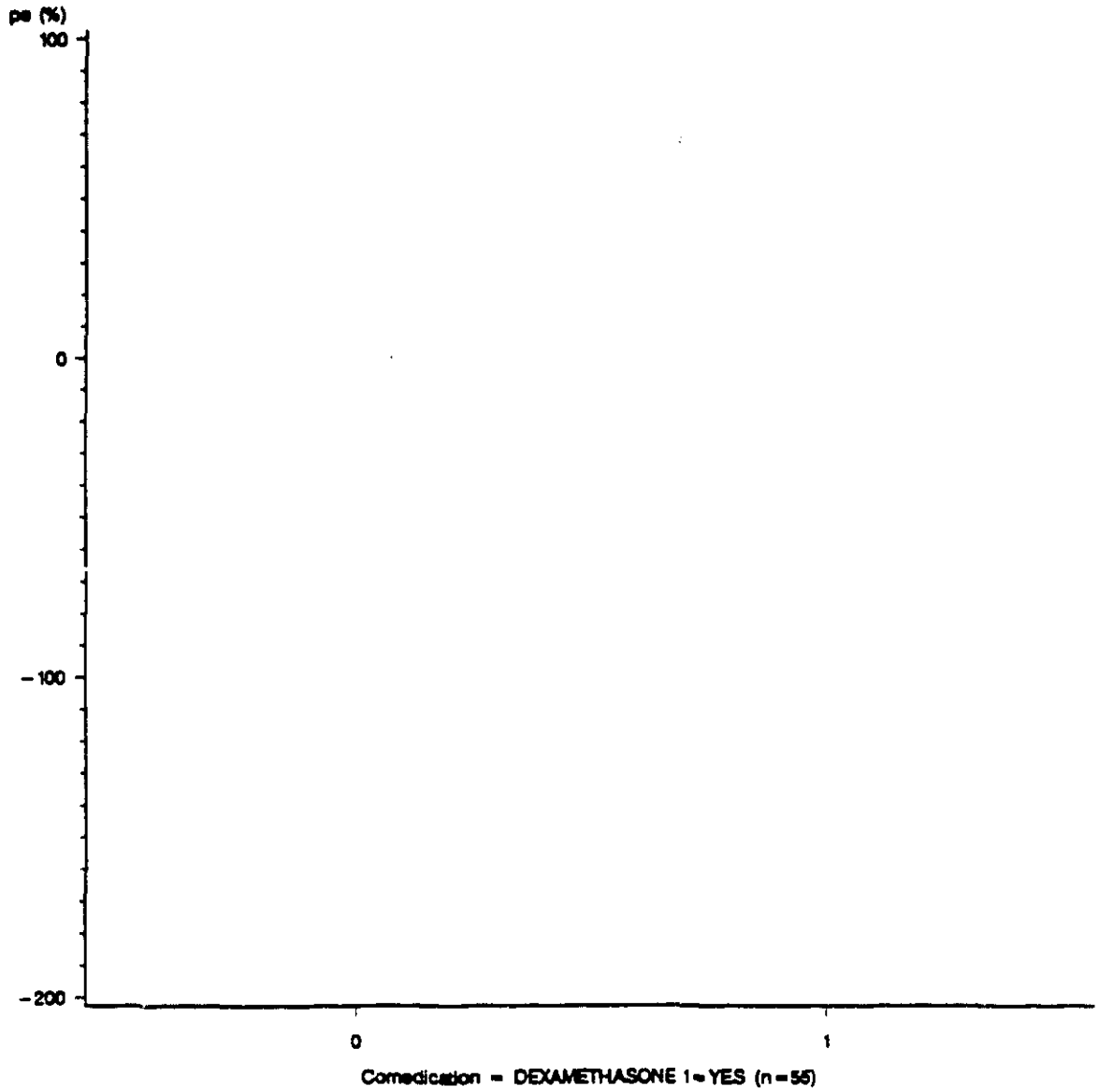
In conclusion, there is no evidence in our data base, that the administration of dexamethasone affects docetaxel clearance. Dexamethasone typical dosage regimen only involved short term oral administration starting the day before or the day of docetaxel administration. Induction may therefore not be achieved with this schedule which it is currently in use clinically.

3 - Reference

1 - R. Bruno and L.B. Sheiner. Population pharmacokinetics of docetaxel (RP 56976, Taxotere®) : Analysis of data from Phase II studies - First cycle of treatment. Report IBP/Biodyn N° 1835 issued July 11, 1994.

Docetaxel – Phase II Studies

Comparison of pe (n=577)



Taxotere Phase I Study in Japan

'92 8.5

Taxotere Individual Pharmacokinetic Parameters after IV infusion - Revised

Patient	Dose mg/m²	Dose mg	Infusion Time(hr)	Peak plasma concentration (ng/ml)	$t_{1/2}$ (hr)	$(AUC)_0^T$ (hr·ng/ml)	$(AUC)_0^\infty$ (hr·ng/ml)	CL (l/hr·m²)	Apparent MRT (hr)	Actual MRT (hr)	Vss (l/m²)	0-48 hr Urinary excretion (% of dose)
	10	12.7		298.7	2.7	275.6	350.3	28.5	2.80	2.30	65.6	4.20
	20	24.0		610.0		444.3	530.3	37.7	2.79	2.29	86.3	1.08
	20	24.0		741.4		594.6	716.8	27.9	2.84	2.34	65.3	2.52
	20	24.0		487.1		902.8	1021.1	19.6	3.22	2.47	48.4	4.24
	20	25.7		516.5		932.8	1038.6	19.3	2.20	1.70	32.8	+
	20	24.6		1571.5		2249.4	2574.6	7.8	2.30	1.80	14.0	3.33
	50	70.0		1102.7		2033.6	2114.5	23.6	1.59	0.97	22.9	3.38
	50	77.5		2247.0		1873.5	2144.2	23.3	3.39	2.81	65.5	4.29
	50	77.5		933.5		1448.5	-	-	-	-	-	3.02
	50	77.5		739.2		591.5	-	-	-	-	-	4.72
	50	76.0		820.8		1081.5	-	-	-	-	-	+
	50	76.0		1073.1		1240.0	-	-	-	-	-	1.22
	50	76.0		1031.8		1087.8	1156.2	43.2	2.47	1.76	76.0	+
	50	73.0		1658.1		2404.0	2528.3	19.8	2.26	1.51	29.9	4.08
	50	75.0		1437.3		1506.8	1805.8	27.7	4.71	4.15	115.0	0.84
	50	66.0		1948.1		1507.9	1546.9	32.3	1.19	0.69	22.3	2.96
	60	79.0		1565.0		1896.8	1941.2	30.9	1.32	0.82	25.3	0.83
	60	96.0		1085.7		1120.4	1232.5	48.7	2.49	1.99	96.9	0.50
	60	95.2		2442.0		2959.4	3167.8	18.9	2.46	1.95	37.0	1.64
	60	91.2		1442.8		2956.1	3306.4	18.1	7.66	7.16	129.6	1.18
	60	80.0		971.1		1926.2	2022.3	29.7	2.24	0.91	27.0	4.11
	60	98.4		2173.1		2514.5	2942.5	20.4	9.62	9.12	186.0	+
	70	115.5		2741.8		3716.6	3933.3	17.8	2.02	1.52	27.1	3.21
	70	105.0		2265.3		2002.7	2132.1	32.8	1.95	1.45	47.6	4.17
	70	93.0		2080.2		3200.4	3363.6	20.8	2.27	1.44	30.0	+
	70	105.0		2437.2		5261.1	5593.9	12.5	5.07	4.32	54.0	+
	70	95.0		1912.1		1987.6	2093.4	33.4	1.85	1.35	45.1	4.12
	70	96.0		1738.1		2907.9	2995.6	23.4	1.89	1.39	32.5	0.21
	70	90.0		2702.4		3999.3	4228.5	16.6	4.47	3.97	65.9	3.40
	70	90.0		2371.0		3237.8	3467.0	20.2	5.00	4.50	90.9	1.92
	90	136.0		3564.7		3905.6	4024.7	22.4	1.53	0.91	20.4	4.63
	90	127.0		2025.7		3897.8	4018.2	22.4	1.71	1.21	27.1	4.62
	90	140.0		2728.5		4896.5	5077.5	17.7	1.93	1.07	18.9	3.09

- : not evaluable, + : no results

$t_{1/2}$: method of residuals (KY-2, -3 are not evaluable.)

AUC : trapezoidal method (observed value) and extrapolation of the terminal phase to infinity.

CL : Dose / AUC_0^∞

Vss : CL × acutual MRT, actual MRT = (apparent MRT) - (infusion time/2)

AUC_0^∞ of KY-2, -3 and KY-1, -2 are not evaluable. (AUC extrapolation accounts for more than 30 % of experimental AUC.)

micro

D. Peak
SEP 26 1995

CONSULTATIVE REVIEW TO HFD-150

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #3
25 September 1995

A. 1. NDA 20-449

SPONSOR Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

2. PRODUCT NAMES: TAXOTERE®

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is a sterile solution for infusion following dilution. Each carton contains 2 components: a vial of concentrated drug solution and a vial of diluent solution. The drug product is packaged in 7 cc glass vials containing 0.5 mL (20 mg) and 15 cc vials containing 2 mL (80 mg) for single dose use. Each 20 mg dose is packaged with 1.5 mL solvent in a 7 cc vial. Each 80 mg dose is packaged with 6 mL solvent in a 15 cc vial. After combining the concentrate and solvent, premixed drug is diluted with 0.9% Sodium Chloride solution or 5% dextrose solution to a final drug concentration of 0.3 to 0.9 mg/mL, and this is infused over a 1 hour period.

4. METHOD(S) OF STERILIZATION: The drug concentrate component is manufactured by processing. The solvent component is manufactured process.

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: 27 July 1994 (subject of Microbiologist's Review #1, 20 December 1995)

2. DATE OF AMENDMENT: 14 April 1995 (subject of Microbiologist's Review #2, dated 17 July 1995), and 14 September 1995 (subject of this review)

3. RELATED DOCUMENTS: References pertinent to this submission are provided in Table 1, below.

Table 1. Applicable DMFs referenced in cover the letter of the NDA.

DMF Holder	DMF #	Subject
Rhone-Poulenc Rorer, Vitry-Sur-Seine, France		Bulk Drug Solution
Rhone-Poulenc Rorer, Dagenham, Essex, UK		Drug Product
		Glass Vials
		Stoppers

4. ASSIGNED FOR REVIEW: 25 September 1995

C. REMARKS: The applicant responds in this amendment to a question concerning the process for sterilization of stoppers, and provides information and commitments concerning bioburden and its impact on solution filtration.

D. CONCLUSIONS: The application is recommended for approval.

9-25-95

David Hussong, Ph.D.

9/26/95

cc:

Original NDA 20-449
HFD-160/Consult File
HFD-150/CSO/D. Pease
HFD-150/Chemist/S. Koepke
HFD-160/D. Hussong

drafted by: D. Hussong, 09/25/95
R/D initialed by: P. Cooney, 09/26/95

JUL 19 1995

CONSULTATIVE REVIEW TO HFD-150

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #2
17 July 1995

A. 1. NDA 20-449

SPONSOR Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

2. PRODUCT NAMES: TAXOTERE®

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is a sterile solution for infusion following dilution. Each carton contains 2 components: a vial of concentrated drug solution and a vial of diluent solution. The drug product is packaged in 7 cc glass vials containing 0.5 mL (20 mg) and 15 cc vials containing 2 mL (80 mg) for single dose use. Each 20 mg dose is packaged with 1.5 mL solvent in a 7 cc vial. Each 80 mg dose is packaged with 6 mL solvent in a 15 cc vial. After combining the concentrate and solvent, premixed drug is diluted with 0.9% Sodium Chloride solution or 5% dextrose solution to a final drug concentration of 0.3 to 0.9 mg/mL, and this is infused over a 1 hour period.

4. METHOD(S) OF STERILIZATION: The drug concentrate component is manufactured by processing. The solvent component is manufactured process.

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: 27 July 1994 (subject of Microbiologist's Review #1, 20 December 1995)

2. DATE OF AMENDMENT: 14 April 1995 (subject of this review and sent in 2 consults dated 27 April 1995 and 11 July 1995))

3. RELATED DOCUMENTS: References pertinent to this submission are provided in Table 1, below.

Table 1. Applicable DMFs referenced in cover the letter of the NDA.

DMF Holder	DMF #	Subject
Rhone-Poulenc Rorer, Vitry-Sur-Seine, France		Bulk Drug Solution
Rhone-Poulenc Rorer, Dagenham, Essex, UK		Drug Product
		Glass Vials
		Stoppers

4. ASSIGNED FOR REVIEW: 1 May 1995

C REMARKS: The original NDA submission resulted in 4 general questions addressing broad areas of sterilization validation, component engineering and environmental control.

D. CONCLUSIONS: The application may be recommended for approval upon correction of in-process sterilization acceptance specifications.

7-18-95

David Hussong, Ph.D.

Pltz 7/19/95

Encs: 5

cc:

Original NDA 20-449
HFD-160/Consult File
HFD-150/CSO/D. Pease
HFD-150/Chemist/S. Koepke
drafted by: D. Hussong, 07/13/95
R/D initialed by: P. Cooney, 07/19/95

CONSULTATIVE REVIEW TO HFD-150

JAN 3 1995

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
20 December 1994

A. 1. NDA 20-449

SPONSOR Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

2. PRODUCT NAMES: TAXOTERE®

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is a sterile solution for infusion following dilution. Each carton contains 2 components: a vial of concentrated drug solution and a vial of diluent solution. The drug product is packaged in 7 cc glass vials containing 0.5 mL (20 mg) and 15 cc vials containing 2 mL (80 mg) for single dose use. Each 20 mg dose is packaged with 1.5 mL solvent in a 7 cc vial. Each 80 mg dose is packaged with 6 mL solvent in a 15 cc vial. After combining the concentrate and solvent, premixed drug is diluted with 0.9% Sodium Chloride solution or 5% dextrose solution to a final drug concentration of 0.3 to 0.9 mg/mL, and this is infused over a 1 hour period.

4. METHOD(S) OF STERILIZATION: The drug concentrate component is manufactured by processing. The solvent component is manufactured sterilization process.

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: 27 July 1994

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: References pertinent to this submission are provided in Table 1, below.

Table 1. Applicable DMFs referenced in cover the letter of the NDA.

DMF Holder	DMF #	Subject
Rhone-Poulenc Rorer, Vitry-Sur-Seine, France		Bulk Drug Solution
Rhone-Poulenc Rorer, Dagenham, Essex, UK		Drug Product
		Glass Vials
		Stoppers

4. ASSIGNED FOR REVIEW: 9 September 1994

C. REMARKS: The submission is a new NDA application with a separate sterility assurance section. A great amount of information was provided, in part because there are 2 container sizes, and 2 product solutions each sterilized using different methods.

D. CONCLUSIONS: The application is not recommended for approval for reasons of sterility assurance.

This review does not address stability issues. The chemist should evaluate the effect of the sterilization on the ethanol in the solvent component of this product.

David Hussong, PhD.

12-23-94

1/3/95

cc:

Original NDA 20-449
HFD-160/Consult File
HFD-150/CSO/D. Pease
HFD-150/Chemist/R. Lowenthal
drafted by: D. Hussong, 12/20/94
R/D initialed by: P. Cooney, 12/23/94

Chem

V. pearce

APR 29 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-449 **CHEM.REVIEW #:** 05 **REVIEW DATE:** 11-Apr-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NC	11-Mar-96	12-Mar-96	13-Mar-96
BL	25-Mar-96	26-Mar-96	27-Mar-96
NC	01-Apr-96	02-Apr-96	04-Apr-96

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

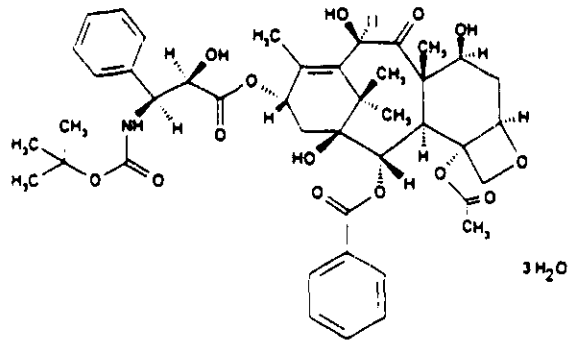
DRUG PRODUCT NAME

Proprietary:	Taxotere®
Nonproprietary/USAN:	Docetaxel Sterile Solution for Injection, Concentrate
Code Name/#:	RP56976
Chem.Type/Ther.Class:	1 P/neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic Breast Carcinoma
- Metastatic Non-Small Cell Lung Cancer

DOSAGE FORM: Sterile Concentrated non-Aqueous Solution
STRENGTHS: 20 mg or 80 mg/vial
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular Formula: $C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight: 861.94
CAS Number: 148408-66-6

RELATED DOCUMENTS (if applicable):

DMF	DMF
DMF	DMF
DMF	DMF

DMF DMF
DMF

CONSULTS:

Consult	Status	Comments
EER	completed	
Methods Validation	hold	
Microbiology	completed	
Statistics	pending	
Environmental Ass.	completed	

REMARKS/COMMENTS: The new correspondence NC, dated March 11, 1996 addressed the CMC issues listed Agency's fax, dated February 23, 1996, requesting information. Responses to the deficiencies are acceptable.

The amendment BL, dated March 25, 1996 and new correspondence, dated April 1, 1996 reponded to our comments on labelings.

CONCLUSIONS & RECOMMENDATIONS: Outstanding CMC issues have been resolved. Approval is recommended, pending satisfactory statistical evaluation of proposed expiration dating of the drug substance and the drug product.

Yung-Ao Hsieh 4-11-96
Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

RHWood 4-29-96
Rebecca H. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc:
Orig. NDA 20-449
HAD-150/Division File
HAD-150/RHWood
HAD-150/YAHsieh
HAD-150/DPease

D. Plaa

FEB 23 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls
(Labelings and Package Insert)

NDA #: 20-449 **CHEM.REVIEW #:** 04 **REVIEW DATE:** 22-Feb-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (AL)	01-Dec-95	04-Dec-95	09-Dec-95
Amendment (BL)	02-Feb-96	12-Feb-96	14-Feb-96

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

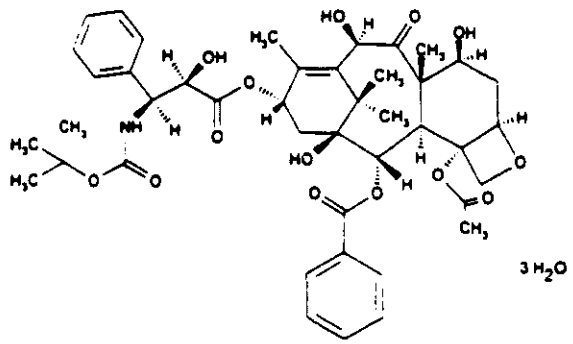
DRUG PRODUCT NAME

Proprietary:	Taxotere®
Nonproprietary/USAN:	Docetaxel Sterile Solution for Injection, Concentrate
Code Name/#:	RP56976
Chem.Type/Ther.Class:	1 P/neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic Breast Carcinoma
- Metastatic Non-Small Cell Lung Cancer

DOSAGE FORM: Sterile Concentrated non-Aqueous Solution
STRENGTHS: 20 mg or 80 mg/vial
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular Formula: $C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight: 861.94
CAS Number: 148408-66-6

Pages 2-3
Deleted
Draft Labeling

III. Recommendation/Conclusion:

It is recommended that the comments/requests listed in the Draft Information Request be conveyed to the applicant. The deficiencies should be addressed prior to approval.

Yung-Ao Hsieh 2-22-96
Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

RHWood 2-23-96
Rebecca H. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc:
NDA 20-449
HFD-150/Div. File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/DPease

1) · Pc ai
2-23-96

DIVISION OF ONCOLOGY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-449 **CHEM.REVIEW #:** 03 **REVIEW DATE:** 31-Jan-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BC)	30-Nov-95	12-Dec-95	05-Dec-95

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

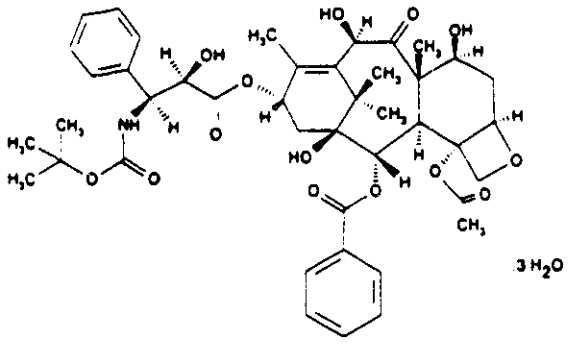
DRUG PRODUCT NAME

Proprietary:	Taxotere®
Nonproprietary/USAN:	Docetaxel Sterile Solution for Injection, Concentrate
Code Name/#:	RP56976
Chem.Type/Ther.Class:	1 P/neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic Breast Carcinoma
- Metastatic Non-Small Cell Lung Cancer

DOSAGE FORM: Sterile Concentrated non-Aqueous Solution
STRENGTHS: 20 mg or 80 mg/vial
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular Formula: $C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight: 861.94
CAS Number: 148408-66-6

RELATED DOCUMENTS (if applicable):

DMF	DMF
DMF	DMF
DMF	DMF
DMF	DMF

DMF

CONSULTS:

Consult	Status	Comments
EER	completed	
Methods Validation	Hold	Methods require modification
Microbiology	Pending	
Statistics	Hold	Statiscal consult sent on 9/22/95
Environmental Ass.	completed	

REMARKS/COMMENTS: This amendment addresses the CMC issues listed Agency's Approvable Letter dated October 27, 1995. Deficiencies associated with drug product specifications, analytical method and manufacturing process in the firm's responses have been identified: The proposed 0.2% limit of quantitation (LOQ) of the regulatory HPLC analytical method can not adequately quantitate unidentified impurities at levels between 0.1% and 0.2%, although the proposed specifications of the drug product have limited the total > 0.1% unidentified impurities to ≤ 0.5%. Furthermore, impurities such as RPR 10118 and related compounds are not properly controlled. In addition, in-process testing data of the bulk Taxotere® solution showed that in some lots, contents of total unidentified impurities (> 0.1%) are so high, that drug product manufactured from these bulk Taxotere® solutions would not meet the established limit of ≤ 0.5% for total unidentified impurities (> 0.1%).

Since degraded samples in animal studies have demonstrated increasing toxocities, it is imperative that the impurity levels in the drug product be adequately controlled.

CONCLUSIONS & RECOMMENDATIONS: The deficiencies which are listed in the Draft Information Request should be communicated to the applicant. It is recommended that all the deficiencies should be fully addressed prior to approval.

Yung-Ao Hsieh 1-31-96
Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

RHWood 2-23-96
Rebecca H. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc:
Orig. NDA 20-449
HAD-150/Division File
HAD-150/RHWood
HAD-150/YAHsieh
HAD-150/DPease

DIVISION OF DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-449 **CHEM.REVIEW #:** 02 **REVIEW DATE:** 28-Sep-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (AZ)	20-Jan-95	23-Jan-95	17-Aug-95
Amendment (BZ)	14- Apr-95	20-Apr-95	17-Aug-95
Amendment (BZ)	23-May-95	24-May-95	17-Aug-95

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

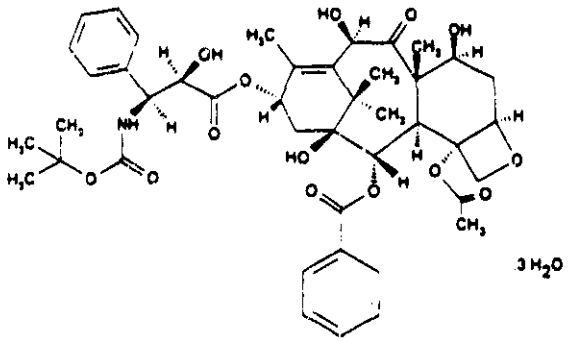
DRUG PRODUCT NAME

Proprietary:	Taxotere®
Nonproprietary/USAN:	Docetaxel Sterile Solution for Injection, Concentrate
Code Name/#:	RP56976
Chem.Type/Ther.Class:	1 P/anti-neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic Breast Carcinoma
- Metastatic Non-Small Cell Lung Cancer

DOSAGE FORM: Sterile Concentrated non-Aqueous Solution
STRENGTH'S: 20 mg or 80 mg/vial
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular Formula: $C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight: 861.94
CAS Number: 148408-66-6

RELATED DOCUMENTS (if applicable):

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

CONSULTS:

Consult	Status	Comments
EER	completed	
Methods Validation	Hold	Methods require modification
Microbiology	Pending	
Statistics	Hold	Stability data needs to be updated
Environmental Ass.	completed	

REMARKS/COMMENTS: The drug substance is synthesized from

The drug product is supplied as a concentrate in polysorbate 80 (single dose vials of 20 mg/0.5 mL or 80 mg/2 mL with a premix % ethanol in Water for Injection). Since % degraded Taxotere® appeared to exhibit increased neurotoxicity in single-dose and five-daily-dose animal studies, the stability of the drug product is a significant issue (see Addendum 1 to Review and Evaluation of Pharmacology and Toxicology Data, Dated 7-27-1994). In addition to impurities carried over from the drug substance, additional degradants have been identified in Taxotere® concentrate. The Agency has requested that data demonstrating that the proposed impurity limits of the shelf-life specifications do not exceed levels observed to be safe in pre-clinical and clinical trials be submitted (see FDA Request for Information, from Dr. J. Beitz, dated 11-9-1994); yet, primary data of levels of impurities and degradants in trial batches at the time of infusion to patients have not been provided (see the firm's reponses of 4-7-1995 and of 5-23-1995). The same HPLC conditions and method of quantitation are used for analyzing docetaxel and the drug product. However, the prescribed HPLC method has not been adequately validated to show that it is capable of detecting and quantitating potential degradants. The HPLC method used for related substances has a limit of quantitation of only % and no data to support the ability to detect potential process impurities or degradants have been provided. Updated stability data of three 80 mg industrial-scale batches and three 20 mg industrial-scale batches after 12 months storage have been submitted. The proposed shelf-life, based on data of these industrial-scale batches, for Taxotere® 80 mg is 15 months and that for the Taxotere® 20 mg is 12 months. Statistical analyses are consulted to HAD-715 for review.

