CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20449/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20449/S004

Trade Name:Taxotere for Injection Concentrate

Generic Name:(docetaxel)

Sponsor: Rhone-Poulenc Rorer

Approval Date: January 6, 1998

Indication: Provides for the modification of the package insert to add certain adverse events which have been received through postmarketing surveillance.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20449/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-449/S004

JAN - 6 1998

Rhone-Poulenc Rorer
500 Arcola Road
P.O. Box 5091
Collegeville, PA 19426-0995

Attention: Ronald F. Panner
Senior Director, Worldwide Regulatory Affairs

Dear Mr. Panner:

We acknowledge your supplemental new drug application dated November 21, 1997, received November 24, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere (docetaxel) for Injection Concentrate.

The supplemental application provides for the modification of the package insert to add certain adverse events which have been received through postmarketing surveillance. The revised text is found under the ADVERSE REACTIONS: Ongoing Evaluation section of the package insert. The patient package insert is attached to the package insert and the patient package insert is referenced in the PRECAUTIONS section under Information for Patients to refer to attached Patient Information Leaflet .

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on November 21, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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 Ann Staten, Project Manager, at 301-594-5770.

Sincerely yours,

/S/ 1/5/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20449/S004

FINAL PRINTED LABELING

APPROVED
1-6-98

NDA 20-449
Taxotere® (docetaxel)
for Injection Concentrate

Labeling: Div File S-004
NDA No: 20-449 Rec'd. 11-24-97
Reviewed by: Amy Staten 12-31-97

"FINAL PRINTED LABELING"

Package Insert

N-5493C Rev. 7/97

Caution: Federal law prohibits dispensing without prescription.

TAXOTERE