CONCLUSIONS & RECOMMENDATIONS: The deficiencies which are listed in the Draft Deficiency Letter to the Applicant, Chemist's Part, should be communicated to the applicant. It is recommended that all the deficiencies should be fully addressed prior to approval.

Yung-Ao Hsieh 10-2-95

Yung-Ao Hsieh, Ph.D.
Review Chemist, HAD-150

cc:
Orig. NDA 20-449
HAD-150/Division File
HAD-150/RHWood RHWood 10-23-95
HAD-150/YAHsieh
HAD-150/DPease

D pearl

NOV , 9 1994

DIVISION OF DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls for Drug Substance Section

NDA #: 20-449 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 07-NOV-94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	27-JUL-94	27-JUL-94	02-AUG-94

REVIEWER: Richard Lowenthal, M.S.

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

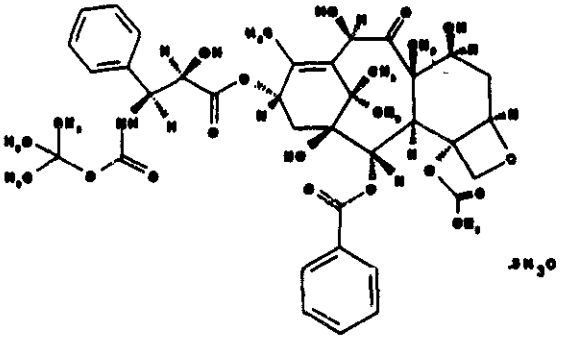
Proprietary:	Taxotere
Nonproprietary/USAN:	Docetaxel Sterile Solution for Injection, Concentrate
Code Name/#:	RP56976
Chem.Type/Ther.Class:	1 P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: - Metastatic Breast Carcinoma
- Metastatic Non-Small Cell Lung Cancer

DOSAGE FORM: Sterile Concentrated non-Aqueous Solution
STRENGTHS: 20 mg or 80 mg/vial
ROUTE OF ADMINISTRATION: Intravenous Infusion
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



Chemical Name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Molecular Formula: $C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight: 861.94
CAS Number: 148408-66-6

RELATED DOCUMENTS (if applicable):

DMF DMF
DMF DMF

DMF
DMF
DMF

DMF
DMF

CONSULTS:

Consult	Status	Comments
EER	Pending	
Methods Validation	Hold	Methods require modification
Microbiology	Pending	
Statistics	Hold	Stability data needs to be updated
Environmental Ass.	Pending	

REMARKS/COMMENTS: The drug substance is manufactured

Drug product issues revolve around the specifications (two set have been submitted, release and shelf life) and stability of the drug product. Specification require additional methods for Heavy Metals, Chiral Purity and tightened impurity limits. The HPLC method used for related substances has a limit of quantitation of only % and no data to support the ability to detect potential process impurities or degradants has been provided. Stability with the drug product formulation is extremely poor at 4 °C and studies have demonstrated that at 25 °C over % potency loss in 15 days. Stability studies performed on material manufacturing by the commercial process in the commercial facilities is provided for 6 months. Supportive data is from material in a different facility and modified manufacturing process. Comparative data is provided at 25 °C, however, this data may not be relevant due to the rapid rate of degradation. Comparison of the 4 °C data demonstrates a significant difference in the rate of degradation. The stability protocol should be modified to include adequate temperatures, time points and methods. The stability of the drug is a significant issue since degraded samples tested in animal studies have demonstrate a consistently increasing toxicity as the material degrades (see pharmacology review).

CONCLUSIONS & RECOMMENDATIONS: NDA 20-449 is **NOT APPROVABLE** for chemistry manufacturing control. The RPR manufacturing process should be modified as described in the review or removed from the application. Specifications should reflect those demonstrated to be safe in animal and human clinical studies. Expiration dating should be re-evaluated based on the commercial process and revised specifications. An appropriate stability protocol should be used for expiration date extension.

Richard Lowenthal, M.S.
Review Chemist, HFD-150

cc:
Orig. NDA 20-449
HFD-150/Division File
HFD-150/RLowenthal
HFD-150/CSO/DPease
HFD-150/JBlumenstein/E.Tolgyesi
HFD-102/CKumkumian (#1 only)
R/D Init by: SUPERVISOR
filename: N20449r1.000

9/5 11/14/94

EA + Fons;

FREEDOM OF INFORMATION ENVIRONMENTAL ASSESSMENT FOR NDA 20-449 TAXOTERE® (DOCETAXEL) FOR INJECTION CONCENTRATE

TABLE OF CONTENTS

SECTION 1: Date:

July 21, 1994

SECTION 2: Name of applicant/petitioner:

Rhône-Poulenc Rorer Pharmaceuticals, Inc.

SECTION 3: Address:

500 Arcola Road
P. O. Box 1200
Collegeville, PA 19426-0107

SECTION 4: Description of the proposed action:

4(A) Description of proposed requested approval

Rhône-Poulenc Rorer Pharmaceuticals, Inc., is requesting approval of the use of Taxotere® (docetaxel) for Injection Concentrate for the treatment of patients with metastatic or locally advanced breast carinoma in whom previous therapy has failed or patients with metastatic or locally advanced non-small cell lung cancer in whom previous therapy has failed. Taxotere is a parenteral concentrate containing 40 mg docetaxel/ml to be diluted with an alcohol/water (13% w/w) solvent to produce a "premix". At the time of patient use this premix is further diluted in isotonic sodium chloride or glucose solution. Taxotere is available in 2 dosage presentations, namely as a 2.0 mL vial (80 mg docetaxel) to be diluted with 6.0 mL solvent or as a 0.5 mL vial (20 mg docetaxel) to be diluted with 1.5 mL solvent. The final concentration of docetaxel must be between 0.3 and 0.9 mg/mL.

4(B) Need for Action

Taxotere® for Injection Concentrate is indicated for the treatment of advanced breast cancer and advanced non-small cell lung cancer as a chemotherapeutic agent.

4(C) Production Locations

The production of Taxotere® can be separated into 4 key operations.

A summary of the sites involved is shown below and futher details are provided in Confidential Appendix 1.

SUMMARY OF PRODUCTION PROCESS, SITES, AND RESPONSIBILITIES.

Yew Needle Collection

RPR [Sedaherb, Muggenburg] (Europe) & Indena (Europe, India)
(Refer to DMF

⇩

Extraction of 10-deacetyl baccatin III (10-DAB)

RPR, Germany & Indena, Italy (Refer to DMF #s)

⇩

Chemical Synthesis of docetaxel

RPR, France

⇩

Manufacture of Taxotere®
Injection Concentrate with associated
13% Alcohol/H_2O solvent

RPR, France & UK

4(C)(1) Collection of the yew needles

For RPR GmbH:

1. Paul Müggenburg GmbH & Co.
   Bahnhofstraße 2
   D-25486 Alvesiohe
   GERMANY

2. Sedaherb
   Z.A. Du Colombier
   71610 Saint Lager sur Dheune
   FRANCE

The processed yew needles from these 2 sources are then provided to RPR, Cologne, Germany (see 4(C)(2) below) for extraction of 10-DAB.

3. INDENA S.p.A.
   Via Ripamonti
   9920100 MILAN - ITALY

For a complete description of the collection and extraction process and Environmental Assessment information of 10-DAB at Indena please refer to their Type I and II DMFs #10,463 and 10,462, respectively. A letter authorizing RPR's reference to their DMF's can be found in section 3.4(b)(i)(5) of this NDA.

4(C)(2) Extraction of 10-deacetyl baccatin III (10-DAB):

10-DAB (RP 61387) is a commercially available product. For this NDA, 10-DAB will be obtained from two sources as follows:

RHÔNE-POULENC RORER Gmbh
Nattermanallee 1
D 5000 - COLOGNE, GERMANY

INDENA S.p.A.
Via Ripamonti
9920100 MILAN - ITALY

For a complete description of the extraction process and Environmental Assessment information of 10-DAB at Indena please refer to their Type I and II DMFs #10,463 and 10,462, respectively. A letter authorizing RPR's reference to their DMF's can be found in section 3.4(b)(i)(5) of this NDA.

4(C)(3) Chemical Synthesis of Docetaxel

4(C)(3)(a) Starting materials.

The chemical synthesis begins with two key starting materials, namely:

1. 10-DAB - RP 61387 (sources described above)
2. methyl ester of N-tert-butoxycarbonyl-3-phenylisoserine (RPR 104493 - side-chain synthesized from benzaldehyde to be grafted on to the chemically protected 10-DAB)

4(C)(3)(b) The side chain, (RPR 104493) is synthesized at:

RHÔNE-POULENC RORER
Villeneuve-la-Garenne Plant
35, avenue Jean Jaurès
92390 VILLENEUVE-LA-GARENNE
FRANCE

4(C)(3)(c) Drug Substance, docetaxel (RP56976) synthesis sites.

The Drug Substance, docetaxel (RP 56976) is synthesized through a four stage process at the following facilities:

RHÔNE-POULENC RORER
Centre de recherches de Vitry-Alfortville
13 Quai Jules Guesde
94403 VITRY SUR SEINE
FRANCE

SERIPHARM
Technopole Universitaire
Rue Démocrite
72000 LE MANS
FRANCE

4(C)(4) Manufacture of the Drug Product, Taxotere for Injection Concentrate.

The drug product, Taxotere® for Injection Concentrate is manufactured as a bulk solution at:

RHÔNE-POULENC RORER
Centre de recherches de Vitry-Alfortville
13 Quai Jules Guesde
94403 VITRY-SUR-SEINE
FRANCE

and as the sterile finished product with solvent (ethanol/water) at:

RHÔNE-POULENC RORER
Rainham Road South
DAGENHAM
Essex RM 10 7 X S
UNITED KINGDOM

4(D) Location where the product will be used and disposed:

4(D)(1) Use

Taxotere® is intended to be used worldwide for the treatment of breast cancer and non-small cell lung cancer. It is anticipated that the distribution of Taxotere® will be worldwide.

4(D)(2) Rejected and Returned Goods

4(D)(2)(a) Drug Substance: Docetaxel

Rejected or expired docetaxel will be recovered by an approved rework procedure for docetaxel practiced at the RPR Vitry, France manufacturing site. Quantities of drug substance which cannot be recovered will be subjected to chemical destruction in caustic aqueous alcohol (Appendix 2 for Decontamination Procedure and docetaxel destruction procedure) at the production site and the resulting solution disposed of by an approved waste handler.

4(D)(2)(b) Drug Product: Taxotere®

Rejected and returned Taxotere® at the Dagenham, United Kingdom site will be maintained at the Dagenham site and returned to the Vitry Production site for recovery of docetaxel. Taxotere® from which the drug substance cannot be recovered, will be disposed of at the Dagenham site in accordance with the "Waste Disposal Procedure #S201-01" as referenced in Confidential Appendix 78 of this document.

Rejected and returned Taxotere® in the United States will be incinerated by Chambers Medical Technology of South Carolina, Hampton, SC, a fully owned subsidiary of Chambers Development Company, Inc., Pittsburgh, PA. This facility is duly licensed by the state of South Carolina. Please refer to Appendix 3 for Chambers' permits issued by the state of South Carolina. The permits include Water Pollution Control Permit (SC0042242), Bureau of Air Quality Control Construction Permits (0280-0021-CD, 0280-0021-CE and 0280-0021-CF) and the permit application for Municipal Solid Waste Incineration and Pyrolysis. The State of South Carolina has authorized Chambers to receive and incinerate rejected and returned goods from Rhône-Poulenc Rorer Pharmaceuticals, Inc. Please refer to the May 6, 1994 letter included in Appendix 3.

SECTION 5 Identification of Chemical Substances

5(A) Introduction

The physical and chemical properties of the drug substance docetaxel, the related isolated intermediates and raw materials are referenced in this section. The excipient, polysorbate 80, for the drug product, Taxotere® and the drug substance impurities and metabolites are also referenced with chemical and physical information.

3-19-12

5(B) Chemical Substances

5(B)(1) Drug Substance - docetaxel

The drug substance exists in the anhydrous and trihydrate forms. The latter form is the one used in making the drug product Taxotere®.

5(B)(1)(a) Names and Codes

Established generic name: Docetaxel

Chemical name: (2*R*,3*S*)-N-carboxy-3-phenylisoserine, *N-tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. (WHO Drug Information, Vol. 7, No. 4, 1993 - Prop. INN: List 65)

Other Established Chemical Names:

- USAN 1994 List

(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N-tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

- IUPAC

4-acetoxy-2α-benzyloxy-5β,20-epoxy-1,7β,10β,13α-tetrahydroxy-9-oxo-tax-11-ene, 13-ester with (2*R*,3*S*)-*N-tert*-butoxycarbonyl-3-phenylisoserine, trihydrate

- Chemical Abstract index name

1) Benzenepropanoic acid, .beta.-[[(1,1-dimethyethoxy) carbonyl]amino]-.alpha.-hydroxy-, 12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy 4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester trihydrate, [2aR[2a.alpha.,4.beta.,4a.beta.,6.beta., 9.alpha.(.alpha.R*,.beta.S*), 11.alpha.,12.alpha.,12a.alpha.,12b.alpha.]]

2) Benzenepropanoic acid, .beta.-[[(1,1-dimethyethoxy) carbonyl]amino]-.alpha.-hydroxy-, 12b- (acetyloxy)-12-(benzoyloxy)-2a,3,4 4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy 4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR[2a.alpha.,4.beta.,4a.beta.,6.beta.,9.alpha. (.alpha.R*,.beta.S*), 11.alpha.,12.alpha.,12a.alpha.,12b.alpha.]]

CAS registry number:

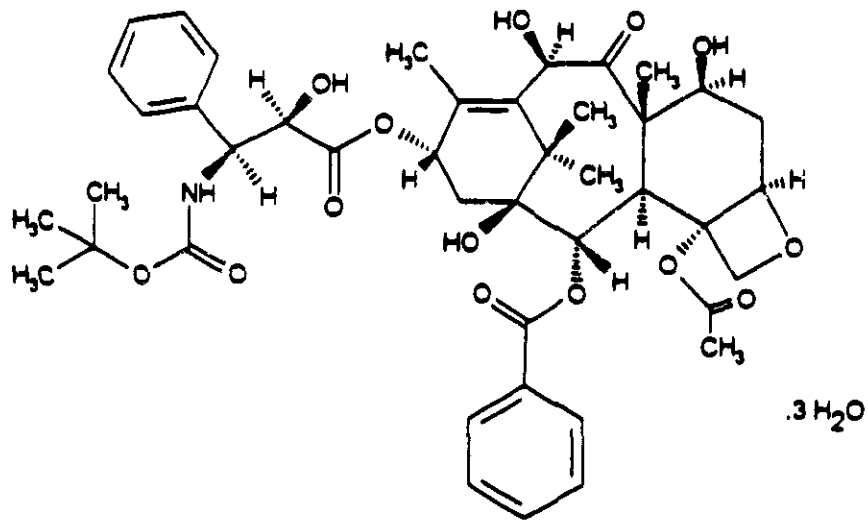
1) 148408-66-6 [trihydrate form]
2) 114977-28-5 [anhydrous form]

Proprietary name: TAXOTERE

Laboratory code number: RP 56976

5(B)(1)(b) Structural Information

Chemical Structure: (WHO Drug Information, Prop.INN: List 68)



Docetaxel (RP 56976) - structure above

Molecular Formula:
$C_{43}H_{53}NO_{14} \cdot 3H_2O$ (trihydrate)
$C_{43}H_{53}NO_{14}$ (anhydrous)

Molecular Weight:
861.94 (trihydrate)
807.89 (anhydrous)

5(B)(1)(c) Physical and Chemical Characteristics/MSDS

Appearance: White to off-white, coarse powder with agglomerates (trihydrate)

Melting Point: Melting point: ill-defined - no exploitable peak in DSC and determination of the capillary melting point impossible due to product decomposition.

Water Solubility: approximately 2 ug/mL

Partition Coefficient: LogP = 3.2

Chemical Family: Taxoids

MSDS: See Appendix 4

5(B)(2) Drug Product Excipient - polysorbate 80

5(B)(2)(a) Names and Codes

Chemical Name: Sorbitan, mono-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivatives

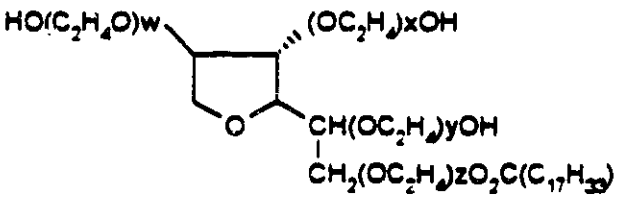
INN/USAN: polysorbate 80

Trade Names: Tween 80, Sorlate, Montanox (supplier's trade name)

CAS Number: 9005-65-6

5(B)(2)(b) Structural Information

Chemical Structure:



Sum of w,x,y,z is 20

Polysorbate 80 - structure above

5(B)(2)(c) Physical and Chemical Characteristics/MSDS

Appearance: clear oily liquid, yellow to brownish yellow.

Chemical Family: Nonionic surfactant

MSDS: See Appendix 5

5(B)(3) Isolated Process Intermediates

5(B)(3)(a) 10-DAB

5(B)(3)(a)(i) Names and codes

Chemical Names: 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1, 7β,10β,13α-tetrahydroxy-9-oxo-tax-11-ene; 10-deacetyl baccatin III

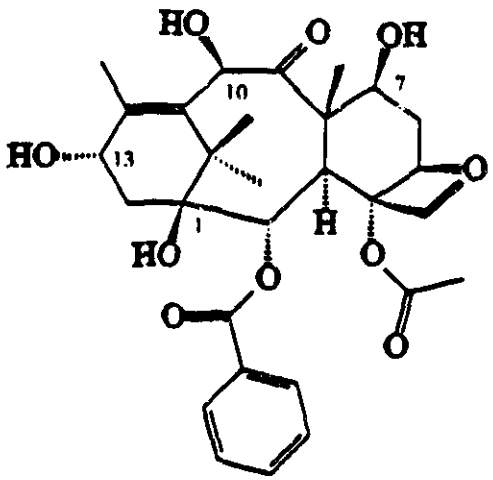
Code Name: RP 61387

Common Names: 10-DAB, Tetraol

CAS Number: 32981-86-5

5(B)(3)(a)(ii) **Structural Information**

Chemical Structure:



F P 61387 - structure above

Molecular Formula: $C_{29}H_{36}O_{10}$

Molecular Weight: 544.60

5(B)(3)(a)(iii) **Physical and Chemical Characteristics/ MSDS**

Appearance: White to slightly yellow powder

Chemical Family: Taxanes

MSDS: See Appendix 6.

5(B)(3)(b) **Synthetic Process**

Information for this section on the isolated synthetic process intermediates is provided in tabular form as a confidential attachment, see Confidential Appendix 7.

5(B)(4) **Major Process Impurities and Degradants**

Certain synthetic process related impurities, specified at below one percent in the drug substance, and degradants in the drug product have been identified.

Information and chemical structures for these process related impurities and drug product degradants are provided as Confidential Appendix 8.

5(B)(5) Major Metabolites

The primary mode of docetaxel metabolism in humans has been elucidated. From studies with carbon-14 labeled docetaxel the metabolites have been identified and quantified relative to the dose of docetaxel. A multistage oxidative pathway produces a series of primary metabolites that have been structurally identified. A confidential summary description of the study results and the structures of identified metabolites are provided in Confidential Appendix 9.

5(B)(6) Chemical Process Raw Materials

5(B)(6)(a) Extraction Process to Produce 10-DAB

5(B)(6)(a)(i) Rhône-Poulenc Rorer GmbH Cologne, Germany.

The extraction and purification process to produce 10-DAB (RP 61387) for production of docetaxel employs six different organic solvents and water. Table I below provides the chemical and background information for the organic solvents used in the process. Confidential Appendix 10 provides the information on the quantity of each organic solvent used in the production of 1 Kg of 10-DAB.

5(B)(6)(a)(ii) Indena, Milan Italy

Please refer to Indena's Type I and II DMF #s 10462 and 10463 for the extraction and purification of 10-DAB.

5(B)(6)(a)(iii) Annual Production

The annual production of 10-DAB is anticipated to range from for the next five years.

5(B)(6)(b) Chemical Process to Produce Docetaxel

The multistep synthetic process, schematic outline provided as Confidential Appendix 11, to prepare docetaxel (RP56976) from 10-DAB (RP 61387) employs a variety of chemical raw materials. The chemical and background information for the chemical process raw materials is provided in Table II below. The maximum quantity of each chemical process raw material required to produce 1 Kg of docetaxel drug substance is presented in Confidential Appendix 12.

TABLE I

CHEMICAL RAW MATERIALS FOR PRODUCTION OF 10-DAB

CHEMICAL NAME	CAS#	M.W.	M.F.	APPEARANCE
Acetone	67-64-1	58.08	C_3H_6O	Clear Liquid
Acetonitrile	75-05-8	41.05	C_2H_3N	Clear Liquid
Diisopropylether	108-20-3	102.2	$C_6H_{14}O$	Clear Liquid
Ethanol	64-17-5	46.0	C_2H_6O	Clear Liquid
Methanol	67-56-1	32.04	CH_4O	Clear Liquid
n-Butylacetate	123-86-4	116.20	$C_6H_{12}O_2$	Clear Liquid

TABLE II

CHEMICAL PROCESS RAW MATERIALS

CHEMICAL NAME	*CAS#*	*M.F.*	*M.M.*	*APPEARANCE*
1,2-Dichloroethane	107-06-2	$C_2H_4Cl_2$	99	Colorless liquid
2,2,2-Trichloroethyl chloroformate	17341-93-4	$C_3H_2Cl_4O_2$	212	Colorless liquid
4-Pyrrolidinopyridine	2456-81-7	$C_9H_{12}N_2$	148.2	Yellowish solid
Acetic Acid	64-19-7	$C_{12}H_{12}O_{12}$	60	Colorless liquid
Acetone	67-64-1	C_3H_6O	58	Colorless liquid
Alpha Methylbenzyl Amine R(+)	3886-69-9	$C_8H_{11}N$	121.2	Colorless liquid
Ammonium Chloride	12125-02-9	NH_4Cl	53.5	White crystals
Ammonium Hydroxide 20%	1336-21-6	NH_4OH	35	Colorless liquid
Benzaldehyde	100-52-7	C_7H_6O	106.1	Colorless liquid
Cyclohexane	110-82-7	C_6H_{12}	84.2	Colorless liquid
Di-tert-butyl Dicarbonate	24424-99-5	$C_{10}H_{18}O_5$	218	White solid
Dichloromethane	75-09-2	CH_2Cl_2	84.9	Colorless liquid
Dicyclohexylcarbodiimide	538-75-0	$C_{13}H_{22}N_2$	206.3	Colorless solid
Diisopropyl Ether	108-20-3	$C_6H_{14}O$	102	Colorless liquid
Ethyl Acetate	141-78-6	$C_4H_8O_2$	88.1	Colorless liquid
Ethyl Alcohol	64-17-5	$C_{12}H_{12}O$	46	Colorless liquid
Ethyl Vinyl Ether	109-92-2	C_4H_8O	72.1	Colorless liquid
Hexane		C_6H_{14}	86.2	Colorless liquid
Hydrochloric Acid 37%	7646-01-0	HCl	36.6	Colorless liquid
Isopropyl Alcohol	67-63-0	C_3H_8O	60.1	Colorless liquid
Methyl Alcohol	67-56-1	CH_4O	32	Colorless liquid
n-Hexanes	110-54-3	C_6H_{14}	86.2	Colorless liquid
Potassium Hydroxide	1310-58-3	KOH	56	White solid
Potassium Tert-butylate	865-47-4	C_4H_9KO	112.2	White powder
Pyridine	110-86-1	C_5H_5N	79	Colorless liquid
Pyridinium p-Toluene sulfonate	24057-58-1	$C_{12}H_{13}NO_3S$	251.3	White solid
Pyrogen free Water	7732-18-5	H_2O	18	Colorless liquid
Silica Gel	112926-00-8	SiO_2	60	White powder
Sodium Chloride	7647-14-5	NaCl	58.5	White crystals
Sodium Hydroxide 10M	1310-73-2	NaOH	40	Colorless liquid
Sulfuric Acid 95%	7664-93-9	H_2SO_4	98	Colorless liquid
Tert-butyl Bromoacetate	5292-43-3	$C_6H_{11}BrO_2$	195	Yellowish liquid
Toluene	108-88-3	C_7H_8	92	Colorless liquid
Zinc	7440-66-6	Zn	65.4	Grey powder

SECTION 6 Introduction of Substances into the Environment

6(A) Introduction

As noted by the listing of RPR production sites in Section 4 of this filing, the production of docetaxel drug substance and Taxotere® drug product involve a sequence of RPR industrial sites. None of these sites are located within geographic areas governed by the United States of America. A schematic flow-chart (See Confidential Appendix 1) is provided to clarify the correlation of production process stages with each particular production site.

6(B) Environmental Compliance for Non-US Sites

6(B)(1) Extraction of 10-DAB

6(B)(1)(a) Germany - Environmental Compliance Cologne Site

The process at RPR GmbH, Cologne involves extraction of 10-DAB from yew needles without any chemical steps.

6(B)(1)(a)(i) Statement of Compliance

Provided as Appendix 13 is a statement of compliance for the RPR GmbH, Cologne site by responsible RPR officials for the site. The statement applies to the production of 10-DAB for use as a key intermediate in the production of docetaxel.

6(B)(2)(a)(ii) Information Related to Permits and Certification

Provided as Appendix 14 is a RPR statement of compliance with the local German environmental regulations for the manufacturing process of 10-DAB. Included with that statement are permit and certification notices for the following activities related to 10-DAB production. Documents are provided as English translations with the associated German language original.

Appendix	Permit/Certification
15	Site Building Permit
16	Technical Center Building H14
17	Store/Fill Flammable Liquids
18	Storage Tank Certification
19	Drug Processing and Storage
20	Modification of Extraction Facility
21	Changes of Existing Facility
22	Inclusion of n-Butylacetate

6(B)(1)(a)(iii) OSHA Regulated Materials

None of the chemical materials used in the extraction process to prepare 10-DAB at the RPR GmbH, Kohn site are in the category of OSHA regulated substances as defined by SARA 313.

6(B)(1)(a)(iv) 10-DAB Process Waste Streams

The 10-DAB (RP 81387) is produced by an extraction and purification process from natural materials that does not invcive chemical modification of the desired substrate. The waste streams from the production include solid residues, waste water and liquid wastes for incineration. The process is anticipated to be relatively stable for the next five years with extraction of less than of dried yew needles per year. Provided as Appendix 23 is a tabular listing of the seven process waste streams which includes as applicable; 1) the waste stream number, 2) the German waste Key number, 3) the type of disposal, 4) the licensed transport company, 5) the licensed disposal or incineration company, 6) the license number, and 7) the date and Allowance number for declaration to appropriate authorities. Provided as Confidential Appendix 24 is an Extraction process schematic which graphically describes the operations involved i. each step of the process and provides identification of the seven waste streams. Provided as Confidential Appendix 25 is a tabular description of the waste streams related to the process schematic with indications of the quantity of each waste produced on the basis of 1) kilograms per week, 2) kilograms per kg of 10-DAB produced and 3) total metric tons in 1994. Included in Confidential Appendix 26 is a summary schematic correlation of the process steps and the resulting waste streams. Within the RPR GmbH, Cologne facility the waste handling procedures are well documented. The plant waste water is monitored by continuous automatic measurement of solvents and pH; waste water that exceeds permissible limits is collected for separate treatment. Air handling systems are in place to separately handle dusty or solvent contaminated air.

6(B)(1)(b) Indena - Environmental Compliance

Please refer to Appendix 27 (Indena's FOI) and to Indena's Type I and II DMFs #10462 and 10463. A letter authorizing RPR's reference to their DMF's can be found in section 3.4(b)(i)(5) of this NDA.

6(B)(2) Chemical Synthesis of Docetaxel

All of the chemical synthetic processes occur in France. The appropriate governmental authorities have provided attestations of compliance with applicable environmental regulations for the three RPR sites involved with docetaxel production and Taxotere® solution preparation in France. The letters of attestation for these three sites are provided as follows:

Site Name	Appendix
VILLENEUVE LA GARENNE (VLG)	28
VITRY-SUR-SEINE (CRVA-PROC)	29
LE MANS, SERIPHARM	30

6(B)(3) Manufacture of Taxotere

Taxotere® is manufactured as a bulk solution at RPR, Vitry-sur-Seine. A letter attestation for this site is provided in Appendix 29. The Taxotere® sterile filling and packaging process at the RPR Dagenham, UK site includes only the receipt of bulk Taxotere® solution, sterile filling of vials, analysis, storage and distribution. No chemical process modifications of the drug substance are involved.

6(B)(3)(a) Statement of Compliance, UK

Provided as Appendix 31 is a RPR certification showing compliance with the British environmental regulations applicable to the process for sterile filling of Taxotere® into vials at the Dagenham facility.

6(B)(3)(b) Information Related to Permits for Waste Disposal, UK

Provided as Appendix 32 is a summary of the governmental permit and license numbers applicable to the disposal of waste water and solid waste streams from the Taxotere® vial filling process at the RPR Dagenham site.

6(B)(3)(c) Engineering Controls for Emissions, UK

Provided as Confidential Appendix 33 is a Dagenham Site map indicating the location of the Buildings 37, 31 and 33 used in the various aspects of the Taxotere® filling process. Provided as Confidential Appendix 34 is a tabular presentation of the engineering and procedural controls in the Taxotere® process steps to insure the minimization of emissions from the process.

6(C) Calculation of Expected Environmental Concentration (EEC)

In the fifth year of commercial production the total quantity of docetaxel drug substance projected to be produced for use as Taxotere® in the United States is pounds. Use of Taxotere® is expected to lead to total amount (pounds) of docetaxel entering public and private sewer systems from human waste. A calculation of the total waste water treatment plant load can be made in two ways as shown below; method one gives a maximum EEC of ppm when the total United States waste water is considered and method two gives a maximum EEC of ppm when only a single average urban area (St. Petersburg, Fl) is considered.

6(C)(1) A Maximum EEC based on release of the Drug Substance uniformly within the U.S.

Using the equation presented by the Pharmaceutical Manufacturers Association in their guidance document for preparation of environmental assessments and an estimated fifth-year consumption of kilograms of docetaxel:

ppm (in U.S. environment) = lbs/year x (8.9×10^{-6})

derived from ppm = (A)(B)(C)(D)(E)(F) where:
A = pounds produced divided by one year (fifth-year production estimate)
B = one year divided by 365 days (length of year)
C = one day-person divided by 150 gallons (average daily water use per person in U.S.)
D = one divided by 246,000,000 persons (population of U.S.)
E = one gallon divided by 8.34 pounds (weight of a gallon of water)
F = 1,000,000 (conversion to parts per million)

kilograms docetaxel is equivalent to pounds docetaxel. The maximum expected environmental concentration in the U.S. is calculated to be:

ppm (in U.S. environment) =
ppb (in U.S. environment) =
ppt (in U.S. environment) =

5(C)(2) A maximum EEC based on release of docetaxel in an average urban area

Using a procedure similar to that shown above for the entire U.S., calculations are presented below for a typical urban area assuming that all 60 kilograms are used and disposed in one urban area. St. Petersburg, Florida, for which data are available was selected as a typical urban area (Sludge Management & Disposal for the Practicing Engineer, Vesiland, P.A., Hartman, G.C., Skene, E.T., 1988, Lewis Publishers). The city has a population of 240,000 (1983) and a waste water treatment works volume of 53.8 million gallons per day (1983). This averages 220 gallons per person per day and was used with the estimated fifth-year production of kilograms of docetaxel.

ppm (in urban environment) = lbs/year x (8.2×10^{-6})
derived from ppm = (A)(B)(C)(D)(E)(F) where:
A = pounds produced divided by one year (fifth-year production estimate)
B = one year divided by 365 days (length of year)
C = one day person divided by 220 gallons (avg. per capita volume influent to WWTP)
D = one divided by 240,000 persons (population of St. Petersburg, FL)
E = one gallon divided by 8.34 pounds (weight of a gallon of water)
F = 1,000,000 (conversion to parts per million)

kilograms docetaxel is equivalent to pounds docetaxel. The maximum expected environmental concentration if all the Docetaxel were used within a single urban area is calculated to be:

ppm (in urban environment) =
ppb (in urban environment) =

6(D) Recovery and Disposal of Returned Goods

Rejected and returned Taxotere® will be incinerated by Chambers Medical Technology of South Carolina, Hampton, SC, a fully owned subsidiary of Chambers Development Company, Inc., Pittsburgh, PA. This facility is duly licensed by the state of South Carolina. Please refer to Appendix 3 for Chambers' permits issued by the state of South Carolina. The permits include Water Pollution Control Permit (SC0042242), Bureau of Air Quality Control Construction Permits (0280-0021-CD, 0280-0021-CE and 0280-0021-CF) and the permit application for Municipal Solid Waste Incineration and Pyrolysis. The State

of South Carolina has authorized Chambers to receive and incinerate rejected and returned goods from Rhône-Poulenc Rorer Pharmaceuticals, Inc. Please refer to the May 6, 1994 letter included in Appendix 3.

SECTION 7 Fate of Emitted Substances in the Environment

7(A) Introduction

The drug substance docetaxel, as the active component of Taxotere®, is a relatively complex organic molecule with several functional groups which could be anticipated to be susceptible to hydrolysis, biodegradation or chemical degradation. The physico-chemical properties of docetaxel, as summarized in the table in Section 7(C)(2) below, suggest the types of environmental fate studies which should be carried-out on the molecule. The relatively low water solubility and the partition coefficient, with no ionizable functional groups, suggest that the soil sorption and desorption characteristics of docetaxel needed to be studied along with the susceptability to hydrolysis and biodegradation. The results of these studies are provided in this section. The very low anticipated annual production and use quantities of docetaxel (≤ Kg/year) suggested that calculation of the worst case maximum expected environmental concentration should be done for comparison with information generated in studies such as the microbial inhibition and static acute toxicity. The expected environmental concentrations were calculated as described previously in Section 6(C) and the result of those calculations also presented here in Section B.

7(B) Estimated environmental concentrations and exposures as a result of drug product use.

Calculations were performed in order to estimate the worst-case concentration of docetaxel that could possibly be present in the United States. The estimate assumes that all docetaxel produced for sale in the U.S. (based on fifth-year post approval production estimates, kg) will be administered to patients and disposed of directly into sewage systems. This calculation overestimates the environmental concentration of docetaxel in at least two ways. One, it assumes that all the docetaxel produced is sold and used by patients, and that none is left unsold, is unused by patients, or expires and is returned for disposal outside sewage treatment systems. Two, it assumes that all of the docetaxel administered to patients is excreted into sewage treatment systems. Patient metabolism will obviously reduce the quantity of docetaxel reaching the environment, as will discharge into private septic systems. Nonetheless, is calculated to be the maximum expected environmental concentration in the U.S. following the estimate presented above.

Another calculation was performed assuming that all 60 kg is to be used in one urban area within the U.S. in one year. This estimate was produced using St. Petersburg, Florida as a representative urban area for the U.S. St. Petersburg has a population of 240,000 residents (1983) and four municipal sewage treatment plants. The per capita water contribution to the volume of water treated is 220 gallons per day. Using these figures, and assuming that all the produced docetaxel is discharged into the treatment system, the average concentration would be '

7(C) Release Compartments

7(C)(1) Certification of Compliance with GLP and Use of Accepted Methods

Data summarized below and used for evaluation of the environmental distribution were obtained from studies conducted in accordance with FDA Good Laboratory

Practice. These studies were designed to comply with the procedures and formats presented in the FDA Environmental Assessment Technical Assistance Handbook.

7(C)(2) Physico-Chemical Fate Data Summary Table

The following table summarizes the physico-chemical data obtained for docetaxel as the pure trihydrate.

Docetaxel, trihydrate Physico-Chemical Data	
Melting Point:	Ill-defined
Vapor Pressure:	N.A.
Water Solubility	2ug/mL
Partition Coefficient:	Log P=3.2
Dissociation Constant:	None
Hydrolysis (Half-Life):	113 days, pH=5 28 days, pH=7 <1 day, pH=9
Aerobic Biodegradation (Half-Life):	<14 days

7(C)(3) Discussion of Data and Prediction of Environmental Release Compartment.

7(C)(3)(a) Sorption and Desorption

The propensity for human drug substances to be transported from disposal sites is determined by factors contributing to their distribution, mobility and persistence in the environment. Partitioning between solid and aqueous phases influences mobility by controlling sorption and leaching rates. A measure of a compound's tendency to sorb and desorb readily can predict the ultimate disposition of residues as either bound to soil/sludge, or as freely soluble material.

Docetaxel was studied to determine its sorption and desorption properties following the FDA Environmental Assessment Technical Assistance Handbook Section 3.08. (Please refer to Confidential Appendix 35 for the complete report.) Three soil types were used with both reagent water to mimic "soft" water, and 0.01 M $CaCl_2$ to approximate "hard" water. At a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all three soil types ranged from 41.3 to 66.7% in $CaCl_2$ and from 47.8 to 53.1% in reagent water. When desorption was tested, 39.0 to 78.3% and 63.4 to 68.8% of the sorbed docetaxel could be removed from reagent water and $CaCl_2$, respectively. This indicated that docetaxel was only slightly bound to the three types of soils tested. The preliminary screening portion of the study demonstrated that no significant difference in sorption occurred between reagent water and $CaCl_2$ solution for all three soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Arkansas	3.53	4.58	375	486
Kansas	10.2	5.11	469	235
Wisconsin	6.47	5.66	193	169

Arkansas soil: 35% sand, 51% silt, 14% clay, 1.6% organic matter, pH 5.9, cation exchange capacity 9.8 meq/100 g.

Kansas soil: 31% sand, 43% silt, 26% clay, 3.7% organic matter, pH 6.5, cation exchange capacity 22.4 meq/100 g.

Wisconsin soil: 59% sand, 29% silt, 12% clay, 3.4% organic matter, pH 7.5, cation exchange capacity 17.1 meq/100g.

Results of the definitive test conducted in 0.01 M $CaCl_2$ at concentrations ranging from 25 to 1.4 µg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Arkansas	2.99	318	1.05	0.996
Kansas	3.40	156	1.24	0.995
Wisconsin	3.54	106	1.19	0.978

7(C)(3)(b) Hydrolysis

Docetaxel was studied to determine its potential for hydrolysis following the FDA Environmental Assessment Technical Assistance Handbook Section 3.09. (Please refer to Confidential Appendix 36 for the complete report.) Hydrolysis as a pathway for degradation is important from an environmental perspective since most pharmaceuticals will enter the environment in a dissolved form, whether from discharge from the site of production or from patient use. Hydrolysis occurs when hydroxide or another aqueous ion reacts with a chemical in solution.

Hydrolysis was investigated at three pHs, 5.0, 7.0 and 9.0. Results demonstrated that docetaxel readily hydrolyses to more polar compounds. The half-lives were determined to be 113 days at pH 5, 28 days at pH 7 and less than one day at pH 9. These data indicate that docetaxel will not persist in the environment and effects, if any will be short termed.

7(C)(3)(c) Biodegradation in Water

Biodegradation is a process by which organic chemicals may be significantly reduced in their structural complexity in the environment through biological means. Knowledge of the potential for biodegradation of a chemical is often critical in the assessment of environmental exposure and impact of the chemical. The objective of the study was to determine the potential for biodegradation of docetaxel under standard laboratory conditions. The biodegradation studies were conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 3.11. (Please refer to confidential Appendix 37 for the complete report.)

A 28-day aerobic biodegradation study in water was performed with ^{14}C-docetaxel. Test flasks were incubated at 22 °C in the dark to minimize the potential for photolysis, and inoculated with a bacterial population obtained from a combination of garden soil and a domestic sewage treatment plant. The quantity of carbon dioxide ($^{14}CO_2$) released as a result of microbial degradation in water was measured. ^{14}C-glucose was also tested in the same manner in separate flasks as a reference chemical. HPLC-RAM measurements were performed periodically to determine whether partial degradation of ^{14}C-docetaxel had occurred.

From the docetaxel flasks, the cumulative $^{14}CO_2$ collected over 28 days was negligible relative to the dose initially applied. ^{14}C-volatile organic products were also not detected from these flasks. From the ^{14}C-glucose flasks, greater than 60% of the dosed radioactivity was collected as $^{14}CO_2$. While these results showed no evidence for the complete biodegradation of docetaxel to carbon dioxide, analysis of the test solution containing docetaxel were performed using HPLC-RAM throughout the study. Results of these analyses indicated complete biotransformation to products chromatographically similar to those observed in the hydrolysis study. At the relatively neutral pH of the biodegradation study, the half-life in the three flasks were determined to be less than 14 days. Since the hydrolysis study yielded a half-life of 28 days at pH 7, the significantly accelerated rate was attributed to microbial processes.

7(D) Major Metabolites

The primary mode of docetaxel metabolism in humans has been elucidated. From studies with carbon-14 labeled docetaxel the metabolites have been identified and quantified

relative to the dose of docetaxel. A multistage oxidative pathway produces a series of primary metabolites that have been structurally identified. A summary description of the study results and the structures of identified metabolites are provided in Confidential Appendix 9.

Based upon equivalence of the backbone chemical structure of the metabolites with docetaxel, and the demonstrated non-persistence for docetaxel, the individual docetaxel human metabolites were not subjected to environmental fate and effects testing.

SECTION 8 Environmental Effects of Released Substances

8(A) Summary statement of the projected absence of adverse effect

Production, use and discharge of docetaxel into the environment will pose no adverse effect on humans, animals, plants or environmentally significant organisms. For organisms tested, results indicated that no threat to any of the tested organisms are possible at concentrations at or near those calculated to occur upon approval of this NDA.

8(B) Presentation of data from Microbial Inhibition and Static Acute Toxicity studies

As a measure of the toxicity of any chemical, the determination of the lowest concentration at which inhibition of microbial growth occurs is important because of the possible ramifications if that concentration is exceeded in the environment. A microbial growth innibition study was conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.02. (Please refer to Confidential Appendix 38 for the complete report.) The microbial inhibitory concentration (MIC) of docetaxel was determined for each of five species. A preliminary test using concentrations of 0.1 to 100 ppm (0.1 mg/L to 100 mg/L) showed no effects to all five species investigated at all concentrations tested including 100 mg/L (the highest concentration). Based on the results of the preliminary exposure, a definitive test was not conducted. The MICs reported were defined as the lowest concentrations of docetaxel that completely inhibited the growth of the test organism.

Species	Docetaxel MIC (mg/L)
Aspergillus niger	>100
Trichoderma viride	>100
Clostridium perfringens	>100
Bacillus subtilis	>100
Nostoc	>100

The acute toxicity (concentration at which 50% of the organisms are affected or EC_{50}) of docetaxel to *Daphnia magna* (a freshwater invertebrate), was investigated. This organism is often tested and considered to be one of the most sensitive aquatic species available for standardized aquatic studies. The no observed effect concentration (NOEC) was determined as well at the EC_{50}. The NOEC is defined as the highest concentration at or below which there was no toxicant-related immobilization, or physical or behavioral

abnormalities when compared to the control. The study was conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.08. (Please refer to Confidential Appendix 39 for the complete report). During the daphnids acute toxicity study, immobilization or sub lethal effects were observed among daphnia's exposed to the highest measured concentration (16, 9.3 and 5.8 mg/L) following 24-hours of exposure. After 48-hours' exposure, 100% were immobilized at concentrations of 16, 9.3 and 5.8 mg/L. Immobilization was 15% at 3.6 mg/L and 10% at 2.1 mg/L. No immobilization was observed in either the solvent control or the control solutions. The outcome of the study was a calculated 48-hour EC_{50} for daphnia's exposed to docetaxel of 3.7 mg/L. The 48-hour NOEC for this study was extrapolated by linear regression analysis to be 1.1 mg/L.

8(C) Summary of Comparison of Results seen in the Static Acute Toxicity Study with the Calculated Environmental Concentrations

The narrowest margin of safety for docetaxel is based on the NOEC for *Daphnia magna* (the most sensitive species tested) and is calculated by dividing 1.1 mg/L by mg/L (the minimum expected concentration based on distribution of all docetaxel over the entire United States). This calculation results in a safety margin of Consideration of the distribution of all docetaxel in one urban area results in a safety margin of (1.1 mg/L divided by mg/L).

8(D) Conclusion Statement on the Projection of No Effect on the External Aquatic Environment

Based on the documented rapid degradation pathways and the large safety margins (greater than), docetaxel has been shown to have no effect on the external aquatic environment. Docetaxel was shown to degrade in water with a half life of less than 28 days under sterile conditions and less than 14 days under microbially populated conditions. This clearly demonstrates that docetaxel will not persist in the environment. Furthermore, docetaxel was shown to have no effect on a wide variety of microorganisms at concentrations as high as 100 mg/L. The EC_{50} to Daphnia magna was determined to be 3.7 mg/L and the no observed effect concentration was calculated to be 1.1 mg/L. This lowest risk concentration is more than times higher than that which would occur if all the produced Docetaxel were used in one urban area, and more than times higher than that when the entire U.S. is considered.

SECTION 9 Use of Resources and Energy

9(A) Yew Needle Collection

9(A)(1) Introduction

The collection of yew needles involves the yearly trimming of the young shoots of ornamental yew trees (i.e. using a renewable resource with no deforestation).

For this NDA, and for its own production of 10-DAB, **Rhône-Poulenc Rorer** has **contracts** with two European companies: **Sedaherb, France** and **Müggenberg GmbH, Germany** (see addresses below) for the supply of yew needles. These companies have been engaged in the plant extraction business for more than 30 years and are well established.

Paul Müggenburg GmbH & Co.
Bahnhofstraße 2
D-25486 Alvesiohe
GERMANY

Sedaherb
Z.A. Du Colombier
71610 Saint Lager sur Dheune
FRANCE

For the extraction of 10-DAB manufactured at RPR, Cologne, Germany, the yew needles are received from the two above-named sources.

RPR has contracted Indena as a supplier of 10-DAB, which they extract from yew needles. Please refer to Indena's Type I and II DMFs (10462+10463) for complete information.

9(A)(2) Paul Müggenburg GmbH & Co., Germany

Summary of Company

Paul Müggenburg GmbH & Co., a privately owned company has been working for more than 50 years in the field of Botanical Products. They are located in Alvesiohe, approximately 30 km north of Hamburg. They follow the Washington Guidelines for the Conservation of Medicinal Plants and have established, wherever possible, good agricultural practice (GAP) see Confidential Appendix 46. (See Confidential Appendix 40 for a RPR contract with Muggenburg for yew needle collection.) Organization charts of the company and Taxus Project are provided in Confidential Appendix 41; job descriptions for each individual are included in Confidential Appendix 42.

Collection Process

In Europe, Taxus is an internationally protected plant and no company or individual is allowed to violate the existing laws. In Germany, the "Bundesamt für Naturschutz" is responsible to survey and guarantee the compliance with these laws. In Germany it is forbidden to collect Taxus from wild grown areas, such as forests, National Parks, and protected areas, whether or not it is privately owned land or public/government owned.

Paul Müggenburg GmbH & Co. therefore took a different approach for the collection of Taxus. They were aware that Taxus is mainly cultivated for the production of hedges throughout Europe. They published an advertisement in the official gardeners' magazine "TASPO" (see Appendix 43) and received several responses from gardeners who regularly trim Taxus hedges. Previously, the gardeners would dispose of the Taxus needles by burning or composting them. Paul Müggenburg GmbH & Co. offered either to pick up the fresh cut material or to trim the hedges with their own people.

Paul Müggenburg GmbH & Co. also contacted tree nurseries for a list of customers who had purchased large quantities of Taxus. The nurseries themselves trim the hedges and ornamental plants once or twice a year to make

them marketable. Paul Müggenburg GmbH & Co. provides a trailer or other transportation unit on to which the clippings are loaded.

Müggenburg receives 100% of yew trimmings from cultivated plants, 35% from private backyards, 25% from cemeteries/public gardens and 40% from tree nurseries. No wild trees are trimmed. Please refer to Appendix 44. for certification that no wild plants are trimmed. Also, please refer to Appendix 45 for photographic examples of privately owned lands, parks and gardens.

The collection process begins with the identification of "Taxus" plants by botanists, gardeners, or other experienced personnel. Permission to cut the plants is given by the land owners or other officials prior to beginning the trimming process. Only "healthy" hedges and trees are trimmed. Before trimming the ground is cleaned. The hedges and trees are trimmed with knives or electric tools and the clippings are bagged continuously. Only the young shoots are trimmed and no harm is done to the plant. Normal re-growth occurs after trimming. During the day the clippings are stored in a cool, windy and shaded area to prevent fermentation of the trimmed plant material. The plant cuttings are transported in clean ventilated trucks equipped with racks to prevent fermentation and excess heat. At Müggenburg's facility, the trucks are promptly unloaded and the plant material is visually inspected. From each receipt of fresh taxus clippings a small sample (1-5 twigs) is taken, dried and sent to Rhône-Poulenc Rorer.

The fresh cuttings are chopped immediately before drying, which takes place within two days from the trimming process. The cuttings are dried in hot air dryers where the temperature does not exceed 60°C. After drying, the material is visually inspected and tested for moisture (< 12%). The dried yew cuttings are chopped with a combination of hammer -, cutting - and turbomills to particle size on average of 0.75mm with a range ofrom 0.25mm to 2mm (± 10%). The chopped material is sifted to separate the dust and larger wooden particles. The chopped, dried material is stored in light protected bags in a cool, dry area.

Each bag of dried, chopped, sifted material is sampled. Samples of individual bags are blended to represent the quality of the sub lot. After the sub lot is released based on testing of the sample, several sub lots are combined to form the final four metric ton lot, packed in poly-woven bags. The content of each four metric ton lot shall be 0.8% 10-DAB

Please refer to Confidential Appendix 46 for Müggenburg's Taxus Masterfile. It contains a Taxus Flow Chart, SOP for Taxus Granular and overviews of each significant operation.

To ensure that Paul Müggenburg GmbH & Co. suppliers do not harm the environment, every supplier must sign the delivery form for "fresh Yew cuttings". If the document is not signed, the clippings are not accepted and the supplier is not financially compensated. (See Confidential Appentix 47).

To further ensure acceptable practices by suppliers an audit is conducted by Paul Müggenburg GmbH & Co. botanists. After a hedge has been trimmed the botanist visits the supplier and inspects the condition of the plants. The supplier is given suggestions and advice if the trimming process can be improved. The

botanist can recommend that the supplier be abandoned after an unsatisfactory audit.

By accurate, computerized receiving documentation Paul Müggenburg GmbH & Co. can track each lot of yew needles to its origin and the name of the person who collected/trimmed it. (See Appendix 48)

Description of Facilities

Paul Müggenburg GmbH & Co. maintains in Alvesiohe a warehouse and production facility, where Taxus for RPR is produced. All buildings are constructed for the production of a natural raw material. The fresh Taxus is dried in two stationary floor dryers, direct loaded or with drying racks. Dry hot air is blown through the material until it reaches the appropriate dryness. The dried material is put into the cutting machine, the material is precrushed by a hammermill, finecrushed by a turbomill and screened. The screened material put into bags and transported to the blender. After blending the material is screened again to removed the dust and filled into bags.

Geographic Areas for Collection

Taxus is collected only in countries where Paul Müggenburg GmbH & Co. can control the harvest by documentation and supplier relations. They collect only in: Argentina, Austria, Belgium, Czech Republic, Denmark, Germany, Great Britain, Croatia. Luxemburg, Netherlands, Norway, Poland, Slovakia, Spain, Sweden and Turkey Please refer to Appendix 49.

Expert Botanical Reports

Expert botanical reports from Müggenburg and Dr. Frank Polheim (Professor of Plant Breeding, Humboldt University in Berlin) are included in Appendix 50. These reports affirm that yew trees are easily cultivated and are tolerant to pruning. The trees recover quickly from any type of pruning. Please see Appendix 51 of photographs of the regrowth of yew plants after trimming. Also included in Appendix 50 are 2 reports by Dr. Osthoff which discuss the Taxus genus and cultivation of yew trees.

9(A)(3) Sedaherb

Summary of Company

Sedaherb is a French company which collects and dries plant material for chemical extraction. Sedaherb certifies that the yew needles are collected in Europe and processed in accordance with the regulations protecting the yew trees. (See Confidential Appendix 52) An organization chart and individual job descriptions (with translations) are provided in Confidential Appendix 53.

Collection Process

Presently, in Europe, Taxus is an internationally protected plant. In France, following decisions taken by the Minister for Agriculture and National Conservancy Agency, prefects (the government representatives) in every department of France have implemented decrees strictly banning any and all

destruction of the yew. (See Appendix 54) The French regulations allow for the collection Taxus cuttings in the wild for experimental, scientific or industrial purposes after consultation and approval by the relevant departments.

Sedaherb obtains agreements on a yearly basis with the National Office of Forests (O.N.F.), a public administration with unique responsibility for all national forests. See Appendix 55 for 1993 Annual Authorization for the Collection of Yew Shoots in the State-owned Forests of Saint-Baume and Prefecture des Hautes-Alpes. Please see Appendix 56 for photographs of a national forest area.

Sedaherb also meets regularly with private owners of forests, parks and gardens and receives authorization to pick up the cuttings provided by the land owner. Please see Confidential Appendix 57 for examples of the agreements between Sedaherb and the land owners. Completed agreements are also included in Confidential Appendix 57.

Over the past eight years Sedaherb has established a list of over 500 sites, in Europe, suitable for the collection of yew needles. Each site is indexed according to the owner's name, address and telephone number. A unique number is assigned to each site which enables Sedaherb to identify individual batches of yew needles as they are processed.

The company's well-adapted procedures for gathering young yew shoots (approximately two years old), according to strict guidelines, guarantee the trees' conservation in good health.

Please refer to Confidential Appendix 58 for a flow chart and summary of Sedaherb's Taxus harvest/processing procedure.

Each year a prospecting team headed by a botanist conducts a systematic inspection of potential yew gathering sites and draws up a file, with information concerning resources and constraints (environmental protection). Samples are taken for new sites and sent to RPR for analysis of 10-DAB content.

Based on the botanist's evaluation and 10-DAB content the prospective harvesting sites are organized and the harvest is begun. The harvest takes place between early summer and early autumn (July 1 - September 30 for 1994). According to the individual characteristics of the site, the work is assigned to a clipping team, supplied with all appropriate equipment, or to a picking team. Each team receives the complete file of the specific site.

A Clipping Team consists of four individuals responsible for gathering the cut shoots from hedges and trimmed ornamental yews. The shoots are clipped onto plastic sheets, then put into polypropylene bags and held for drying. The shoots are dried less than eight hours after clipping. Please see Appendix 59 for the instructions for the pruning of ornamental yew trees.

A Picking Team generally consists of a team captain, an assistant and 20 gathers. The Picking Team was established for natural forests and trees in the wild. Only non-lignified young shoots less than two years old are gathered from trees.

The young shoots are recognized by their central stem, green and supple, between 20 and 30 cm long with a diameter of less than 8 mm. Young shoots are gathered below. The apical bud of the tree is not trimmed.

Twice each day the cuttings are weighed: end of the morning and mid-afternoon.

During the gathering process the harvest area is supervised by the team captain or assistant. At the end of the day the harvest area is surveyed by the land owner or agent.

Please see Appendix 60 for instructions for the collection of yew shoots in natural forests and wild trees.

The yew trimmings are dried less than eight hours after cutting. They are dried for approximately 10 hours by hot air which does not exceed 55°C. Six fixed and two mobile dryers are set up to ensure a drying delay of less than eight hours after harvesting, to avoid fermentation. The water content of the cuttings is reduced to less than 10%. One thousand kilos of fresh shoots yield approximately 400 kilos of dried material. The product is inspected after drying and then stored in woven polypropylene bags. Please see Sedaherb's drying protocol in Appendix 61.

The bags of dried cuttings are shipped to Sedaherb's facility on a weekly basis. The bags are emptied to visually inspect the quality of the young shoots, checking for fermentation, foreign matter and lignified branches. The dried cuttings are chopped, screened (for the removal of wood), milled (for control of particle size) and stored in silos. Lots of four metric tons each are separated to allow adequate tracking of the Taxus origin, i.e. geographic origin of collected/clipped shoots. The composition of each four ton lot is known and Sedaherb makes every effort to constitute homogeneous batches depending on their collection period, geographic origin and shoot type (collection/clipping) and site.

The harvest sites are inspected again, after harvest, to ensure the branches grow back normally. Regrowth is normally vigorous and healthy. In the case of adverse conditions (drought), the site is given an additional year's rest.

In 1993, 70% of the yew shoots were from the trimming of hedges and ornamental trees and 30% of the yew shoots were from trees in the wild (national forests).

Facilities

Included in Confidential Appendix 62 is a floor plan for Sedaherb with a summary of specific areas.

Geographic areas for Collection

Currently Sedaherb collects yew shoots in France, United Kingdom, Czech Republic and Slovak Republic. Sedaherb intends in the future to collect from Switzerland (1994), Belgium (1995) and Poland (1995). Please refer to Appendix 63 for a list of source countries. Appendix 63 also contains preliminary

correspondance between Sedaherb and the Swiss government regarding the collection of yew needles.

9(B) Historical Sites and Endangered Species

9(B)(1) Introduction

The processes involved in the production of docetaxel drug substance and Taxotere® drug product will not have an impact upon endangered species or historic sites listed in the national register of the United States. Moreover, the following information of this section is provided to confirm that the processes for production of docetaxel and Taxotere® carried-out at the sites identified in Section 4 will not have an impact upon endangered species or registered historic sites.

9(B)(2) Cologne - Extraction of 10-DAB

Provided as Appendix 64 is a RPR statement that no endangered species are found within the specified surrounding area and that historic buildings situated in excess of 10 Km from the site will not be endangered by any incidents on site. A large area map is available.

9(B)(3) Villeneuve La Garenne - Preparation of the side chain RPR 104493 (BHE)

Provided as Appendix 65 is a RPR statement that there are no historical sites nor normally resident endangered species located within a radius of the Villeneuve La Garenne site that they would be affected by the normal operations or foreseeable emergencies at the site.

9(B)(4) Vitry-sur-Seine - Preparation of Docetaxel and Bulk Taxotere® Solution

Provided as Appendix 66 is a RPR statement that there are no historical sites nor normally resident endangered species located within a radius of the Vitry-sur-Seine site that they would be affected by the normal operations or foreseeable emergencies at the site.

9(B)(5) Le Mans, Seripharm S.A. - Chromatographic Process

Provided as Appendix 67 is a certification by Seripharm S.A. that no rare species or historical monuments are endangered by activities at the site. A list of all historical monuments within 15 Km of the Seripharm site is available for review.

9(B)(6) Dagenham - Sterilization and Filling of Taxotere®

Provided as Appendix 68 is a certification that there are not endangered species or historical sites located such that they are endangered by normal operations or foreseeable emergencies on the site. An Ordnance Survey Map of the area is available for review.

9(C) Information on the Impact of Resource and Energy Use

9(C)(1) Yew Needle Collection

The energy and utilities used in the collection of yew needles to support production of 10-DAB have been provided in Confidential Appendix 69 for the collection of of biomass by Sedaherb. In summary the gathering, drying, processing and transport of the dried biomass uses the following amounts of energy or fuel per ton of biomass:

Electricity
Gas (liquified petroleum)
Diesel Oil
Gasoline
Oil

A calculation of the total energy consumption, converted to electrical equivalence, during the collection, drying, grinding and transport processes by Müggenburg is in agreement with the above where per ton of dried biomass the consumption is equivalent to .

9(C)(2) Drug Substance/Product Process

9(C)(2)(a) Cologne - Extraction of 10-DAB

The energy and utilities used in the production of 10-DAB by extraction from yew needles and purification of the extract are steam for distillation of solvents, electricity and water used for cooling and vacuum generation. The total electrical and steam generation requirement is expressed as of 10-DAB.

9(C)(2)(b) Villeneuve La Garenne, Vitry-sur-Seine - Production of Docetaxel and Bulk Taxotere® Solution

The energy and utilities used in the production process for docetaxel are electricity and water for cooling and vacuum generation. For the entire chemical sequence the electrical usage has been calculated as of docetaxel. For the anticipated average annual production for the United States over the next five years this represents of the normal electrical usage for the sites. For the entire chemical process the water consumption has been calculated at of docetaxel. For the anticipated average annual production of docetaxel for the United States for the next five years this represents of the water consumption for the sites. The breakdown for these calculations is provided as Confidential Appendix 70.

9(C)(2)(c) Seripharm - Chromatographic Purification

The energy and utilities consumed in the chromatographic purification of docetaxel including the distillation of solvents includes electricity, water and natural gas. Expressed in terms of consumption per kilogram of docetaxel produced these are:

Electricity
Water
Gas

9(C)(2)(d) Dagenham Sterilization and Filling of Taxotere®

The energy and utilities used in the production process for sterilization and filling of Taxotere® are electricity, water, steam, nitrogen and compressed air. For the entire pharmaceutical process the energy consumption has been calculated as of docetaxel and the water consumption as of docetaxel. For

the anticipated average annual production for the United States over the next five years this represents of the normal energy usage and of the water consumption for the Dagenham site.

9(C)(3) Transportation Related

9(C)(3)(a) Yew Needle Collection for RPR Production of 10-DAB

The energy consumed in transportation during the collection process is included in the section 9(c)(1) above.

9(C)(3)(b) RPR Production of 10-DAB

The total annual transportation requirement for delivery of needles, delivery of solvents and removal of wastes is or about by truck.

9(C)(3)(c) Docetaxel and Taxotere® Production

For the transportation of 10-DAB, intermediates, docetaxel and bulk Taxotere® solution between Cologne, Villeneuve-La-Garenne, Vitry-Sur-Seine, Seripharm and Dagenham the annual total is calculated as of docetaxel.

9(D) Summary Conclusion on the Impact of Resource and Energy Use

In summary the total energy and resource consumption in the production of Taxotere® will not represent an unwarranted environmental burden. For perspective the total energy consumption transportation of chemicals, can be calculated as equivalent to approximately assuming the worst case of only 40 mg vials produced.

SECTION 10 Mitigation Measures

10(A) Introduction

This section will describe the mitigation measures which are in place as engineered controls or as operational procedures for the mitigation of adverse events in the production of Taxotere®.

10(B) Engineering and Procedural Controls

10(B)(1) Engineered Controls on The Process and Facilities

In Section 6 of this document there are described engineering controls which are in place in the Cologne and Dagenham facilities.

10(B)(2) Material Control and Employee Protection

10(B)(2)(a) Cologne - Extraction of 10-DAB

Provided as Appendix 71 is a certification of compliance with all health and safety requirements related to the production of 10-DAB. To confirm that workers within the 10-DAB production unit in RPR GmbH Building

H14 facility are protected from hazardous exposure a study of the appropriate areas was performed. The summary of the hazardous material monitoring results is provided as Confidential Appendix 72.

10(B)(2)(b) Villeneuve La Garenne - Chemical Production of Docetaxel Side Chain

Provided as Appendix 73 is a certification of compliance for the Villeneuve La Garenne site for all health and safety requirements related to the production of RPR 104493 (BHE) for docetaxel. Confirmation is also provided that design concepts have been incorporated in the facility to prevent exposure to materials used in the BHE process and that employees involved with BHE production are subject to periodic health surveillance.

10(B)(2)(c) Vitry Sur Seine - Production of Docetaxel and Bulk Taxotere® Solution

Provided as Appendix 74 is a certification of compliance for the Vitry Sur Seine docetaxel production site for all health and safety requirements related to the preparation and handling of the docetaxel. Noted in the certification are engineering and exposure control measures which have been applied for the facility, including periodic health surveillance of the employees working with docetaxel and the bulk solution. Provided as Confidential Appendix 75 is a listing of control procedures for the docetaxel production which cover organizational, safety and cleaning procedures. Within these procedures are described the additional controls to insure prevention of human and environmental exposure as a result of operations within the docetaxel sensitive materials workshop. The Drug Master File - Type 1 for the "Ateliers De Docetaxel" filed with FDA on May 24th includes in Section 11.9 on cleaning for equipment, clothing and individual protection as well as in Section IV on material control descriptions of additional procedures applied to insure employee protection.

10(B)(2)(d) Le Mans, Seripharm - Chromatographic Purification

Provided as Appendix 76 is a certification of compliance with all health and safety requirements by Seripharm during the production process for docetaxel. Included in Attachment 76 is a listing of the standard operating procedures employed at Seripharm for equipment and material handling.

10(B)(2)(e) Dagenham - Sterilization and Filling of Taxotere®

Provided as Appendix 77 is a certification of compliance with all health and safety requirements in the production of Taxotere®. In the production process related to the Taxotere® drug product special care must be exercised to insure worker safety. Provided as Confidential Appendix 78 is a summary of the special training provided to members of the

Taxotere® production team and a listing of the standard operating procedures being put in place to control the production operation.

10(C) Site Emergency Plans

10(C)(1) Cologne Site

The RPR Cologne facility has in place an emergency response action plan. A table of contents page for the Emergency Action Plan is provided as Appendix 79.

10(C)(2) Villeneuve La Garenne Site

The Villeneuve La Garenne site has in place an emergency response action plan. A listing of the table of contents for the Emergency Action Plan is provided as Appendix 80.

10(C)(3) Vitry Sur Seine Site

The Vitry Sur Seine site has in place an emergency response action plan. A listing of the contents for the site "Internal Operations Plan" is provided as Appendix 81.

10(C)(4) Le Mans Seripharm Site

The Seripharm S.A. facility at Le Mans has an Emergency Action Plan in place as an Operating Procedure which is provided as Confidential Appendix 82.

10(C)(5) Dagenham Site

The Dagenham site has an emergency action procedure entitled "Site Emergency Procedures" which is provided as Confidential Appendix 83.

SECTION 11 Alternatives to the proposed action:

11(A) Consequences of no action/impact of non-approval

One consequence of no action or non-approval of this new drug application would be that the drug product is not available to the patients who need it, resulting in additional human suffering and death.

11(B) Projected Collection

Projected (1995 - 1999) ratios for collection for worldwide needs are based on best estimates from current data. Yield improvements are still expected concerning the biomass (selection and propagation of trees with high 10-DAB content), the chemical process and the formulation process.

The following table provides a 5-year projection of the approximate quantities of yew tree to be trimmed (in 1000's), dried yew needles (metric tons), 10-DAB (kg) and docetaxel (kg) for worldwide need.

	Yew Trees (x1000)	Yew Needles (ton)	10-DAB (kg)	Doxetaxel (kg)
1995				
1996				
1997				
1998				
1999				

The current RPR facility in Cologne can process up to . of Taxus granular. Only out of the will be collected from public land by Sedaherb. Additional 10-DAB will be supplied by Indena. For information on their collection of yew needles please refer to their DMF #10,462 and #10,463.

In 1992 RPR established 3 Taxus baccata L. pilot plantations with plants that are 10 to 15 years old. The yew plants were trimmed for the first time in August 1993 in order to optimize cultivation parameters for future plantation of selected trees. The ection of Taxus baccata L. trees with high content of 10-DAB has been started in 1989. Simultaneously basic research on optimization of propagation of those slow growing trees has been engaged. At the same time, other potential sources of the biomass have been investigated and identified.

A development study for dedicated plantations will continue for the next two years. Please refer to an interim report in Appendix 84.

11(C) **Statements to confirm no adverse effect on yew tree (as supported by information under Section 9)**

It is well known for ages that Taxus is one of the best trees for topiary. It means that all plants, if they are trimmed, will produce new growth. This is especially true for the yew which bears quiescent buds on their branches and trunk and are therefore able to put out new shoots when the branches and trunk have been cut. The regrowth capacity of the yew is at its highest in the young branches.

One specific example of the regrowth capacity of Taxus is the old hedges at Levens Hall in the UK. Please refer to the pictures in Appendix 85. These hedges are 300 years old and are trimmed once or twice annually between 20 and 30% of the yew needles are trimmed without damage to the hedge itself. The trimming of the yew hedge rejuvenates the plants by stimulating new growth and thus guaranteeing a lo g life.

Moreover, if yew clippings are not used in making medicines such as docetaxel, these would simply be wasted and are known to be toxic to certain animals.

SECTION 12 List of preparers

The preparers of this Environmental Assessment include:

Jean-Louis Fabre
Michel Blin
William Studt
Paul Fackler
Damaris DeGraft-Johnson
Donald G. Eshenick

A curriculum vitae for each preparer is included in Confidential Appendix 86.

SECTION 13 Certification

Certification Statement is included as Appendix 87.

SECTION 14 References

None

SECTION 15 Appendices

INDENA EA FOI COPY

1. Date:

July 7, 1994

2. Name of applicant:

Indena S.p.A.

3. Address:

Via Ripamonti, 99
20100 MILAN - ITALY

4. Description of proposed action

A. Description of the proposed approval

Indena S.p.A. requests approval of the manufacture of 10-Deacetylbaccatin III (10-DAB). This compound is a naturally occurring compound extracted from yew needles.

10-DAB is one of the raw materials used in the manufacture of docetaxel, the active ingredient of Taxotere® for Injection Concentrate. Taxotere® is intended to treat advanced breast cancer and advanced non-small cell lung cancer.

B. Need for the action

10-DAB will be used as a raw material for the manufacture of docetaxel, the active ingredient of Taxotere® for Injection Concentrate.

C. Location where the compound will be produced:

10-DAB will be extracted from yew needles at:

Indena
Via don Minzoni, 6
20090 SETTALA (MI) - ITALY

D. Location where the compound will be used

10-DAB is a raw material in the manufacture of docetaxel, the drug substance for Taxotere® for Injection Concentrate. Docetaxel will be synthesized through a four-stage process at the following facilities:

RHÔNE-POULENC RORER
Villeneuve-la-Garenne Plant
35, avenue Jean Jaurès
92390 VILLENEUVE-LA-GARENNE
FRANCE

Rhône-Poulenc Rorer
Centre de recherches de Vitry - Alfortville
13 Quai Jules Guesde
94403 VITRY SUR SEINE
FRANCE

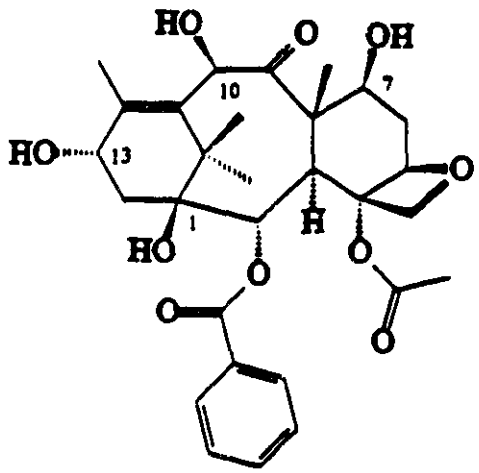
5. Identification of chemical substance

Chemical Name: 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β,13α-tetrahydroxy-9-oxo-tax-11-ene

Code Names: RP 61387, 10-DAB

CAS Number: 32981-86-5

Chemical Structure:



RP 61387 - structure above

Molecular Formula: $C_{29}H_{36}O_{10}$

Molecular Weight: 544.60

Appearance: White to slightly yellow powder

6. Introduction of substances into the environment

Waste generated during 10-DAB preparation process is divided into five categories:

1. Exhausted plant material
2. Solid residues generated in the process
3. Solvent vapors generated in the process
4. Aqueous wastes from the process and cleaning
5. Solvent waste from cleaning

1. Exhausted Plant Material - these wastes are discharged into steel containers. They are held for disposal by specialized firms; they are disposed of in authorized waste deposits. (Please refer to Enclosure 10 of DMF 10462.)

2. Solid Residues - These wastes are discharged into steel containers. They are held for disposal (as toxic wastes) by the specialized firms; they are disposed of by incineration. (Please refer to Enclosure 11 of DMF 10462.)

3. Solvent Vapors - Solvent vapors coming from concentrations, distillations, etc., are eliminated by the plant for treatment of polluted air of the factory. (Please refer to Enclosure 7 of DMF 10462.) GLC analyses on residual solvents content are carried out on the air at the exit of the plant, under control of the proposed USSL Authorities. (Please refer to Enclosure 4 of DMF.)

4. Aqueous Wastes - These wastes come from apparatus cleaning. They are combined together, and, after pH control and correction (if required) with basic solutions, they are sent to the plant for treatment of waste water inside the factory.(Please refer to Enclosure 6 of DMF 10462.). Water coming out from the treatment plant are not directly discharged into water courses, but used for irrigation purposes. Aqueous wastes are controlled inside the firm, by COD and physico-chemical parameters determination, and by an external qualified laboratory for all the parameters required by law. (Please refer to Enclosure 12 of DMF 10462.)

5. Solvent Wastes - These wastes are discharged into steel containers, and held for disposal (as toxic wastes) by specialized firms; they are disposed of by incineration or recovered in authorized plants. (Please refer to Enclosure 13 of DMF 10462.)

7. Fate of emitted substances in the environment

Not Applicable

8. Environmental effects of released substances

Not Applicable

9. Use of resources and energy

A. Historical sites and endangered species

The proposed action will not adversely affect any historical, architectural, archeological or cultural sites. No endangered species will be impacted.

B. Harvest and cultivation of Yew needles

1) Harvest of Yew needles

Yew needles are currently harvested in the Himalayan region of India from naturally growing, i.e., wild, plants and not from cultivated plants.

The first time a wild plant is cut, you can prune the 2- to 3-year old branches, always leaving about one-half of the foliage. It is best if the cuttable branches that you do not cut are regularly distributed throughout the foliage so they can act as a lymph circulation pump. Also, it is better not to cut the highest foliage too drastically.

The following year, the same tree can be pruned again, cutting those branches that were not pruned the previous year and some that were and have regrown, always taking care to leave at least one-half of the foliage.

Similar operations can be carried out in successive years, The importance of leaving at least one-half of the foliage intact cannot be over-exaggerated because this ensures the survival and regrowth of the plant.

Another pruning system is to cut only two-year old branches leaving the three-year old leaf-bearing ones to energize the plant. This system is most easily applied to young plants, which are thus treated more or less as one would treat an ornamental hedge.

Whatever the method chosen, these precautions are indispensable to enable the plant to retain its lymph circulating capacity and its photosynthesizing ability, which are both necessary to maintain the balance of nutritive substances essential to wood and leaf growth.

With respect to processing treatment, it should be kept in mind that in the period that elapses between harvesting and desiccation, the material is extremely perishable; it must be protected until desiccation is complete.

Certain fundamental rules must be followed, and collectors must be instructed therein. Otherwise, the active principle content will be degraded and the value of the batch reduced. These rules, which are to be distributed to all collectors, are the following:

- During collection, lay out the branches in thin layers and do not, on any account, leave them in sacks.
- Only just before coming back to the village can the material be put in jute sacks, taking care not to compress it, which would hinder ventilation.

- Absolutely to be avoided for the transport of material not yet dried are sacks in woven polypropylene or, even worse, plastic sacks (polyethylene and similar).
- On arrival at the village the sacks must be immediately emptied and the material placed in a dry location protected from rain and dew. During the day, they are to be laid thinly (not more than 5cm) on, if possible, a clean drying ground.
- The branches and leaves should be turned over at least three times a day to speed up the desiccation.
- Only when the material is fully dried (weight loss on oven desiccation at 60°C for fifteen hours, less than 10%) can it be considered proof against fermentation by enzymes or against attack by molds and bacteria. At this point, it can be put in sacks for transport and subsequent warehousing.
- If cut plants are to be transported by any sort of vehicle, the greatest possible care must be taken to avoid deterioration. The vegetation must on no account be compressed, but be laid on planks in such a way as to facilitate the free passage of air and the vehicle should never be left in the sun because this sets off and encourages degradation.
- If sacks of not fully dried material are to be transported, compression of the same is to be avoided by putting each layer of sacks on planks so that the weight of those above does not bear on those below.

To assist the harvesters and collectors, written instructions are provided. (A copy is attached.)

2) Cultivation Project

The aim of the cultivation project is to completely replace the harvesting of material from spontaneously grown plants with that from cultivated plants. The project estimates that cultivated plants will reach good productivity by the year 2000, and will produce 200 tons of vegetable drug from 3 million cultivated plants.

Industrial production will start in 1998, with approximately 50 tons of vegetable drug. From that year on, harvesting from spontaneous plants will begin to decrease year by year, while harvesting from cultivated plants will increase.

In the event of an increase in demand for 10-DAB, other cultivation fields can be started, which would give the first harvest by the fourth year after purchase of the small plants.

In practice, the purchase of 1 million small plants will allow a first harvest of about 50 tons of drug by the fourth year, and about 100 tons by the ninth year.

Crops will be grown in two distinct geographical areas, namely the Himalayan Region and Europe; different ways of reproduction of the plants will be followed in the two cases: cuttings or seeds.

These differences in the reproduction methods are a consequence of the significant differences existing in the starting materials. Himalayan material is much more variable from region to region, sometimes even from one plant to another. In the case of reproduction by seeds, the wide genetic differences would generate a non-homogeneous population; it is necessary, therefore, to select mother plants from which to collect cuttings.

On the contrary, Taxus baccata is already cultivated in Europe starting from seeds, for the production of small nursery plants. This material is very homogeneous. No significant differences can be found from one specimen to another for 10-DAB content.

A more detailed scheme of the two cultivation projects is reported in the following paragraphs.

Himalayan Region - In this region, some areas were detected in which the material shows 10-DAB contents higher than in others; inside these areas a number of mother plants have been selected from which cuttings are collected in autumn. Cuttings are planted from October to December, in 200-sq. meter greenhouses; 150,000 - 180,000 cuttings can be raised in each greenhouse.

Cuttings are rooted in an inert substrate and are protected during the process with suitable phytosanitary treatments. After radication has taken place (which requires 5-6 months), cuttings are transplanted into growth liners. Two to three years later, they are transplanted to the cultivation fields, with an average density of 80,000 plants per hectare.

Plants are pruned when they are in the liners, to enhance branch formation; in this way drug harvest, though in small quantities, is already possible in the first years of cultivation.

At present about 50,000 rooted cuttings are available, planted in different areas of the region, to compare the different results. 600,000 cuttings have been put into greenhouses for rooting. In the next two years, 750,000 cuttings are scheduled to be put in rooting every year. By 1996, it is anticipated to have at least 1.5 million plants planted out in cultivation fields. (plants/cuttings=70%)

Europe - In this region a strong production of nursery plants cultivated from seeds is already available. For garden centers market, several million small plants are available every year, and this number can be increased by request.

Small plants, two years old, are available on the market, (marked 2/0 in the following paragraphs); Indena will have them nursed for two years more, in pot or in nursery (plants then marked 2/2), to obtain vigorous plants that can be transplanted in cultivation fields.

At present 10,000 small 2/0 plants have been purchased. After another year, these will be planted out in cultivation fields. In the meantime, 750,000 small plants (2/0) have been purchased, which will be cultivated in pot or in nursery by the producer and will be delivered to us (as 2/2) at the end of the winter 1994-95 ready to be planted.

Recently we bought an additional 800,000 plants, 2/1 (100,000) and 2/2 (700,00), that have been planted in fields and will begin to produce in 1995.

750,000 small plants (2/0) more will be purchased in 1994, and will be delivered at the end of the winter of 1995-96. Starting from spring 1996, 2.3 million plants will be available transplanted into cultivation fields (except the mortalities).

In addition to these two main cultivation programs, projects for developing cultivation in other geographical areas are being studied; they have not yet been defined in detail at present.

Please refer to the attached expert report on the Genus Taxus written by Dr. O. Servettaz (University of Milan).

C. Information on the impact of resource and energy usage

1. The consumption of water is about 160 m^2 per kilo of 10-DAB.

2. The energy used in 10-DAB extraction is about 5000 kW/h per kilo of 10-DAB.

10. Mitigation measures

A. Production waste

As described in Section 6 of this document, the waste generated during the production of 10-DAB is adequately controlled. Exhausted plant material is disposed by specialized firms in authorized landfills. Solid residues are incinerated by specialized firms. Aqueous wastes are used for irrigation purposes and are not directly discharged into water courses. Solvent vapors are released into the atmosphere under the control of USSL authorities. Solvent wastes are either incinerated or recovered in authorized facilities.

B. Spill control procedures

Adequate spill control procedures and practices are in effect at Indena S.p.A. All departments are internally linked to the firm's acid sewer system and flow directly to the Waste Treatment Plant.

11. Alternatives to the proposed action

One alternative is not to isolate the 10-DAB from the yew needles and thus not produce the drug substance, docetaxel, and ultimately the drug product, Taxotere®. This alternative would result in additional human suffering and death.

12. List of preparers

Dr. Enrico Frangi
Damaris DeGraft-Johnson
Donald G. Eshenick

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there is little doubt that, where they not as wildlings segregated geographically, they would be accepted as subspecies or varieties of one species".

In Asia, the Taxus species recognized by the mayority of the authors are the following ones: *T. baccata* L. from western Asia to the Himalayan region, *T. wallichiana* Zucc. in Himalaya and Tibet, *T. cuspidata* Sieb. et Zucc. in China (in the provinces of Jilin, Liao-ning, Shandong, Jiangshu and Jiangxi), in Russia, in Korea and in Japan, and *T. sumatrana* (Miq.) de Laub. from Hymalaia to China and in the south in the Indo-Malayan region until Celebes.

T. wallichiana Zucc. and *T. sumatrana* (Miq.) de Laub. are the most discussed species: the first one is considered by many authors as a synonym of *T. baccata* L., and the second one is considered by some botanist as a single species (see De Laubenfels - Coniferales in Flora Malesiana ser.I, vol. 10³, 1988), while according to other authors it is to be divided into 4 different species (see Flora Republicae Popularis Sinicae tomus 7, 1978): *T. chinensis* (Pilger) Rehder, *T. chinensis* var. *mairei* (Lemée et Lévl.) Cheng et L.K. Fu [considered as a species and not a variety: *T. mairei* (Lemée et Lévl.) Hu et Liu], *T. yunnanensis* Cheng et L.K. Fu and *T. celebica* (Wall.) Li.

For what concerns the Hymalayan region, therefore, 3 species are present, whose diffusion areas overlap more ore less markedly: *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu; observations on the place confirm the presence of hybrids, which constitute terms of passage between the two species.

In addition to natural hybrids, man-made hybrids exist, the best known of which are *T. x hunnewelliana* Rehder, obtained from *T. canadensis x T. cuspidata* and *T. x media* Rehder, which is the hybrid of *T. baccata x T. cuspidata*. These hybrids are generally fertile, so demonstrating that there are few genetical differencies between the parent species, although they have been geographically segregated for a long time in widely separated areas: the species in question, as described before, respectively come from Europe, from Asia and from North America.

In Europe and especially in the United States gardeners have selected a huge number of cultivars, starting both from species and from the two aforementioned hybrids. The actual number of these cultivars is continuously increasing, as new cultivar production is going on; an estimate of the present situation is reported below:

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T. baccata L. – 15 cultivars

T. cuspidata Sieb. et Zucc. – 15 cultivars

T. x media Rehder – 65 cultivars

T. x hinnewelliana Rehder – 5 cultivars

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Morfology

From the morfological point of view there are no highly significant differencies among the different species of *Taxus*; differencies are mainly in the habitus of the plant, in the arrangement of branches, of leave on the twigs and of reproductive organs. In analysing the characteristics of the genus *Taxus* it is always necessary to keep in mind that different leaves of a same plant are not morfologically all equivalent: on a same twig, the basal leaves are generally very short and thin, the intermediate ones are of much bigger dimensions, and the terminal ones are smaller than the intermediates, but bigger than the basal ones. There are differencies, too, between the terminal twigs of the lower branches and the apical ones, or those corresponding to the growth of higher branches

Generally it is not difficult, apart from exceptional cases, to recognize a *Taxus* species in the wild; it becomes however very difficult to identify the species of origin when only dried leaves are available for classification.

In the case of Taxus ornamental cultivars, classification is even more difficult, because these plant are generally propagated by branch cuttings, and the successive growth takes place as if the branch was still attached to the mother plant, that is, maintaining the characteristics of that specific branch and not developing those of the whole plant. From basal branch cuttings more or less spreading speciment will be generated, while from apical branches more or less erected plants will develop, till to fastigiate.

It is also to be noted, in addition, that no universal analytical keys exist for *Taxus* genus; the existing keys are all coming from floras, therefore they are regional, as their purpose is to distinguish plants in the wild. Therefore, if the origin of the material to be identified is unknown, recognition becomes very difficult, sometimes unpossible; if instead the geographical origin of the material is sure, and this has been collected from spontaneous trees, three cases are possible, depending on the continent of origin:

- in the case of material of European origin, the only possible species is *Taxus baccata* L.
- if the material comes from America, it can be still doubtlessy identified if the exact origin is known, as the 4 American *Taxus* grow in well separated regions
- if the material comes from Asia the identification is much more difficult, as the 4 -7 Asian species, as described before, have more or less overlapping growth regions, with the only exception of *T. celebica*, which is a rare and never harvested species.

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Difficulties are particularly high for material from the Himalayan region, where *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu have widely overlapping growth region and, together with the species, many hybrids are present which, as already reminded, show all the possible intermediate charactersistics between the parent species.

In the wild *T. baccata* L. can be distinguished from *T. wallichiana* Zucc. for the arrangement of the leaves on the twigs; in the first species leaves, due to a torsion of the petiole, are all arranged on a single plan, as it happens in the majority of taxus trees; in the second one, on the contrary, leaves are disordinately arranged; leaves are strip-shaped and usually straight or slight falciform, apex is acute, bud scales occur frequently in the small branch base.
In *T. yunnanensis* Cheng et L.K. Fu the leaves are lanceolate to strip-lanceolate, mostly falciform, seldom straight, apex is from acuminate to acute, bud scales shed or partly remain in the small branch base.

Morfological control

In the case of plant material coming from the Hymalaian region identification concerns the 3 species which grow in that region, that is: *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu.

Examining leaves and twigs, which is the material used for 10-deacetylbaccatin III extraction, it must be taken into account that the material is generally very fragmentated, with the leaves almost always detached from the twigs, and squeezed as a consequence of desiccation. The main purpose of the control is to morfologically identify the material, which is described as follows:

Leaves are brilliant green to brownish-green in colour, sessile or briefly petiolate, linear-flattened, glabrous, up to 30 (35) mm long and 2-2.5 mm wide, acute to pointed at the apex, straight or curved-falciform, with an asymmetric (rarely a symmetric) base, an upper surface bright and darker than the lower surface, a mat lower pagina, with an evident central nervation, margin sometimes flat, more often revolute downward. In the dried leave the central nervation is apparent mainly in the upper pagina; on this side it is sometimes flanked by two deep grooves.

The twigs, cylindrical, from green to brown in colour, must be not more than 4 mm thick; they exhibit scares from fallen leaves, showing a spiralled insertion, and traces of leaves, decurring downward. Strobiles are sometimes present: male strobiles are more or less spherical, 5 mm in

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diameter when completely developed, shortly pedunculate, completely contained in the bracteas when young; the two superior bracteas are more developed than the others; female strobiles have only one ovule, with micropilus protruding from the bracteas, which are similar to the bracteas covering male strobiles. Small immature fruits are rarely present.

Examined under a microscope, the leaf section shows: the upper face epidermis, of isodiametric or sometimes slightly elongate cells, protected by a very thick cuticular layer; below this the photosynthetic palisade-like parenchyma, with cylindrical cells in one or two layers; then the lacunous parenchyma, with very large cells that are sometimes filled with starch granules; at last, the lower epidermis.

The epidermis of the lower pagina of the leaf has distinct aspects in the different zones: in the distal part it is similar (but thinner) to the upper face epidermis , with more often elongate cells protected by a cuticle, in the two zones, were stomata are sunken, epidermal cells show cuticle with very manifest papillous crests; in the portion below the central nervation the cuticle surface may be more or less papillous. In the central part of the section a single nervation is visible, consisting into a single cribro-vascular bundle, into which the xylematic components are apparent together with the phloematic components, surrounded by the bundle parenchyma; sideways to the bundle there are two groups of transfusion tracheids.

The stem section shows: the epidermis, of isodiametric or more often elongate cells, protected by a cuticle, the cortical parenchyma, without secretory channels, the primary and secondary phloema, the cambium and the central cylinder, characterised by the presence of homoxylus wood, in one or two layers, and by a central pith.

Particular attention is devoted to check the absence of resiniferous vessels in the leaf (as in other conifers); the stomatic region must not show 2 whitish zones (*Cephalotaxus* spp.) and the apex may be acuminate but must not terminate with a rigid and spiny point (*Torreya* spp.).

Certainly determined samples have been examined of *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu. It has been noted that between the first and the second species no significant differencies can be detected, as dried leaves show very similar characteristics, so that sometimes differencies are greater among different leaves of the same species than between those of the two species

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Taking into account that not all the botanists agree on the distinction between these two taxus species, and the absence of doubtlessly distinctive characters, it can be concluded that it is not possible to distinguish *T. baccata* L. from *T. wallichiana* Zucc.

T. yunnanensis Cheng et L.K. Fu. shows some differencies.
In the case of trees grown at moderately high quotes, the most significant differencies are summarized as follows: leaves are generally wider and thinner than those of *T. baccata* L. and of *T. wallichiana* Zucc., more often (not always) are S-shaped, the palisade tissue often consists of a single layer and the epydermical zone under the central nervation shows a smooth and not papillous surface.
It is to be noted, however, that in the case of trees grown at higher quotes the differencies described are much less evident.

It can be concluded that a batch of plant material coming from the Hymalaian region and complying with the botanical macroscopic and microscopic characters described before could actually belong not only to the species *T. baccata* L.; presence of *T. wallichiana* Zucc. material is not detectable by morfological control of fragmented dried material; *T. yunnanensis* Cheng et L.K. Fu if not detected during selection, may sometimes be present; in any case, this can be only a small percentage, less than 5 per cent.

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Chemical Tests

Practically, a potential contamination of *Taxus baccata* L. leaves and twigs by a certain amount of *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu material cannot be excluded by plant material analysis.

In order to demonstrate if a potential presence of *T. wallichiana* Zucc. and *T. yunnanensis* Cheng L.K. Fu in *T. baccata* L. material could significantly influence the characteristics and quality of the 10-deacetylbaccatin III obtained, preparation tests on a pilot scale were performed, by extracting, isolating and purifying, separately, pure samples of *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng L.K. Fu. This work was performed in Indena Labs.

The 3 samples, were collected in the following growing areas:

1) *T. baccata* L.	Region: Mandy	State: Himachal Pradesh
2) *T. wallichiana* Zucc.	Region: Nainital	State: Uttar Pradesh
3) *T. yunnanensis* Cheng L.K. Fu	Region: Bomdila	State: Arunachal Pradesh

For botanical identification criteria described in Encl. 1 were applied.
Chemical and physical analysis of the 3 plant material samples was performed in Indena Labs. according to the methods and specifications described in the Document "Manufacture and packaging", Section IV, point A, of DMF 10462 (see the enclosed analytical certificates AR 0143, AR 0144 and AR 0145, respectively, Encl. 2). Isolation of 10-deacetylbaccatin III and results are in Encl. 3

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Conclusions

Potential contamination of *T. baccata* L. with *T. wallichiana* Zucc. and *T. yunnanensis* Cheng L.K. Fu does not constitute a problem in relation to 10-deacetylbaccatin III preparation, as the quality of the product obtained is not affected by the actual species of the plant starting material. These tests, on the contrary, demonstrate that *T. wallichiana* Zucc. and *T. yunnanensis* Cheng L.K. Fu are perfectly suitable and practically equivalent to *T. baccata* L. as starting material for 10 - deacetylbaccatin III preparation.

O. Servettaz

Prof. Orietta Servettaz

Milan, June 22, 1994

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Encl. 1

TAXUS SPECIES

In India grow 3 different Taxus species:

1) *T. baccata* L. 2) *T. Wallichiana* Zucc. 3) *T. yunnanensis* Cheng et L.K. Fu

These species have overlapping diffusion areas, and observations on the place confirm the presence of hybrids, with all the possible terms of passage between the parent species.

In order to get 3 univocally determined plant material samples, as requested for chemical investigation, 3 different areas were chosen for sample collection, in which only *T. baccata* L., *T. wallichiana* Zucc. and *T. yunnanensis* Cheng et L.K. Fu, respectively, grow, to minimize the probability of finding hybrids.

Botanical classification was performed on the place, as differencies are more evident on the whole tree, while they become minimal on dried material, which is generally fragmented and consists mainly of detached twigs and leaves.

The harvesting areas of the 3 species and the distinctive morfological characters are as follows

1) *T. baccata* L. Region: Mandy State: Himachal Pradesh
Altitude: 1000 m

Tree, up to 15 m high; leaves linear, thick, ordinately arranged on the 2 sides of the twigs in a comb-fashion, apex shortly acute; seeds ovoidal, 4.5-6.5 mm long, 4-5 mm wide

2) *T. wallichiana* Zucc. Region: Nainital State: Uttar Pradesh
Altitude: 1500 m

Tree or big shrub, up to 12-15 m high; leaves linear, thick, irregularly arranged on the 2 sides of the twigs, not in a comb-fashion, apex shortly pointed; seeds more or less cylindrical, 6.5 mm long, 4.5-5 mm wide

3) *T. yunnanensis* Cheng L.K. Fu Region: Bomdila State: Arunachal Pradesh
Altitude: 1200 m

Tree, up to 20 m high; leaves from linear to falcate to S-shaped, thin, ordinately arranged on the 2 sides of the twigs in a comb-fashion, apex from pointed to shortly acute, seeds ovoidal, pointed at the apex, 5 mm long, 4 mm wide.

O.S.

3-16-183

MINISTERE DE L'ENVIRONNEMENT

REPUBLIQUE FRANÇAISE

LE DIRECTEUR DE LA PREVENTION
DES POLLUTIONS ET DES RISQUES

Neuilly, le 29 DEC. 1993

Attestation de conformité à la réglementation en matière d'environnement

Le site RHONE-POULENC RORER de VILLENEUVE LA GARENNE, établissement classé, est selon la réglementation sous le contrôle technique permanent des services administratifs compétents : Service Technique des Installations Classées, Direction Régionale de l'Industrie, de la Recherche et de l'Environnement, Agence de l'Eau.

Les résultats de ce contrôle montrent que les fabrications en place, destinées à la production de BHE (Boc Hydroxy Ester) chaîne latérale du DOCETAXEL, sont réalisées sur ce site conformément aux réglementations en vigueur, en matière d'environnement.

En foi de quoi, je soussigné, LEGRAND Henri, Directeur de la Prévention des Pollutions et des Risques, certifie que le site RHONE-POULENC RORER de VILLENEUVE LA GARENNE respecte les obligations de la législation française pour la protection de l'environnement.

En conséquence, la présente attestation a été rédigée pour servir et valoir ce que de droit.

Fait à NEUILLY, le

The RHONE-POULENC RORER site of VILLENEUVE LA GARENNE which is classified according to the French regulations, as under the permanent technical control of competent administrative departments : Technical Department for Listed Facilities, Regional Department of Industry, Research and Environment, Waste Water Treatment Agency.

The results of this control demonstrate that the manufacturing operations in place leading to the production of BHE (BOC HYDROXY ESTER) part of DOCETAXEL are conducted on this site in compliance with current environmental regulations.

In witness whereof, I undersigned, LEGRAND Henri, Director of the Department of prevention of pollution and risks, certify that RHONE-POULENC RORER site of VILLENEUVE LA GARENNE fulfill the requirements of the French regulations with respect to environment protection.

Consequently, the present certificate is issued to be worth and used for whatever purpose by whom it may concern.

NEUILLY, le

29 DEC. 1993

14, Boulevard du Général-Leclerc - 92524 Neuilly-sur-Seine - Tél. : (1) 40-81-21-22 - Télex : [illegible]

Sigma Chemical Co.
P.O. Box 14508
St. Louis, MO 63178
Phone: 314-771-5765

Aldrich Chemical Co., Inc.
1001 West St. Paul
Milwaukee, WI 53233
Phone: 414-273-3850

Fluka Chemical Corp.
980 South Second St.
Ronkonkoma, NY 11779
Phone: 516-467-0980
Emergency Phone: 516-467-3535

SECTION 1. - - - - - - - - - CHEMICAL IDENTIFICATION- - - - - - - - - -
PRODUCT #: D0667 NAME: 10-DEACETYLBACCATIN III APPROX. 95% (HPLC) FROM TAXUS BREVIFOLIA

SECTION 2. - - - - - COMPOSITION/INFORMATION ON INGREDIENTS - - - - - -
CAS #:32981-86-5
MF: C29H36O10

ADDITIONAL INFORMATION
CONTAINS METHYL ALCOHOL, CHEMICAL ABSTRACTS REGISTRY NUMBER 67-56-1.
CONTAINS ACETONITRILE, CHEMICAL ABSTRACTS REGISTRY NUMBER 75-05-8.

SECTION 3. - - - - - - - - - - HAZARDS IDENTIFICATION - - - - - - - - - -
LABEL PRECAUTIONARY STATEMENTS
TOXIC
TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.
TARGET ORGAN(S):
EYES
CENTRAL NERVOUS SYSTEM
IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE POSSIBLE).
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
WEAR SUITABLE PROTECTIVE CLOTHING.
DO NOT BREATHE DUST.

SECTION 4. - - - - - - - - - - FIRST-AID MEASURES- - - - - - - - - - -
IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES.
IN CASE OF CONTACT, IMMEDIATELY WASH SKIN WITH SOAP AND COPIOUS AMOUNTS OF WATER.
IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
WASH CONTAMINATED CLOTHING BEFORE REUSE.

SECTION 5. - - - - - - - - - - FIRE FIGHTING MEASURES - - - - - - - - - -
EXTINGUISHING MEDIA
WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

3-19-96

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

SECTION 6. - - - - - - - - - ACCIDENTAL RELEASE MEASURES- - - - - - - - -

WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

SECTION 7. - - - - - - - - - - HANDLING AND STORAGE- - - - - - - - - - -

REFER TO SECTION 8.

SECTION 8. - - - - - - - EXPOSURE CONTROLS/PERSONAL PROTECTION- - - - - -

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
SAFETY SHOWER AND EYE BATH.
MECHANICAL EXHAUST REQUIRED.
WASH THOROUGHLY AFTER HANDLING.

SECTION 9. - - - - - - - - PHYSICAL AND CHEMICAL PROPERTIES - - - - - - - -

APPEARANCE AND ODOR

SOLID.
MELTING POINT: 232-236 C
SOLUBILITY: WATER-INSOLUBLE

SECTION 10. - - - - - - - - - -STABILITY AND REACTIVITY - - - - - - - - - -

STABILITY

STABLE.

INCOMPATIBILITIES

STRONG OXIDIZING AGENTS

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
NITROGEN OXIDES

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

SECTION 11. - - - - - - - - - - TOXICOLOGICAL INFORMATION - - - - - - - - -

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
CAUSES EYE AND SKIN IRRITATION.
MATERIAL IS IRRITATING TO MUCOUS MEMBRANES AND UPPER RESPIRATORY TRACT.
EXPOSURE CAN CAUSE:
DAMACE TO THE EYES
DAMAGE TO THE LIVER
DAMAGE TO THE HEART
DAMAGE TO THE KIDNEYS
GASTROINTESTINAL DISTURBANCES
MAY CAUSE CONVULSIONS.
TARGET ORGAN(S):
EYES
CENTRAL NERVOUS SYSTEM
LIVER, KIDNEYS
BLOOD, LUNGS

3-19-97

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

SECTION 12. - - - - - - - - - - ECOLOGICAL INFORMATION - - - - - - - - - -

DATA NOT YET AVAILABLE.

SECTION 13. - - - - - - - - - - DISPOSAL CONSIDERATIONS - - - - - - - - - -

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER. OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

SECTION 14. - - - - - - - - - - TRANSPORT INFORMATION - - - - - - - - - -

CONTACT SIGMA CHEMICAL COMPANY FOR TRANSPORTATION INFORMATION.

SECTION 15. - - - - - - - - - - REGULATORY INFORMATION - - - - - - - - - -

TLV AND SOURCE

FOR METHYL ALCOHOL - SKIN:
ACGIH TLV-TWA: 200 PPM (260 MG/M3); STEL: 250 PPM (310 MG/M3).
OSHA PEL: 8 H TWA 200 PPM (260 MG/M3); STEL: 250 PPM (310 MG/M3).
FOR ACETONITRILE:
ACGIH TLV-TWA: 40 PPM (70 MG/M3); STEL: 60 PPM (105 MG/M3).
OSHA PEL: 8H TWA 40 PPM (70 MG/M3); STEL: 60 PPM (105 MG/M3).
MAY CONTAIN UP TO:
2% METHANOL CAS# 67-56-1
2% ACETONITRILE CAS# 75-05-8
THESE PRODUCTS ARE SUBJECT TO SARA SECTION 313 REPORTING REQUIREMENTS.

SECTION 16. - - - - - - - - - - OTHER INFORMATION- - - - - - - - - - - -

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA, ALDRICH, FLUKA SHALL NOT BE HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL TERMS AND CONDITIONS OF SALE.

3-19-98

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

November 21, 1995

DUPLICATE

Partial submission

Robert Delap, M.D., Acting Director
Oncology Group (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex 2 Document Room
1451 Rockville Pike
Rockville, MD 20852

NDA #20-449
Taxotere® (docetaxel)
for Injection Concentrate

Amendment to an Approvable NDA
(Second Partial Submission)

Dear Dr. Delap:

Reference is made to the above-captioned approvable New Drug Application and to Dr.Temple's letter dated October 27, 1995. Further reference is made to our November 3, 1995 and November 6, 1995 submissions, which contained, in duplicate, responses to items 1 and 2 found on pages 1 and 2 of the approvable letter, as well as answers to items 1 and 2 found on page 3 of the letter.

This submission contains, in duplicate, our response to the item described as MEDICAL/PHARMACOLOGY-TOXICOLOGY/CHEMISTRY found on page 1 of Dr. Temple's letter. It also contains responses to all seven items described under the category MEDICAL found on pages 1 through 3, as well as responses to all of the items requested in the **POST-APPROVAL STUDIES AND ANALYSES** category found on pages 8 and 9.

We expect to make the third and final submission of materials under this Amendment during the week of November 27, 1995. It will contain responses to all CHEMISTRY/MANUFACTURING/CONTROLS questions as well as our proposed LABELING, including a draft patient package insert.

We look forward to continued positive interaction with the Agency, and would like to take this opportunity to thank the Oncology Group for its prompt review of the Taxotere® NDA.

Please contact me at (610) 454-3037 if you have questions or comments regarding this Amendment.

Sincerely,

Anne-Margaret Martin

Anne-Margaret Martin
Senior Manager
Regulatory Affairs

AMM/aes

enclosures

cc: via fax: Ms. Dorothy W. Pease, Project Manager (w/o atts.)
Regulatory file

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT Rhone-Poulenc Rorer Pharmaceuticals, Inc.	**DATE OF SUBMISSION** 11/21/95
ADDRESS *(Number, Street, City, State and Zip Code)* 500 Arcola Road Collegeville, PA 19426	**TELEPHONE NO.** *(Include Area Code)* (610) 454-3037
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-449

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	**PROPRIETARY NAME** *(If any)*
docetaxel	Taxotere®

CODE NAME *(If any)*	**CHEMICAL NAME**
RP56976	(2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,-10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. (WHO Drug Information, Vol. 7, No. 4, 1993 - Prop. INN: List 68)

DOSAGE FORM	**ROUTE OF ADMINISTRATION**	**STRENGTH(S)**
Sterile Solution for Injection Concentrate	Intravenous Infusion	80mg 20mg

PROPOSED INDICATIONS FOR USE

treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND
IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	**HOLDER OF APPROVED APPLICATION**

STATUS OF APPLICATION *(Check one)*

PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL 610-454-8000

May 19, 1995

Via Fax and
Certified Mail (With Enclosures)

Robert Temple, M.D.
Director, Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857.

Dear Dr. Temple:

Please refer to our telephone conversation on May 17, 1995 in which our concerns were expressed with regard to the review for Taxotere® (NDA 20-449) dated May 16, 1995. Because of the heavy emphasis placed on comparability with paclitaxel, and the apparent reliability on these comparisons, at least in part, in the formulation of the conclusion that Taxotere® does not have an acceptable therapeutic index, we feel that it is appropriate to point out areas where we believe conclusions may have been based on unwarranted assumptions. In addition, we would like to point out areas where we feel answers to some of the concerns were provided to the Agency (in the May 16 ODAC Briefing Document, copy enclosed) subsequent to the writing of the review.

The intent of this letter is to serve as background for a meeting scheduled for May 26, 1995, where we hope to discuss fully FDA's concerns and the impact of these concerns on the development of Taxotere®.

Myelosuppression

Septic deaths: The FDA review points out that comparisons between paclitaxel and docetaxel are difficult to make. Nonetheless, a comparison is made between two groups of breast cancer patients treated at doses that are either approved (paclitaxel 135-175 mg/m2 over 3 h) or proposed (docetaxel 100 mg/m2 over 1 h). The resulting conclusion was that the septic death rate was fivefold higher for docetaxel than paclitaxel in patients who are quoted by the reviewer as having similar baseline characteristics.

We feel that this comparison is not valid because the proportions of breast cancer patients with anthracycline-resistant disease in paclitaxel and docetaxel trials are not similar. As shown in Table 22 of the Briefing Document provided to FDA on May 16, in anticipation of a June review by ODAC, 67% of 162 patients treated with docetaxel in second-line pivotal trials had primary resistance to anthracyclines. The figure for paclitaxel according to the package insert, was ~16% in the 471 patients enrolled in the paclitaxel pivotal trial. Furthermore, the definition of anthracycline-resistance in the RPR trials was more stringent (relapse had to occur during adjuvant therapy with anthracyclines, whereas patients in the paclitaxel study could have relapse up to 6 months after the completion of the adjuvant program).

Therefore, the comparison of rates of septic death is not appropriate; there is no basis for the quoted difference of fivefold. Furthermore, a readily identifiable population of hepatically impaired patients at higher risk of septic death has been identified so that the rate of septic death in patients without liver impairment is lower. These data are discussed in the May 16 Briefing Document.

Neutropenia: The FDA review correctly states that the incidence of Grade IV and febrile neutropenia reported for docetaxel is greater than the incidence reported for paclitaxel in advanced breast cancer patients treated according to the doses in the package insert.

We agree that Grade IV and febrile neutropenia is likely to be more frequent with docetaxel because of the relative cytotoxic potency. Please note this is in contrast to conclusion 2 of our March 95 Safety Report where febrile neutropenia was inappropriately included with the items quoted "comparable to other recently approved agents". This error has been rectified in the May 16 Briefing Document.

With regard to febrile neutropenia, although differences in the rate are expected, the magnitude of the difference may be explained in part by the differences in baseline patient characteristics. When paclitaxel was used in patients with "poor" baseline characteristics in the NCI treatment referral center (TRC) program at 135 mg/m^2 over 24 h in heavily pretreated breast cancer patients, febrile neutropenia occurred in 46% of patients. Furthermore in this group, 42% of patients received G-CSF, 37% of all patients had a dose reduction, and the incidence of infections was 37%. As pointed out above, anthracycline-resistant patients constituted a larger proportion of the overall population of breast cancer patients in which docetaxel was studied. As confirmed in the NCI paclitaxel experience, severe neutropenia is more likely to occur in these more severely ill patients.

The magnitude of the difference may also be explained in part by the conventions for the computation of the febrile neutropenic episodes. The RPR definition of febrile neutropenia included any treatment period in which fever (at least 1 day > 38ºC) occurred and neutropenia grade IV occurred, but not necessarily concomitantly. This conservative definition will also result in a high incidence of febrile neutropenia.

Fluid retention

We agree with FDA that fluid retention represents an issue with this compound and have been developing methods to reduce the impact of this event, most notably, premedication with steroids. While we agree that the use of steroids has not consistently lowered the overall incidence of fluid retention, we believe that premedication with steroids has a positive effect on its severity and outcome. With 5-day steroids, severe fluid retention was significantly less frequent (4.8% vs 20%, $p = 0.0032$, see Table 8 of March 95 report). In the same table, the incidence of any fluid retention was also significantly lower in the premedicated group ($p=0.0005$). We also address in the May 16 Briefing Document the issue raised concerning the possible effect of a reduced number of cycles contributing to a favorable fluid retention profile where in Table 11, p. 15 we present data from premedicated patients treated in US pivotal breast cancer trials with the same median number of cycles ($n=5$) as patients without premedication.

FDA states that ODAC requested a randomized trial of steroids versus no premedication be performed. RPR believes that a no-steroid premedication arm may be difficult to test in a clinical trial since a prospective randomized trial has demonstrated a highly significant favorable effect of corticosteroid premedication (TAX 265), and also because of the beneficial effect of corticosteroids on hypersensitivity reactions.

The FDA has expressed great concern about the persistence of fluid retention. Although some patients may have some discomfort due to persistent fluid retention for several weeks or even months after docetaxel discontinuation, this does not imply the presence of a severe or life threatening condition. Furthermore, very few patients discontinued docetaxel due to fluid retention before cycle 4, so that most patients will have the potential to receive some benefit.

Because fluid retention does not appear to be of major significance for paclitaxel, we are aware of the need to fully characterize the risk that fluid retention poses for docetaxel so that FDA can arrive at appropriate conclusions based on a benefit-to-risk assessment. Please note that RPR is answering additional FDA questions to further clarify the issue of fluid retention. These responses will be submitted prior to our meeting.

Tolerance in patients with liver impairment

This topic is addressed through expanded analyses both in the May 16 Briefing Document and in the answers to the FDA questions that will be submitted shortly. Clearly for patients who are at increased risk of excessive systemic exposure because of reduced hepatic clearance, a dosage reduction is warranted.

Clinical benefit

Ultimately we feel that the concerns raised in the FDA review are real, since not only were they raised by ODAC but are now reemerging in the FDA review. Thus, the risk side of the equation has been fully developed. As pointed out above, especially where comparison to paclitaxel has been made, the magnitude of the risk remains a point for resolution. If the standard for approval is now the benefit/risk of paclitaxel, we feel that comparisons for efficacy should also be developed as was done in the May 16 Briefing Document.

We appreciate your willingness to discuss these issues and look forward to our meeting scheduled for 5:30 PM, May 26. If you have any questions or need for further information, please feel free to contact me at 610-454-3996.

Thank you for your consideration. We look forward to our continued positive interaction in the evaluation of the NDA for Taxotere®.

Sincerely,

James T. Molt
Sr. Director
Regulatory Affairs

JTM/aes

cc. Charles P. Holberg, Ph.D. w/enc.
283 370 619

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL: 610-454-8000

October 19, 1994

VIA TELEFAX & CERTIFIED MAIL

Gregory P. Burke, M.D., Ph.D., Director
Oncology Group (HFD-150)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA #20-449
Taxotere® (docetaxel)

Dear Dr. Burke:

Please be advised that in accordance with 21 CFR 314.102(c) and with the policy described in the Center's Staff Manual Guide 4820.6, we hereby request a 90-day conference with members of your group concerning the above-captioned New Drug Application which was filed on July 27, 1994.

We would like to take the opportunity to discuss the general progress of the review and to obtain Dr. Beitz's feedback relative to the non-small cell lung cancer indication, particularly in light of the ODAC Meeting set for December 13, 1994.

If at all possible, we would greatly appreciate a meeting during the week of October 31, 1994.

Please do not hesitate to contact me at (610) 454-3037 if you have any further questions regarding this matter.

Sincerely,

Anne-Margaret Martin

Anne-Margaret Martin
Manager
Regulatory Affairs

AMM/jag

Co. Corres

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER GMBH

Rhône-Poulenc Rorer GmbH · Postfach 35 01 20 · D-50792 Köln

Nattermannallee 1, D-50829 Köln
Telefon (0221) 508-01
Telefax (0221) 508-2711
Telex 888 1928 rpr d
Telex 22 14 217 rpr
Bank
Deutsche Bank AG Köln 2507 564
(BLZ 370700 60)

Ihr Zeichen Your ref	Ihr Schreiben vom Your letter of	Unsere Abteilung Our department	Unser Zeichen Our ref	Durchwahl Direct line	Datum Date
		P	gl-fu	2000	25.02.93

Production of 10-DAB at theRhône - Poulenc Rorer extraction plant in Cologne

Statement

Rhône - Poulenc Rorer certifies that it is in compliance with, or on an enforcable schedule to be in compliance with, all emission requirements set forth in applicable federal, state, and local statures an regulations as well as permits, consent decrees, and admininstrative orders applicable to the production of 10 DAB by extraction of yew needles Taxoterre at its facilities in Cologne, Germany.

ppa.

H. Glady

i.V.

Dr. R. Losch

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER GMBH

Rhône-Poulenc Rorer GmbH · Postfach 350120 · D-50782 Köln

Nattermannallee 1, D-50829 Köln
Telefon (0221) 509-01
Telefax (0221) 509-2711
Telex 8881928 rpr d
Telefax 2214217 rpr
Bank
Deutsche Bank AG Köln 2507564
(BLZ 37070060)

Ihr Zeichen Your ref	Ihr Schreiben vom Your letter of	Unsere Abteilung Our department	Unser Zeichen Our ref	Durchwahl Direct line	Datum Date
		P	g-fu	2000	29.10.93

Production of 10-DAB at theRhône - Poulenc Rorer extraction plant in Cologne

Statement

The extraction of yew needles as well as the purification of this extract to one of the key raw material 10-DAB for Taxoterre ® is manufactured at the Rhône - Poulenc Rorer site Nattermann in Cologne.

The facility complies with the local German environmental regulations. The manufacturing process of 10-DAB are also in accordance with local German environmental regulations.
(Appendix)

ppa.

H. Glady

i.V.

Dr. R. Losch

STATE TRADE SUPERVISORY OFFICE COLOGNE

Postal Address: State Trade Supervisory Office 5 Cologne 1 P.O. Box 140 140

A. Nattermann & Cie. GmbH
Nattermann-Allee 1

5000 Cologne 30

Offices
Blumenthalstr. 33
(*Administration*)

Konrad-Adenauer-Ufer
79-81

Telephone
7740-1
Direct line: 7740
720841-43

Your note and date

My note
10.32 - 16/79 K/Bau

Cologne
14.08.1979

Certificate of authorization

In accordance with § 6 in connection with §§ 15 and 19 of the Federal Emission Protection Law BImSchG - of 15.03.1974 (BGBl. I p. 721) the company

A. Nattermann & Cie. GmbH
Nattermannallee 1
5000 Cologne 30

is granted permission according to its application of 22.03.1979 to

modify an extraction plant for ca. 90 m³ aqueous extract
on its works premises in
5000 Cologne 1, Nattermannallee 1,
Boundary Cologne, Cadastral register 126/127

Insofar as not otherwise laid down the plant is to be erected and operated according to the application documentation which is taped and sealed to this certificate or to the individual details designated in enclosure 1.

- 2 -

STAATLICHES GEWERBEAUFSICHTSAMT KÖLN

Postanschrift: Staatl. Gewerbeaufsichtsamt · Postfach 140149 · 5000 Köln 1

A. Nattermann & Cie. GmbH
Nattermannallee 1

5000 Köln 30

Dienstgebäude:
☐ Blumenthalstraße 33 (Behördenhaus)
☐ Konrad-Adenauer-Ufer 79-81

Fernsprecher:
7740-1
Durchwahl: 7740
720841-43 App.:

nach Dienstschluß: 7740201
Straßenwagen: 0221 0556464

Ihr Zeichen und Tag	Mein Zeichen	Köln
	10.32 - 16/79 K/Bau	14.08.1979

Großpyrkolator

Genehmigungsbescheid

Nach § 6 i. V. mit §§ 15 und 19 des Bundes-Immissionsschutzgesetzes - BImSchG - vom 15.03.1974 (BGBl. I S. 721) wird der Firma

A. Nattermann & Cie. GmbH
Nattermannallee 1
5000 Köln 30

auf ihren Antrag vom 22.03.1979 die Genehmigung erteilt, auf ihrem Werksgelände in

5000 Köln 1, Nattermannallee 1,
Gemarkung Köln, Flur 126/127,
eine Extraktionsanlage für ca. 90 m^3
wässerige Extrakte zu ändern.

Die Anlage ist entsprechend den Antragsunterlagen, die mit dieser Genehmigung durch Schnur und Siegel verbunden oder im einzelnen in der Anlage 1 bezeichnet sind, zu errichten und zu betreiben, soweit im folgenden nichts anderes bestimmt wird.

3-19-120

APPENDIX 21

STATE TRADE SUPERVISORY OFFICE COLOGNE

Postal Address State Trade Supervisory Office 5 Cologne 1 P.O. Box 140 140
Against receipt
A. Nattermann & Cie. GmbH
Nattermannallee 1

5000 Cologne 30

Offices
Blumenthalstr. 33
(Administration)

Official in charge
Mr. Rieser

Your code and date	My code	Cologne
	2120-99/88 Ri/Wk/Jr	14.071989

Certificate of authorization

In accordance with § 6 in connection with § 15 of the Federal Emission Protection Law BImSchG . of 15.03.1974 (BGBl. I p. 721) the company

A. Nattermann & Cie. GmbH
Nattermannallee 1
5000 Cologne 30

is given authorization for its application of 29.08.1988 to make material changes to

their existing facility for the
industrial-scale manufacture of
medicaments or intermediate
products for medicaments

on its works premises at

5000 Cologne 30
Nattermannallee 1
Boundary Cologne-Müngersdorf
Cadastral register 27.

STAATLICHES GEWERBEAUFSICHTSAMT KÖLN

Staatliches Gewerbeaufsichtsamt · Postfach 140 149 · 5000 Köln 1

Gegen Empfangsbescheinigung

Firma
Nattermann & Cie. GmbH
Nattermannallee 1

5000 Köln 30

Dienstgebäude:
☒ Blumenthalstraße 33
(Behördenhaus)
☐ An der Münze 12 — 18
☐ Hülchrather Straße 2 — 4

Erreichbar ab Hauptbahnhof mit den Straßenbahnlinien 5, 16, 17, 18 bis Reichenspergerplatz

Bearbeiter: Herr Rieser

Ihr Zeichen und Tag

Mein Zeichen
2120- 99/88 Ri/Wk/Jr

Köln
20.7.1989

Operationsanlage

Genehmigungsbescheid

Nach § 6 in Verbindung mit § 15 des Bundes-Immissionsschutzgesetzes - BImSchG - vom 15.03.1974 (BGBl. I S. 721) wird der Firma

Nattermann & Cie. GmbH
Nattermannallee 1
5000 Köln 30

auf ihren Antrag vom 29.08.1988 die Genehmigung erteilt, auf ihrem Werksgelände in

5000 Köln 30,
Nattermannallee 1,
Gemarkung Köln-Müngersdorf,
Flur 27,

die bestehende Anlage zur fabrikmäßigen Herstellung von Arzneimitteln oder Arzneimittelzwischenprodukten

wesentlich zu ändern.

Fernsprecher
0221 / 77 40 - 1
Durchwahl 0221 / 77 40 -504

Fernsprecher nach Dienstschluß
0221 / 7 74 02 01
Streifenwagen 0161 / 2 20 43 15

3-19-123

RHÔNE-POULENC RORER

Verantwortlicher

Betreff: Extraktion von Taxus baccata

Bericht/Protokoll: Besprechungsprotokoll

Ort: Büro Dr. Losch

Tag: 13.1.1992

Anwesend waren: H. Heitmann GAA Köln

H. Dr. Günther
H. Dr. Losch
H. Möhlenbein
H. Deffur
H. Gusinde

Genehmigungsverfahren für die Taxusextraktion

Mit H. Heitmann wurde über den Einsatz von Butylacetat als Lösungsmittel in der Extraktion gesprochen.

Nach Aussage von H. Heitmann sollte zur Information eine Anzeige gemäß §16 Abs.1 BImSchG erfolgen, da das Tanklager G14 für Stoffe der Gruppe A gemäß VBF zugelassen ist und im Gebäude H14 nur in geschlossenen Apparaturen mit dem Lösungsmittel gearbeitet wird. H. Heitmann hält den Einsatz von Butylacetat für eine unwesentliche Änderung des Extraktionsverfahrens. Die Vorschriften nach VBF, VAwS etc. müssen auch in unseren eigenen Interesse eingehalten werden.

Ein Rundgang durch H14 schloß die Besprechung ohne Änderung der obigen Meinung ab.

Die Meldung an das GAA erfolgt erst wenn im Hause RPR endgültig die Entscheidung zum Einsatz von Butylacetat gefallen ist. → nach VBF A2

Gusinde

Verteiler: Anwesende
H. Schwentke
H. Dr. Hillboll z.Kts.

3-19-125

RPR-Cologne **Disposal of Waste streams from 10-ĐAB production** **29.11.1993**

Flow chart stream no.	German waste Key no.	Disposal	licensed transport-company	licensed disposal/ incineration Company	license no.	Responsible declaration to authorities Allowance No.	Date
1	53 503	a)compostage b) usage	Trienekens Robert-Bosch-Str. 8 50769 Köln License No. E 31500760	a) W.U.R.M. GmbH Lövelinger Str. 101 41472 Neuß b) RPR-yew-farm Stöckheimer Weg 50829 Köln	n.a. n.a.	n.a.	n.a.
2	n.a.	waste water	municipal sewer	Municipal Sewage treatment plant Stammheim City of Cologne	n.a.	Preliminary introduction allowance City of Cologne	06.12.1990
3	12 304	Incineration	Trienekens s. above	WESTAB Kanalstr. 71 48432 Rheine	E 566 557 45	0000 448	09.06.1993
4	55 370	Incineration	Trienekens s. above	Kleinholz Westuferstr. 15 45356 Essen	E 113 150 8	E 00 9669	30.10.1992
5	55 370	Incineration	Trienekens s. above	GVS Essener Str. 68219 Mannheim	H 191 394 80	E 0000 16	07.01.1993
5	55 370	Incineration	Trienekens s. above	Widdig Markusstr. 60 53859 Niederkassel	E 382 320 63	WWA 035	21.07.1992
7	55 370	Incineration	Trienekens s. above	GVS Essener Str. 68219 Mannheim	H 191 394 80	E 000 016	07.01.93

3-19-127

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MINISTÈRE DE L'ENVIRONNEMENT

RÉPUBLIQUE FRANÇAISE

LE DIRECTEUR DE LA PRÉVENTION
DES POLLUTIONS ET DES RISQUES

Neuilly, le 28 DEC. 1993

Attestation de conformité à la réglementation en matière d'environnement

Le site RHONE-POULENC RORER de VILLENEUVE LA GARENNE, établissement classé, est selon la réglementation sous le contrôle technique permanent des services administratifs compétents : Service Technique des Installations Classées, Direction Régionale de l'Industrie, de la Recherche et de l'Environnement, Agence de l'Eau.

Les résultats de ce contrôle montrent que les fabrications en place, destinées à la production de BHE (Boc Hydroxy Ester) chaîne latérale du DOCETAXEL, sont réalisées sur ce site conformément aux réglementations en vigueur, en matière d'environnement.

En foi de quoi, je soussigné, LEGRAND Henri, Directeur de la Prévention des Pollutions et des Risques, certifie que le site RHONE-POULENC RORER de VILLENEUVE LA GARENNE respecte les obligations de la législation française pour la protection de l'environnement.

En conséquence, la présente attestation a été rédigée pour servir et valoir ce que de droit.

Fait à NEUILLY, le

The RHONE-POULENC RORER site of VILLENEUVE LA GARENNE which is legally classified according to the French regulations, as under the permanent technical control of competent administrative departments : Technical Department for Listed Facilities, Regional Department of Industry, Research and Environment, Waste Water Treatment Agency.

The results of this control demonstrate that the manufacturing operations in place leading to the production of BHE (BOC HYDROXY ESTER) part of DOCETAXEL are conducted on this site in compliance with current environmental regulations.

In witness whereof, I undersigned, LEGRAND Henri, Director of the Department of prevention of pollution and risks, certify that RHONE-POULENC RORER site of VILLENEUVE LA GARENNE fulfill the requirements of the French regulations with respect to environment protection.

Consequently, the present certificate is issued to be worth and used for whatever purpose by whom it may concern.

NEUILLY, le

28 DEC. 1993

14, Boulevard du Général-Leclerc - 92524 Neuilly-sur-Seine - Tél. : (1) 40-81-21-22 - Télex : 620 124

MINISTERE DE L'ENVIRONNEMENT

REPUBLIQUE FRANÇAISE

LE DIRECTEUR DE LA PREVENTION
DES POLLUTIONS ET DES RISQUES

Neuilly, le 28 DEC. 1993

Attestation de conformité à la réglementation en matière d'environnement

Le site RHONE-POULENC RORER de VITRY-sur-SEINE, établissement classé, est selon la réglementation sous le contrôle technique permanent des services administratifs compétents : Service Technique des Installations Classées, Direction Régionale de l'Industrie, de la Recherche et de l'Environnement, Agence de l'Eau.

Les résultats de ce contrôle montrent que les fabrications en place, destinées à la production de DOCETAXEL et de solution vrac de TAXOTERE, sont réalisées sur ce site conformément aux réglementations en vigueur, en matière d'environnement.

En foi de quoi, je soussigné, LEGRAND Henri, Directeur de la Prévention des Pollutions et des Risques, certifie que le site RHONE-POULENC RORER de VITRY-sur-SEINE respecte les obligations de la législation française pour la protection de l'environnement.

En conséquence, la présente attestation a été rédigée pour servir et valoir ce que de droit.

Fait à NEUILLY, le

The RHONE-POULENC RORER site of VITRY-sur-SEINE which is duly classified according to the French regulations, as under the permanent technical control of competent administrative departments : Technical Department for Listed Facilities, Regional Department of Industry, Research and Environment, Waste Water Treatment Agency.

The results of this control demonstrate that the manufacturing operations in place leading to the production of DOCETAXEL and TAXOTERE solution are conducted on this site in compliance with current environmental regultions.

In witness whereof, I undersigned, LEGRAND Henri, Director of the Department of prevention of pollution and risks, certify that RHONE-POULENC RORER site of VITRY-sur-SEINE fulfill the requirements of the French regulations with respect to environment protection.

Consequently, the present certificate is issued to be worth and used for whatever purpose by whom it may concern.

NEUILLY, le

28 DEC. 1993

14 Boulevard du Général-Leclerc - 92524 Neuilly-sur-Seine - Tél. : (1) 40-81-21-22 - Télex Dampa 62

DRIRE
PAYS DE LA LOIRE

DIRECTION REGIONALE
DE L'INDUSTRIE, DE LA RECHERCHE
ET DE L'ENVIRONNEMENT

MINISTÈRE DE L'ENVIRONNEMENT

Nantes, le 21 octobre 1993

ATTESTATION

La production de DOCETAXEL (matière active pharmaceutique) s'effectue sur le site de la société SERIPHARM au Mans (Sarthe – FRANCE). Cette usine, et en particulier le procédé de production de DOCETAXEL respecte les lois et les règles françaises concernant l'environnement et la sécurité et fait l'objet d'inspections régulières de notre service.

DOCETAXEL (pharmaceutical active drug substance) is manufactured by SERIPHARM at their factory in Le Mans (Sarthe – FRANCE). This plant complies with french environmental and safety regulations, and is regularly inspected by our department.

Pr le directeur et par délégation,
Le chef du service régional
de l'environnement industriel,

Denis BERTEL

Affaire suivie par monsieur Gérard PRIGENT,
adjoint au chef du service régional de l'environnement industriel – réf. : GP/FG/ENV/93/365

DIRECTION
3, rue Marcel Sembat - 44049 NANTES Cedex 04 - Tél. 40 44 82 00 - Télecopie 40 73 46 84

3-19-174

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER LIMITED

RAINHAM ROAD SOUTH
DAGENHAM ESSEX RM10 7XS
TEL: 081-919 3060
TLX. 28691 RPDAGN G
FAX. 081-593 2140

CERTIFICATION OF ENVIRONMENTAL COMPLIANCE

Rhône-Poulenc Rorer certifies that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in applicable federal, state, and local statutes and regulations as well as permits, consent decrees, and administrative orders applicable to the handling and subsequent filling of Taxotere into vials at its facilities in Dagenham, United Kingdom.

For and on behalf of
Rhône-Poulenc Rorer

D. Pulford

Dr. D.W. Pulford
Technical Director

3/2/94
Date

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PRINCIPES ACTIFS

35, AVENUE JEAN JAURES
92395 VILLENEUVE-LA-GARENNE CEDEX
TEL. : (1) 46.85.91.91 - FAX : (1) 46.85.91.61

HISTORICAL SITES AND ENDANGERED SPECIES

There are neither historical sites nor normally resident endangered species located within such a radius that they will be affected by :

1) The normal operation of the site.

2) The consequences of any reasonably foreseeable emergency on the site.

Several historical buildings are situated about 15 km from the site and are not endangered by an incident on the site.

For and on behalf of
Rhône-Poulenc Rorer

JC. CRUBEZY
Plant Manager

G. DEPOST
Safety and Environmental Manager

INTERNAL SAFETY DATA SHEET
RHONE-POULENC RORER CENTRAL RESEARCH
500 Arcola Road, Collegeville, PA 19426-0107
EMERGENCY TELEPHONE: 215-454-5606

TAXOTERE

Last Revision: 05/27/94
Printout Date/Time: 06/27/94 11:15

SECTION 1 CHEMICAL IDENTIFICATION

COMMON NAME: TAXOTERE
SYNONYMS: RP 56976, Docetaxel
INTENDED USE: Antineoplastic - Tubulin Depolymerization Inhibitor

SECTION 2 COMPOSITION/INFORMATION ON INGREDIENT(S)

CHEMICAL NAME: 4-acetoxy-2a-benzoyloxy-5(3,20-epoxy-1,7b,10b-trihydroxy-9-oxo tax-11-ene-13a-yl-(2R,3S)-3-tert-botoxycarbonylamino-2-hydroxy-3-phenylpropionate
FORMULA: C43 H53 N O14 CAS NUMBER: 114977-28-5
EXPOSURE CONTROL LIMIT: N.A. mg/m3 PB-ECL: 4

SECTION 3 HAZARDS IDENTIFICATION

APPEARANCE/ODOR: Coarse white to off-white powder

POTENTIAL ACUTE HEALTH EFFECTS: BASED ON AVAILABLE PRE-CLINICAL DATA:

INGESTION: Extremely toxic by ingestion.

SKIN: Non-irritating to the skin.

INHALATION: Expected to be extremely toxic by inhalation but studies not yet complete.

EYES: Moderately irritating to the eyes.

POTENTIAL OTHER HEALTH EFFECTS BASED ON AVAILABLE DATA: In short-term studies, this compound effected test animals nervous and immune systems, intestinal lining and testes. Based upon initial screens, it is unclear whether it has potential for causing cancer. Specifically, sub-chronic studies in mice and dogs revealed a potential for neurotoxicity (NOEL = 6 mg/m2), myelosuppression and leucopenia (LOEL = 3 mg/m2-dy), necrosis of the intestinal epithelium (NOEL = 6 mg/m2-dy), testicular atrophy (NOEL = 6 mg/m2-dy) and lymphoid organ depletion (NOEL = 3 mg/m2-dy). Ames tests were negative. Other genotoxicity assays were positive. The Guinea-pig Anaphylaxis assay was negative.

SECTION 4 FIRST AID MEASURES

FIRST AID FOR ACCIDENTAL INGESTION: Seek medical attention. Induce vomiting only as directed by medical personnel. Never give anything by mouth to an unconscious person.

FIRST AID FOR SKIN EXPOSURE: In case of contact, flush skin with

plenty of water. Remove contaminated clothing and wash before re-use. Seek medical attention if irritation persists.

FIRST AID FOR INHALATION: If inhaled, remove to fresh air and seek medical attention. If not breathing, give artificial respiration if trained and willing. If breathing is difficult, give oxygen.

FIRST AID FOR EYE EXPOSURE: Immediately flush eyes with plenty of water for fifteen minutes. Seek medical attention if irritation persists.

NOTES TO PHYSICIAN: No treatment notes are available in addition to chronic effects information.

SECTION 5 FIRE FIGHTING MEASURES

FLASH POINT: N.A. F LEL: N.A. ppm UEL: N.A. ppm

FLAMMABILITY CLASSIFICATION: N.A. BURN RATE: N.A.

TOXIC GASES POTENTIALLY GENERATED IN A FIRE: CO, CO2 and oxides of nitrogen may be generated in a fire.

EXTINGUISHING MEDIA: This is an experimental compound and the physical properties have not yet been fully characterized. Foam, water spray, carbon dioxide or dry chemical type fire extinguishers may be used.

FIRE FIGHTING INSTRUCTIONS: Keep personnel removed from and upwind of fire. Wear full firefighting turn-out gear (full bunker gear) and self-contained breathing apparatus (SCBA).

SECTION 6 ACCIDENTAL RELEASE MEASURES

Appropriate personal protective equipment as per section 8 should be utilized by any individual involved in spill clean-up. Clean-up all spills immediately. If dry, recommend use of HEPA vacuum or, if not available, carefully scoop and containerize material. If liquid spill, dike or divert from any drain or pathway to the outside environment, then absorb on paper towels or other absorbent material depending on the size of the spill. Then wet area with water or other appropriate solvent (see section 9) and wipe up with paper towels. Repeat this procedure three times. See section 13 for specific disposal recommendations.

SECTION 7 HANDLING AND STORAGE

HANDLING PRECAUTIONS: Wash thoroughly after handling to avoid accidental transfer of the compound to food that may be subsequently ingested. Keep hands away from face when handling compound.
Do not get compound on skin or on clothing (see section 8 for proper gloves).
Do not breath dust, vapor or mist. Keep container closed when not in use. Use with adequate ventilation (see section 8 for proper engineering control).

Avoid contact with eyes (see section 8 for proper eye protection).

STORAGE: Store in a tightly closed container in a cool, dry location out of direct sunlight.

SECTION 8 EXPOSURE CONTROLS AND PERSONAL PROTECTION

ENGINEERING CONTROLS: Handle all powder forms of this compound in a glovebox or other total containment system. Solutions or suspensions may be handled outside of a glovebox with appropriate spill protection and solvent resistant gloves.

PERSONAL PROTECTIVE EQUIPMENT:

SKIN PROTECTION: Latex gloves or gloves of equal or greater protection are recommended for handling the powder. Gloves specifically impervious to the solvent being used should be worn if handling solutions or suspensions of this compound. Contact R. Stevens at 215-454-3191 for specific glove information at the Collegeville site.

RESPIRATOR: An approved and properly fitted, full-face, negative-pressure HEPA filter respirator or respirator of equivalent or greater protection is recommended for laboratory scale handling of the compound to control exposure below any permissible exposure limit if engineering controls are not being used.

EYE PROTECTION: Safety glasses required. Goggles recommended if potential exists for direct exposure to dusts or splashes.

SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

pH: 6.5 VAPOR PRESSURE (mm Hg): N.A. VAPOR DENSITY (Air = 1): N.A.
BOILING POINT (oC 760 mm Hg): N.A. MELTING POINT(oC): N.A.
SPECIFIC GRAVITY (H2O = 1): 1. LOG P: N.A.
MOLECULAR WEIGHT: 807.89

SOLUBILITY: Solubility in water approximately 0.1 mg/ml, in methanol (20 C) - soluble, in DMF/DMSO (20 C) freely soluble and in dichloromethane (methylene chloride) (20 C) sparingly soluble.

SECTION 10 STABILITY AND REACTIVITY

No significant degradation - buffered solution(pH 2.7-7.9). Degraded to 50% in 14 days - 5:95/CH3CN:0.1N HCl. Degraded instantaneously - 32:68/CH3OH:0.1N NaOH.

SECTION 11 TOXICOLOGICAL INFORMATION

ACUTE PRE-CLINICAL TOXICOLOGICAL INFORMATION:

STUDY	SPECIES	ROUTE	RESULT
Acute	Mice	iv	aLD50 approximately 30 mg/kg
Acute	Rat	po	> 2000 mg/kg

SECTION 12 ECOLOGICAL INFORMATION

ECOTOXICITY: Studies in progress.

ENVIRONMENTAL FATE: Based upon water solubility and Log P (Octanol/Water partition coefficient), this compound should partition to the aquatic compartment fairly exclusively. Confirmatory studies are ongoing.

SECTION 13 DISPOSAL CONSIDERATIONS

Waste must be disposed of in accordance with federal, state and local environmental regulations. Incineration is the preferred method. For specific Collegeville site information, contact C. Fillmore at 215-454-5609.

SECTION 14 TRANSPORT INFORMATION

This is a reserach compound that has not been fully characterized. It has not yet been designated a DOT hazard class, label or placard but should be handled in a spill situation as if it were placarded as poisonous. It has not yet been assigned a U.N. number nor product RQ.

SECTION 15 REGULATORY INFORMATION

This compound is experimental and as such is not specifically listed under RCRA, SARA Title 3, CERCLA and TSCA but may meet the critieria of a hazardous substance under OSHA (see 29 CFR 1910.1200) or RCRA (see 40 CFR 261.20-24). The toxicological and physical properties have not as yet been fully characterized.

SECTION 16 OTHER INFORMATION

Prepared by Rhone-Poulenc Rorer Central Research - Department of Safety and the Environment. If further information or clarification is needed call D. Eherts at 215-454-5606.

PREPARED BY RPRCR DEPARTMENT OF SAFETY AND THE ENVIRONMENT - COLLEGEVILLE.

FDA Corres.

#297

TC 17 May 94
no letter required? JM

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mills, Chair, (HFD-[illegible]) NPM II

FROM: Division of Pulmonary & Oncology Drug Prod. HFD-150
Attention: Richard Lowenthal Phone 4-2125

DATE: 18 Apr. 94

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Taxotere NDA/ANDA# TBD.

Company Name: Rhône-Poulenc Rorer

Established name, including dosage form: docetaxel for Injection

Other trademarks by the same firm for companion products:
None

Indications for Use (may be a summary if proposed statement is lengthy): Cancer (Breast & Non-Small Cell Lung)

Initial comments from the submitter: (concerns, observations, etc.)
None

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Consult #297 (HFD-150)

TAXOTERE Docetaxel for Injection

A review did not reveal names which look or sound like the proposed name other than Taxol which is not thought to be sufficiently similar that an objection should be raised.

The similarity to the established name was noted but will not be objected to since a precedent was established with the approval of Taxol as a proprietary name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Mills, Chair 5/9/94

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee 611
Attention: Ms. Yana Mills, Chair, (HFD-[illegible]) MPN II

FROM: Division of Pulmonary: Oncology Drug Prod. HFD-150
Attention: Richard Lewenthal Phone 4-2195

DATE: 18 Apr. 94

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Taxotere NDA/ANDA# TBD.

Company Name: Rhône-Poulenc Rorer

Established name, including dosage form: docetaxel for Injection

Other trademarks by the same firm for companion products:
None

Indications for Use (may be a summary if proposed statement is lengthy): Cancer (Breast & Non-Small Cell Lung)

Initial comments from the submitter: (concerns, observations, etc.)
None

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

NOV 1 8 1994

NDA 20-449

Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, Pennsylvania 19426

Attention: Frank Vivet, M.D., Ph.D.
Director, Regulatory Affairs

Dear Dr. Vivet:

Please refer to your pending July 27, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Taxotere (docetaxel) for Injection Concentrate.

We also refer to your amendments dated October 7 and 13, 1994.

To complete our review of the Chemistry sections of your submission, we request the following:

1. Please clarify the regulatory reference batch for docetaxel. The structure elucidation and characterization section identifies batch number OP10 PROC 92229 as the batch used for collection of these data. However, the reference standard section describes batch number 20 PROC 93104 (PRS-120) as the official reference lot. It is normally required that those data submitted for the proof of structure and those used to characterize the drug substance physical properties are obtained from the reference batch proposed for use in analytical testing. Explain this discrepancy and provide information to link the batch used in the structure elucidation to the reference lot proposed for analytical methods.

2. Have further solid state studies been performed in non-aqueous solvents to determine the proclivity of docetaxel to form other solvates, hydrates or polymorphic forms? Describe these studies and results. If these studies indicate that other solid state forms are possible, it may be necessary to examine the stability of these solid state forms to ensure that material will remain within acceptable limits throughout the retest period. We are particularly concerned about polymorphs which may form in non-aqueous solvents, such as polysorbate 80, due to the drug product

formulation.

3. A single species of Yew should be identified and utilized in the isolation of 10-DAB. The purity profile of the species chosen should be investigated and compared to the literature for impurities with potential adverse toxicities. Adequate methods and specifications should be proposed for the 10-DAB to ensure that those impurities which may be a concern are adequately controlled and are not introduced into the manufacturing process in unacceptable amounts.

4. For semi-synthetic products derived from natural sources, the regulatory starting material is considered to be the raw natural material (refer to the Center's Drug Substance Guideline). The 10-DAB isolated from the raw plant source should be considered a Pivotal intermediate in the process. Acceptance specifications for the Yew needles described for use in the RPR Germany facility are not acceptable. The following additions and revisions should be included in the specifications.

   a. A complete Botanic description should be provided for each species of Yew which is proposed for use in the isolation of 10-DAB. This description should include the type of foliage used (e.g. twigs NMT 2 cm) as well as physical, microscopic and cellular examinations to ensure that the species chosen for use in the process are adequately identified. This description should be capable of distinguishing different Yew species found in the regions where plant material is collected.

   b. Provide a more precise description of "Foreign Matter". This should include all material which is not the single species of Yew selected for use in the manufacturing process.

   c. A specification for the Assay should be proposed and include a minimum concentration of 10-DAB in the raw plant material. This specification should be supported by manufacturing data which demonstrate that the manufacturing process is capable of extracting material suitable for use for production of docetaxel.

d. The HPLC method used for Assay of the raw plant material should be submitted in detail and contain appropriate validation data.

e. A complete purity profile should be provided for each species of Yew proposed for use in the isolation procedure. All significant impurities should be identified and compared to literature references for known toxicity; submit all literature references used in the analysis. Of particular concern are impurities with known or suspected toxicities and pharmacological activities which differ from those of docetaxel and which may not be detected by the proposed analytical methods used for the 10-DAB and/or docetaxel drug substance.

5. With regard to the testing protocols for reagents and solvents, it is unclear whom the testing is conducted by prior to use in the process. Are test results accepted based on certificate of analysis or is all testing performed by Rhone-Poulenc Rorer?

6. We acknowledge the designation of drug substance manufacturing steps as critical manufacturing steps. However, steps which involve chiral resolution of the side chain and ammonolysis should also be considered a critical step for purposes of in-process control and validation. The production of RPR 104493 (side chain key intermediate) with adequate stereoisomeric purity is controlled by these process steps. Failure to adequately control these manufacturing steps may result in diastereomers of docetaxel for which the ability of the analytical methods to detect have not been adequately demonstrated. Additional data on the chromatography steps should also be provided and these steps should be considered critical purification steps.

7. Additionally, the intermediate RP 67373, which results from the coupling of RP 68839 and RP 108278, should be considered a Key Intermediate and as such will require appropriate test methods and specifications. We further note that under the definitions described in the Center's 1987 Guideline for the Submission of Supporting Documentation in Drug Applications for the

Manufacture of Drug Substances, the 10-DAB must be considered a Pivotal Intermediate and should be controlled in an appropriate manner.

8. The drug substance manufacturing is not adequately described for the purposes of regulatory control. In resubmitting the description for the preparation of docetaxel the following issues should be considered.

   a. The literature has demonstrated that the purity profiles of Yew extracts obtained from different species are significantly different. The purity profile has also been reported to differ with the region and time of year in which the plant is collected. The isolation of 10-DAB should be conducted using a specified species of Yew collected from a specified region and under specified climatic conditions. For each species proposed for the process, the purity profile should be determined and controlled. The methods used should demonstrate the ability to control potentially toxic Taxanes and Taxines which may be present. In addition, the isolation process for the 10-DAB should be described in greater detail based on the use of a single species of Yew. Data to support proposed variations in the process and rework procedures should be provided.

   b. We are troubled, and extremely concerned, by the differences in purity of the two 10-DAB sources. At this time, we prefer a conservative approach and recommend that only the Indena 10-DAB be utilized in the manufacturing process. If you desire to continue manufacturing docetaxel by the alternate manufacturing process devised for RPR 10-DAB, we request that you provide purity profile information on each intermediate and for each chromatography step. The purity profile of the intermediates derived from the Indena and RPR 10-DAB should be compared and any differences justified. The intermediates obtained at each step should be comparable.

   c. A target amount and range for each reagent or solvent used should be specified for all drug substance manufacturing process steps. The proposed ranges should be justified

with appropriate data or based on CGMP considerations. Data provided should be from pilot or commercial scale demonstration batches.

d. Based on the target amounts and ranges for reagents, solvents and intermediates, a protocol for adjusting the amounts based on the reaction scale should be provided. This protocol should clearly describe how the relative amounts of reagents and solvents will be adjusted with changes in the scale of the process.

e. An expected chemical yield, range and purity (if appropriate) should be specified for each process step. Reactions which yield an abnormally high or low amount of product should be investigated.

f. For each process step a maximum time should be specified for that unit operation or process. These times should be justified with appropriate data.

g. For reaction 7B, specify the concentration of hydrochloric acid used in the process in addition to the amount and ranges as discussed above.

h. With regard to the chromatography manufacturing steps, provide data to justify the reuse of silica gel columns for 12 consecutive manufacturing processes. These data should include a demonstration of the ability to remove any residual substances from the silica gel and a determination of the column efficiency after multiple uses.

i. Data should be provided for step 9 to demonstrate the complete removal of residual dicyclohexylcarboimide, dicyclohexylurea and pyrrolidinopyridine from the process. Adequate controls for these reagents or by-products may be necessary for routine control.

j. For step chromatography of RP 56976, describe the disposition of column fractions which do not meet the requirements for collection and mother liquors from crystallization. Recombining fractions with virgin batches of

drug substance or intermediate is unacceptable and all recovered fractions or mother liquors should be held and assigned a discrete batch number. This type of activity is considered a rework and should be supported by submission of appropriate data in an amendment to this application or as a post-approval supplement.

k. For process step . provide data to support the proposed reprocessing of column fractions and mother liquors from the crystallization. The mixing of raw RP 56976 with chromatography fractions from the previous batch and the mother liquors from the previously crystallized material is unacceptable. These fractions should be held as a discrete batch and data provided to demonstrate that the recovery process provides drug substance of comparable purity profile and chemical properties.

9. With regard to the acceptance specifications and tests for the crude Yew Biomass used in the isolation of 10-DAB, we have the following requests.

a. As previously stated a single species of yew should be identified and qualified in the process. Appropriate identification and appearance testing should be submitted to ensure appropriate control over the manufacturing process.

b. A specification for the twig size which is acceptable for manufacturing should be provided along with justification for the selection.

c. The residual water content appears, in our opinion, to be excessive for the dried plant material. Provide some justification for the proposed residue upon evaporation specification with special attention to possible mold growth on the packaged biomass. Evidence that this level of moisture is low enough to prevent mold growth during the proposed storage period should be provided. A maximum storage time period should also be stated in the application and enforced.

10. We are highly concerned with the assay specification for the 10-

a. The specification for Appearance should state that the material is free of visible contamination.

b. For the HPLC identity test, a stated variation for the retention time should be provided in the application.

c. We require that routine testing and appropriate limits be established for acetic acid, cyclohexane, ethyl acetate as well as ethanol. Please provide supportive data on the solvent levels found in, at least, the last 10 batches of drug substance. These solvents should be routinely controlled at appropriate levels as a result of their use in the later manufacturing steps.

d. A specific test for Zn should be developed and an appropriate specification proposed.

e. Impurity limits will require modification as described below.

f. With regard to the specifications for color in a methanol solution, we request that you report data in quantitative units and not as conforms. In addition, data should be provided to demonstrate that the proposed specification is suitable and meaningful as a method of controlling the drug substance quality.

17. With regard to the drug substance HPLC assay method (RPR/RD/CRVA/AN-6937), we have the following comments and requests.

a. The suitability test should be based on the ability to separate RP 56976 (docetaxel) and RPR 102512 (t_{RR} = 0.90). The purpose of this test is to establish that the drug substance and impurities are adequately resolved. We fail to see how the naphthalene used as an internal reference in this test provides assurance that related substances are resolved by the method.

b. Note that the ICH guideline on impurities in drug substance is still in draft and has not been completely implemented by the Agency. We do not feel that under the current

standards of technology that a 0.2% limit of quantitation is acceptable. Literature references have clearly demonstrated that Taxanes are detectable and quantifiable at levels more than 10 fold below that claimed in your method validation. We recommend that linearity should be examined with a greater injection quantity using equivalent volumes. The quantity of material injected (10 ug) has not been adequately justified by validation data.

c. The method of evaluating the limit of detection and quantitation should be fully explained. Is this calculated from the base line noise or the baseline noise plus corrections for drift? We do not recognize the use of base line drift in this calculation.

d. With regard to the method sensitivity, we do not believe the method is adequately sensitive to detect impurities at appropriate levels. Limits of quantitation should be at least 0.05% unless adequately justified in the application. While the ICH draft guideline states that impurities below the limit of quantitation need not be specifically reported, the guidance also states that the method must be capable of detecting and quantitating impurities at appropriate levels. We also must note that methods are published for similar Taxanes which have substantially lower limits of quantitation than those proposed by your firm. We encourage further development of this method, after which, discussion with the Division is recommended.

18. We are concerned with a number of potential impurities and degradation products which have not been demonstrated to be detectable by the analytical method proposed for regulatory control, based on the limits of detection and resolving ability of the method. Of primary concern are the following: 10-DAB (RP 61337); RP 73079 (light degradation product); RP 70653 and other Troc protected species (mono-, di, and tri-substituted); products resulting from the hydrolysis of the B ring benzoate and the C ring acetate; products resulting from the acid catalyzed oxetane ring opening; possible existence of Taxines introduced in the isolation of 10-DAB; and, other Taxane derivatives which may result from those impurities detected in the Yew species selected

for manufacturing. At this time our confidence in your proposed method is limited by these concerns.

19. In addition to the need to develop methods to detect those impurities discussed in the comment above, the impurity limits proposed for the docetaxel as specified are unacceptable. Impurity limits are controlled from two perspectives, the pharmacological/toxicological and the manufacturing control aspect. In no case should impurity limits be above those which have been demonstrated to be safe in animals and man through pre-clinical and clinical studies. In addition, the manufacturing capability and necessity to apply appropriate controls may require lower limits based on the batch history. We therefore request that the following changes be applied to the impurity limits for docetaxel.

    a. The total impurity limit should not exceed 1.5% for all measurable peaks (note the comments on the analytical method and the limit of quantitation). This was the amount observed in Batch FCH 160 and exceeds any total amount observed in the last 20 batches manufactured to date.

    b. The limit for RPR 101118 should be reduced to NMT 0.20%. Batch number 03-PROC-92174 contained up to 0.2% (listed as <0.2%), however, recent manufacturing (last 10 batches) indicated that material can be produced at high levels of purity with less than 0.05% noted.

    c. For the limit on RPR 102049, a purely process related impurity, the manufacturing data from the last 20 batches indicate that this impurity has not been found above the 0.05% level. We request that this compound be limited as an "other related impurity" to less than 0.20%.

    d. For the limit on RP73077, our analysis shows that this impurity has been studied in the major toxicology and clinical studies at the 0.2% maximum amount. Early batches claimed to have been used in pre-clinical pharmacology studies did contain 0.3% of this impurity; however, these studies are not clearly identified and our pharmacologist cannot determine the qualification status of

this degradant. If these early pre-clinical studies are provided, a limit of 0.3% may be permitted.

20. Provide a more detailed listing of all pharmacology, toxicology and clinical studies which have been submitted to support the application and the corresponding batch of drug substance and product used in those studies.

21. We have the following comments and requests regarding the Drug Substance Stability protocol and data.

    a. Stability results indicate that the level of impurity RPR 102049 increases over time and that some of the room temperature and refrigerated batches have failed due to this impurity. Our concern is that RPR 102049 is listed as 4-acetoxy-2-benzoyloxy-13-cyclohexylcarbamoyloxy-5,20-epoxy-1,7,10-trihydroxy-9-oxo-tax-11-ene. This is a cyclohexylcarbamate species which can only arise as a byproduct of the dicylcohexylcarboiimide mediated coupling reaction (. Provide a scientific explanation to account for the dramatic change in this impurity over time. Are any other cyclohexylcarbamate species detected in the drug substance which are not associated with Taxanes?

    b. Data provided for stability studies should be analyzed using an approved statistical analysis protocol which is based on the commercial scale data. Submit a proposal for statistical analysis of the drug substance stability data. Please refer to the Stability Guideline and utilize the statistical programs available from the Division of Biometrics in the Center for Drug Evaluation and Research.

    c. Based on the commercial scale data provided, the retest date should be no greater than 6 months. Once 12 months of data are available, the retest date may be extended to 12 months, provided an approved statistical analysis is used to determine this retest date.

The following concern the Drug Product.

22. Indicate the upper and lower extremes of the proposed batch size

that you intend to manufacture with appropriate justification based on batches manufactured in the commercial facilities. Changes in the manufacturing batch size outside the range supported by data in the application should be submitted to the application as a supplemental new drug application after approval.

23. Clarify the test methods and specifications proposed for testing excipients used in the production of Taxotere. Are the proposed tests performed routinely for each lot of excipient or is an alternate testing protocol used for acceptance of excipients?

24. For each step in the manufacturing process, maximum process times should be established based on manufacturing experience. Stability data may be necessary if extended holding times are proposed for the carboyl during the bulk solution manufacturing process and shipping to

25. Provide data on the extractables detected when using polysorbate 80 with the Millipore DURAPORE filters. Additionally, data on the compatibility of the proposed formulation with these manufacturing components should be provided.

26. Describe appropriate temperature controls during processing and storage. How is the temperature monitored?

27. All information pertaining to the reprocess or rework of bulk solution or unit doses should be submitted to the application.

28. Provide a sampling protocol for conducting the regulatory release testing of Taxotere. This protocol should include information on a uniform sampling procedure which provides an adequate number of samples for release testing. The protocol should also identify the number of samples needed for each regulatory test performed.

29. We have the following requests regarding the drug product specifications and test methods.

    a. A test method and specification for Heavy Metals should be included in the release specifications.

    b. Report all data on Color determinations in a quantitative

manner. Specifications should be justified based on these data.

c. A test method and specification for chiral identity in the drug product should be submitted.

d. The data provided do not adequately support the proposed limits on Related Substances (also see comment on drug substance limits). Provide specific reference to information and justification for the proposed limits on RP 70617 and RP 73077. Impurity specifications for the drug product must be based on appropriate toxicology and clinical data. Additionally, from analysis of the batch results manufactured to date, limits for RPR 110928 and 112248 + X should not exceed levels observed to be safe in pre-clinical and clinical trials. We further note that these impurities were not studied in the pharmacology section and were not monitored during stability.

e. Provide a protocol to account for other impurities noted in the HPLC chromatogram which are not listed in the drug product specifications. All observed impurities must be accounted for and included in the total related substances specification.

f. There are a number of Related Substances which are not controlled despite the fact that these impurities are known or probable degradation products. These compounds include, but are not limited to the following; RP 61387, RP 66779 and RPR 108771. Provide a complete analysis of potential degradation pathways and demonstrate that the method is capable of detecting these potential and known degradation products and that all impurities are adequately controlled by the proposed specifications.

g. We continue to have serious concerns about the analytical methods used for assay and detection of related substance. Please refer to comments in the drug substance section on the methods used and capabilities of these techniques.

30. Provide some justification for the use of ETFE Coated, West PH

703/VII stoppers with polysorbate 80. Compatibility and data on extractables with a solvent more relevant to polysorbate 80 may be necessary.

31. Please indicate who will perform the routine testing for container/closure components.

32. With respect to the stability protocol and results we have the following comments and requests.

    a. The establishment of shelf-life specifications based on the desired expiration date is unacceptable. Specifications must be established based on the characteristics of the product used in toxicology and clinical trials. A single set of regulatory specifications should be established based on these safety data. Once these specifications are established, expiration dating is to be based on the 95% confidence limits for potency and impurities. Please see comments on the specifications for the drug product for proposed limits on impurities. Statistical evaluations should be repeated for potency, each individual impurity and the total impurities based on the new impurity limits established from safety and clinical studies.

    b. Based on the initial data with the commercial process at 4 °C, we do not believe that pilot scale data will be acceptable for support of the expiration date proposed. Significant differences between the rate of degradation for the commercial and pilot scale batches at 4 °C were noted. In addition, the accelerated stability study performed at 25 °C is not valid for comparison with the 4 °C data due to the extremely rapid rate of degradation. Provide updated stability data on the commercial lots and a statistical analysis which compares the initial pilot scale data with those from the commercial manufacturing process. Based upon the change in site and manufacturing process (e.g. changing facilities, transport of carboyl, etc.), the pilot data may not be used to support the proposed shelf life of the product. The expiration date should be set based on actual data available from the commercial manufacturing process and facilities.

c. The protocol for expiration date extension is not acceptable. We request a commitment to repeat stability studies on the next three batches of each dosage strength with the following protocol:

Temperature:	8 °C ± 2 °C
Time Points:	0, 1, 3, 6, 9, 12, 18, 24 months
Tests:	Appearance, Potency, Degradation Products (including all degradants noted in comments above), Sterility (annually), Bacterial Endotoxins (initial only), Clarity of Solution, pH, Color and HIAC.

Expiration date extension beyond that originally awarded will only be permitted based on appropriate statistical analysis of all data acquired under this protocol. Furthermore, based on the room temperature studies and the rapid rate of degradation you have demonstrated, we believe that a temperature indicator place on the vial or in the packaging may be necessary to monitor storage during normal manufacturing and distribution.

34. The Agency has established a limit for Di-(2-ethylhexyl)phthalate (DEHP) of Not More Than 5 ppm in volumes over 100 mL. Based on the data you have provided it is unacceptable to use PVC infusion bags and lines for administration of this drug product. Labeling should be modified to allow only polypropylene bags and lines. Provide a commitment to perform additional suitability data with acceptable IV bags and lines. See the Taxol labeling and a publication by Wuagh, Trissel, Stella, *Am. J. Hosp. Pharm.* 1991, *48*, 1520.

35. The protocol used for In-Use studies is not acceptable. Studies should be repeated with acceptable bags and lines and should include testing for potency, degradants, extractables as well as HIAC and pH. Provide a new protocol and repeat these studies in a timely fashion.

We would appreciate your prompt written response so that we may continue our evaluation of your NDA.

If you have any questions, please contact Ms. Dotti Pease, Project Manager, at (301) 594-5742.

Sincerely yours,

Charles P. Holberg, Ph.D.
Acting Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA20-449
Div. File
HFC-130/JAllen/D.O.
HFD-150/DPease D Upease 11-17-94
HFD-80/DDIR
HFD-150/JBeitz
HFD-150/RLowenthal
HFD-150/JBlumenstein
HFD-150/ETolgyesi
R/D initialed by RLowenthal/11-8-94
JBlumenstein/11-8-94
RGScully/11-15-94 11/17/94

R/D PZimmerman/11-8-94
F/T dwp 11-17-94
INFORMATION REQUEST

MEMO OF TELECON

DATE: 11-8-95

DRUG: Taxotere

NDA/IND #: 20-449 and IND

SPONSOR: Rhone Poulenc Rorer

PARTICIPANTS: Meg Martin, RPR
and Dotti Pease, HFD-150

SUBJECT: Annual Report for IND and Safety Update for NDA

MEETING DISCUSSION: This telecon was in follow-up to the NDA submission of 11-3-95 in partial response to our 10-27-95 AE letter. This submission included 33 volumes of CRFs as well as responses to questions MEDICAL #1 and 2 and clarification items #1 and 2. In our preliminary review of this submission, we noted that some deaths were no longer being reported (to the IND) as "unexpected" (3-day telephone reports) because the ADR had been added to the Investigators Brochure and therefore was no longer "unexpected." This change in reporting had resulted in our questioning the trend of fewer sepsis-related deaths.

SUMMARY/ACTION ITEMS: This telecon conveyed the following FDA requests:

1. ALL treatment-related deaths should be reported (to the IND) as 3-day reports under 312.32(c)(2) whether they are considered "expected" or "unexpected."

2. All disease progression-related deaths may be continue to be reported in the IND annual report.

3. The new Safety Update for the NDA should include:

   a. A cumulative listing of all treatment-related deaths
   b. A cumulative listing of all disease progression-related deaths
   c. An update listing of all treatment-related deaths
   d. An update listing of all disease progression-related deaths

   Otherwise, the 10-25-95 faxed proposal for the IND annual report (attached)

1518

POPULATION PHARMACOKINETICS OF DOCETAXEL IN JAPANESE PATIENTS.

Y. Tanigawara, Y. Sasaki, T. Otsu, H. Fujii, M. Kashimura, T. Sasaki, K. Okumura, and T. Taguchi. Kobe University Hospital, National Cancer Center Hospital East, Rhône-Poulenc Rorer, Japan Society for Cancer Chemotherapy, Japan.

Pharmacokinetics of docetaxel (Taxotere®) have been investigated by a population analysis using the 662 plasma concentration data obtained from 102 Japanese patients who participated in phase I and II clinical trials. Docetaxel disposition was described by a 3-compartment linear model at the dose range of 10-90 mg/m^2. NONMEM analysis showed that the docetaxel clearance was related to the body surface area (BSA, m^2) and serum albumin level (ALB, g/100ml) and inversely correlated with α1-acid glycoprotein level (AAG, mg/100ml) and age. The patients having hepatic dysfunction (HEP=1) indicated by the elevation of GOT or GPT greater than 60 IU/l showed 12% reduction in clearance. The population mean of clearance was described by CL= BSA(37.0-0.0629AAG-0.192AGE+0.542ALB) (1-0.124HEP1). The remaining interindividual variability was 26%. These results were comparable to those obtained in European and American population (Bruno *et al.* ASCO 1995), and the mean clearance for the Japanese and European/American were 20.3 and 20.6 (L/hr/m^2), respectively. This finding suggests no racial difference in the elimination of docetaxel. Since dose limiting toxicity (myelosuppression) was related to the AUC according to a pharmacodynamic analysis, the present population model is useful for optimizing an individual dose of docetaxel to reach the target AUC level.

1519

THE ANALYSIS AND PRELIMINARY PHARMACOKINETICS OF CREMOPHOR® EL (CrEL) IN HUMAN PLASMA.

O. van Tellingen, A. Sparreboom, M.T. Huizing, W.J. Nooijen and J.H. Beijnen. Dept Clinical Chemistry The Netherlands Cancer Institute, Amsterdam, The Netherlands

CrEL is used as a vehicle substance for the formulation of several drugs including paclitaxel. In mice it has been shown that CrEL is the major cause of the non-linear pharmacokinetic behavior of paclitaxel. To study the pharmacokinetics of CrEL in patients after administration of paclitaxel, we have developed a sensitive and selective reversed-phase high-performance liquid chromatographic (HPLC) method, which requires only micro-volumes (20 µl) of plasma. CrEL is saponified in alcoholic potassium hydroxide and, next, the released fatty acid ricinoleic acid is extracted with chloroform and derivatized with 1-naphtylamine. Margaric acid is used as internal standard. A column packed with Spherisorb ODS-1 material and a mobile phase of methanol-acetonitrile-10 mM potassium phosphate buffer pH 7.0 (72:13:15; v/v/v) is used for separation of the reaction products. UV detection at 280 nm provides a lower limit of quantitation of 0.01% (v/v). Preliminary results in humans receiving 175 mg/m^2 of paclitaxel indicate that the peak plasma level of CrEL in patients ranges between 0.5 and 1.0% (v/v). Furthermore, the terminal half-life of CrEL is very long and, consequently, plasma levels higher than 0.3% are still present for upto 48 h after drug administration. Currently, comparative studies are being conducted in several groups of patients (e.g. 3-h vs 24-h infusions, normal vs hepatic dysfunction). Results will be presented.

1520

EFFECTS OF VITAMIN E ON SERUM, TISSUE LEVELS, TOXICITY AND CLINICAL EFFICACY OF ALL-TRANS RETINOIC ACID IN A PHASE I-II TRIAL IN CANCER PATIENTS TREATED WITH MAXIMAL TOLERATED DOSES.

E.C. Rosa, W.S. Blaner, R. Piantadosi, J. Trossman, M.A. Rovito. Department of Medicine, Medical College of Pennsylvania, Philadelphia, PA 19129 and Institute of Human Nutrition, Columbia University, New York, NY 10032.

Among 28 patients with various malignancies entered on a phase I-II trial to determine toxicity reduction of all-trans retinoic acid (ATRA) at maximal tolerated dose (145 mg/m^2) 14 patients received 800 mg of alpha-tocopherol or placebo to determine if the vitamin can alleviate toxicities and its effect on serum and tissue level measurements of ATRA at various time intervals during therapy. Serum and bone marrow ATRA levels were measured by protecting the tissue from light and oxygen; flash frozen in liquid nitrogen and shipped overnight. Tissues were homogenized and an internal standard of ATRA-H^3 was added to each plasma and tissue sample and extracted using a modified procedure by Tang and Russell. ATRA was determined by normal phase HPLC and quantitated from the integrated area under the peak using a standard curve, constructed utilizing authentic standards of ATRA, which related integrated areas to retinoic acid mass. Toxicity of ATRA occurred in 10 (71%) in Vitamin E and in 9 (64%) in placebo treated group.

Patient	Group	Serum(ng/ml)	BM (ng/g)	Toxicity
1	P	1.7, 1.5	44	Skin Grade 2
		19.9, 21.1	12	Skin Grade 2
2	Vit E	21.6, 21.4	44	Skin Grade 1
3	P	110.6, 115.1	77	Skin Grade 1
4	P	1.8, 2.5	93	Skin Grade 1
5	Vit E	2.6, 2.4	Not Detected	Skin Grade 1
		1.4, 1.3	41	Skin Grade 1
6	Vit E	11.6, 10.7	17	Skin Grade 1

The above findings show that Vitamin E did not alter serum or tissue levels other than show a group with high and a group with low ATRA levels in serum and tissues which did not correlate with severity of tissue toxicity. Vitamin E appears to alleviate only the severity without decreasing incidence of ATRA toxicity or altering serum and bone marrow levels. No clinical response was observed in either group of cancer patients except 1 patient with MDS who is currently on therapy for 1 year with stable disease.

1521

BIOEQUIVALENCY STUDY COMPARING TWO FORMULATIONS C HYDROXYUREA 500MG CAPSULES.

MJ Schobelock, RW Pfeifer, K Mosdell, DH Chmielewski and KV Shepard. Roxane Laboratories, Inc., Columbu Ohio.

Hydroxyurea is approved for use in the treatment of melanoma, resistant chron myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of t ovary. The objective of this study was to evaluate the bioequivalence of h hydroxyurea 500mg capsules: a recently approved formulation by Roxa Laboratories, Inc. compared to hydroxyurea manufactured by Immunex (Hydrea® This study was a single-dose, randomized, open-label, two-way crossover study 26 male subjects who had mean (range) values for age, height and weight of 28 years (19 to 42 years), 70.4 inches (65.0 to 75.0 inches), and 170.7 pounds (120 216 pounds), respectively. Four subjects did not complete the study due to protoc violations. Data for the remaining 22 subjects were used in the pharmacokinet analysis. The subjects received the two treatments, separated by a fourteen d washout, according to a randomized, crossover design. A single dose of 2000mg X 500mg) was administered with 240mL of tap water after an overnight fast f each treatment arm. Subjects continued to fast for 4 hours after dosing. Blo samples of 10mL were collected in heparinized tubes immediately prior to the do (time 0) and at 0.17, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 2 hours following the dose. Samples were separated, and plasma frozen un analyzed using a sensitive and specific assay procedure for hydroxyurea. The tw one-sided t-analysis indicates confidence intervals between 80 and 120% of t reference product for Cmax, AUC, AUCinf, Kel and half-life and between 80 a 125% for LCmax, LAUC, and LAUCinf. The percent difference was less than 6 for all parameters, except for Tmax which was 10.7%. Statistical analysis of l log-transformed data indicates that all parameters considered for bioequivalence a between 80 and 125% for the Roxane product compared to the reference. Th study indicates that the hydroxyurea 500mg capsule manufactured by Roxa Laboratories, Inc. is bioequivalent to the hydroxyurea 500mg capsule manufactur by Immunex.

Request for Information: April 2, 1996

TAXOTERE® (docetaxel) for Injection Concentrate

NDA #20-449 Submission dated February 28, 1996

Sponsor: Rhone-Poulenc Rorer

Please convey the following to the sponsor:

1. **Please submit case report forms for the following patients:**

   TAX222
   TAX231
   TAX246
   TAX271
   TAX295
   TAX296
   TAXSI002A

2. **Please submit CIOMS forms for the following patients:**

   TAX226
   TAX226
   TAX238
   TAX245
   TAX264
   TAX264
   TAXSI002A

Julie Beitz MD 4/2/96

Julie Beitz, MD Date

cc:
NDA #20-449
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ D. Pease

During our labeling meeting with Dr. Temple yesterday evening, these questions were raised regarding the package insert for docetaxel. Please clarify the following ASAP:

1. The definitions of normal and abnormal LFTs included in the footnotes of the tables on pp. 11, 12, 26 do not clearly address the status of patients' bilirubin at baseline. If patients with a normal bilirubin at baseline were included in the group with normal LFTs, then are patients with elevated bilirubin included in the group with abnormal LFTs? If patients with an abnormal bilirubin at baseline are actually included in both groups, then the phrase "normal bilirubin" should be omitted from the definition of "normal LFTs".

2. On p. 19, first paragraph, next to last sentence: "Hypersensitivity reactions requiring discontinuation of the Taxotere infusion were reported in five patients *out of how many ?* who did not receive premedication.

3. On p. 22, first paragraph, add a description of neuromotor problems under the heading of NEUROLOGIC.

4. What criteria were used to determine which adverse events to report in the table on p. 25? For example, was there a % incidence used as a cut-off when creating the table?

5. Cardiovascular events (hypotension, dysrhythmia) and nail changes were mentioned in the text on pp. 28-29 but do not appear in the table on p.25. Please include cardiovascular events in the table on p. 25 and in the patient package insert. Please include nail changes in the table on p. 25.

6. Myalgias do not appear in either the table on p.25 of the package insert or in the text that follows, but are discussed in the patient package insert. Please include information on myalgias in the table on p. 25 and in the text of the package insert.

7. On p. 27, under HEMATOLOGIC, second paragraph, the definition of febrile neutropenia is given as "< 1000 cells/mm³". This definition differs from that given in the table on p. 11. Please clarify the definition that should be used in the text on p. 27, and include it as a footnote at the bottom of the table on p. 25.

8. On p. 27, under HEMATOLOGIC, third paragraph, please explain what is meant by "pre-existing conditions".

9. On p. 27, under HYPERSENSITIVITY REACTIONS, first paragraph, please state whether any premedicated patients discontinued treatment due to hypersensitivity reactions.

10. On p. 28, under CUTANEOUS, include a sentence on alopecia.

AUG 3 1994

NDA 20-449

Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, Pennsylvania 19426-0107

Attention: Frank Vivet, M.D., Ph.D.
Director, Regulatory Affairs

Dear Dr. Vivet:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG PRODUCT: Taxotere (docetaxel) 80 mg and 20 mg sterile solution for injection concentrate

DATE OF APPLICATION: July 27, 1994

DATE OF RECEIPT: July 27, 1994

OUR REFERENCE NUMBER: 20-449

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 25 1994 in accordance with 21 CFR 314.101(a). Its due date is January 23, 1995.

Under 21 CFR 314.102(c) and in accordance with the policy described in the Center's Staff Manual Guide 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone.

Should you wish a conference, a telephone report or if you have any questions concerning this NDA, please contact Dotti Pease, Project Manager, at (301) 594-5742.

The NDA number listed above should be referenced at the top of the first page of any communications concerning this application.

Sincerely yours,

/Gregory Burke, M.D., Ph.D. 8/2/94
Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: ORIG. NDA
Div. File
HFD-150/DWPease/
R/D init. by: RGScully 8-2-94
F/T by dwp 8-2-94
ACKNOWLEDGEMENT LETTER

MINUTES OF MEETING

DATE: May 26, 1995

PARTICIPANTS: Rhone-Poulenc Rorer

J-J. Bienaime
J-P. Bizzari, M.D.
R. Bruno, Ph.D.
S. Durrleman, M.D.
C. Leperlier, M.D.
M. Martin
J. Molt, Ph.D.
P. Santabarbara, M.D.
D. VonHoff, M.D. (Consultant)

FDA

R. Temple, M.D., HFD-100
R. Justice, M.D., HFD-150
J. Beitz, M.D., HFD-150
J. DeGeorge, Ph.D., HFD-150
L. Kaus, Ph.D., HFD-426/150
M. Mehta, Ph.D., HFD-426/150
S-J. Wang, Ph.D., HFD-713/150
S. Wilson, Ph.D., HFD-713/150
P. Zannikos, Ph.D., HFD-426/150
D. Pease, HFD-150

SUBJECT: Taxotere NDA 20-449 (RPR's 5-19-95 faxed letter to Dr. Temple - copy attached)

BACKGROUND: RPR had been faxed the latest medical review in preparation for the 6-8-95 ODAC meeting. Applicant was surprised by the review and felt that FDA was not going to be supportive of Taxotere's approval at the ODAC meeting and RPR wanted to know what they could do to change our position. RPR then presented a brief history of the drug's development and a summary of the major clinical issues - efficacy in second line breast cancer, clearance in hepatic impaired patients, discrepancies in numbers of patients, toxic deaths, relationship of performance status to efficacy, and fluid retention.

DISCUSSION: FDA doesn't necessarily have a position on a drug prior to an advisory committee meeting. In this case, we noted we could go either way, according to the ODAC recommendation, but we will probably not be pushing for a vote one way or the other.

FDA is still concerned that the right dose hasn't yet been established. In this regard, we are very interested in the Japanese data, which applicant said they will be able to obtain. This data is in mainly first line patients, but lower doses were used and toxicity was much less (response rate was @ 40%).

With regard to patients with elevated liver function tests, it was clear that patients

with elevated bilirubin levels at baseline should not be treated due to the high incidence of myelosuppression and toxic death they experienced.

We also still don't know the mechanism of corticosteroid effect on fluid retention, whether it effects response or kinetics, whether the corticosteroid is necessary to make the safety profile acceptable, or conversely, whether a 16 week duration of fluid retention (without corticosteroids) is acceptable. In other words, the fluid retention issue has not been resolved satisfactorily.

CONCLUSIONS: RPR would like to withdraw from the June ODAC meeting and work toward the best mechanism for getting Taxotere approved, i.e. respond to our concerns before going back to ODAC. We agreed to remove Taxotere from the June 8 ODAC agenda.

ACTION ITEMS:

1. RPR will supply additional data - dexamethasone's effect on response (actual data); dexamethasone patients' pk data; pre-clinical information on mechanism of fluid retention, degradants, and all other pre-clinical studies not previously submitted; Japanese data. Applicant will give us a timeframe for submitting these data next week. This submission will be a major amendment and will extend the clock 3 months.

2. FDA will cancel Taxotere from the June ODAC meeting and try to reschedule it (July's meeting will most likely be too soon, October more likely).

3. FDA will review the new data as soon as possible and share reviews with RPR.

cc: ORIG. NDA 20-449
Div. File
Attendees
DWPease/1-12-96/n20449.mom/rev. by JBeitz/f/t 2-5-96

Request for Information

Amendment to NDA #20,449

TAXOTERE® (Docetaxel) for Injection Concentrate

From: Division of Oncology and Pulmonary Drug Products, HFD-150

To: Rhone-Poulenc Rorer Pharmaceuticals, INC.

Date: May 5, 1995

Information to be Conveyed to the Sponsor:

The following analysis (see table below) was undertaken to determine the impact of elevated hepatic enzymes on breast cancer patients treated on two of the pivotal trials in the original NDA. Data was derived from tables 14, 15, and 21 of the Data Listings for the TAX233 and TAX267 trials conducted in anthracycline-resistant breast cancer patients.

1. In order to interpret the effect of dose reductions in these patients, it would be necessary to know when these occurred in relation to the onset of infections and stomatitis in each patient.

2. It would be difficult to show that dose reductions affected the incidence of grade 4 neutropenia in these trials, since this toxicity was universal among patients and occurred in roughly 70-90% of evaluable cycles (i.e., cycles with at least one WBC report on days 6-10 of each cycle). It was not possible to determine the incidence of febrile neutropenia grade 4 from the data listings, however. This is perhaps, a more relevant endpoint and should be correlated with baseline hepatic enzyme status and timing of dose reductions.

3. Data listings were not provided for the third pivotal trial in anthracycline-resistant breast cancer, the EORTC TAX286 trial. Evaluation of these patients by hepatic enzyme status at baseline would also be helpful.

Outcomes in Anthracycline-Resistant Breast Cancer Patients
Initial Docetaxel Dose at 100 mg/m^2:
Effect of LFTs at Baseline

Feature/Endpoint	Patient Subset w/ Elevated LFTs[a] N=95	Patient Subset w/ Normal LFTs[a] N=800	TAX233 + TAX267[b] Baseline LFTs Elevated N=27	Normal N=51
Pts w/ Liver Mets	83%	29%	56%	33%
Pts w/ Dose Red'ns	-	-	56%	57%
Response Rate				
-all patients	-	-	41%	55%
-dose-reduced pts	-	-	47%	72%
Median #Cycles				
-all patients	4 (1-19)	4 (1-25)	5 (1-12)	5 (1-15)
-dose-reduced pts	-	-	9 (4-12)	7 (3-15)
Pts w/ Neutropenia				
-grade 3+4	95%	92%	-	-
-grade 4	-	-	96%	96%
-dose-reduced pts			100%	97%
Pts w/ Infections	26%	20%	56%	47%
-dose-reduced pts	-	-	67%	48%
Pts w/ Stomatitis	16%	7%	81%	65%
-dose-reduced pts	-	-	93%	76%
Deaths				
-Toxic	5 (5.3%)	8 (1.0%)	0	0
-Septic	0	5 (0.6%)	1 (3.7%)	0

[a] From Updated Safety Analysis, Appendix V, 3/10/95
[b] Compiled from Tables 14, 15, 21 of Data Listings in TAX233 and TAX267 Study Reports, 7/27/94

THE NINETY-DAY CONFERENCE IN THE OFFICE OF NEW DRUG EVALUATION

1. PURPOSE. The meeting is intended to inform the sponsor of the status and general progress of the review of New Drug Applications (NDA's) for new molecular entities and NDA's or supplemental applications for important new indications. The meeting is also intended to advise the sponsor of important deficiencies that have been identified within approximately 90 days following the filing of the application but which have not yet been communicated to the sponsor. The meeting is not intended to assess the ultimate approvability of an application. Examples of topics for discussion at the 90-day conference are manufacturing and controls deficiencies which chemistry reviewers should provide upon completion of their reviews, and the appropriate format and submission of safety update reports.

2. BACKGROUND. The ninety-day conference is being established because senior management in the pharmaceutical industry have expressed a need to be better informed about the status of their applications during the early period of Agency review.

3. REFERENCES.

   a. NCDB 4200.1 "Processing of Federal Register Documents."

   b. NCDB 4015.1 "Clearance of Speeches, Articles and Other Communication Materials."

   c. NCDB 4800.2 "Scientific Reviews: Roles of Reviewers, Supervisors and Management; Resolution of Differences."

   d. (Docket Number 82N-0293) FDA's Proposal to Revise New Drug and Antibiotic Regulations. See proposed Section 314.102 (b).

4. POLICY. The sponsor of an original NDA for a new molecular entity or an NDA or supplemental application for a therapeutically important new indication will have the right to an informal meeting with Agency reviewing officials approximately 90 days after FDA receives the application. Sponsors of applications covered by this policy will be advised of the opportunity for such a conference as a part of the acknowledgment letter. (See Attachment for suggested language to be included in the letter.) If a meeting is desired, it should be requested at least 15 days before it is held. The Consumer Safety Officer makes the arrangements. These conferences may be held by telephone if mutually agreed upon.

5. RESPONSIBILITIES AND PROCEDURES.

a. The responsible Consumer Safety Officer will:

(1) Assure that the acknowledgment letter sent to sponsors for applications covered by this policy includes notification of the opportunity for the conference.

(2) Document the sponsor's response for the file including:

(a) date received;
(b) requestor;
(c) whether a meeting is requested or a telephone conversation would suffice;
(d) other items to be discussed and who the sponsor intends to have participate.

(3) Coordinate with other Agency reviewing officials and make the necessary arrangements.

(4) Participate in the conference or telephone conversation, and write a memo for the record (coordinate with Agency attendees).

b. The Sponsor will:

(1) Inform the appropriate Consumer Safety Officer that it wants the meeting (at least 15 days before the meeting is to be held).

(2) Indicate who the sponsor's participants will be.

(3) Indicate if the sponsor wishes to discuss other issues and provide any background material on them as requested by the Agency.

(4) Indicate whether a telephone conversation would suffice.

c. The Reviewing Officials will:

(1) Meet with sponsor or discuss over the telephone the status and general progress of the application.

(2) Inform the sponsor of any important deficiencies that have been identified but which have not yet been communicated to the sponsor.

d. The Division Director will:

(1) Assume responsibility for conducting the meetings and determining who will represent the Agency.

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011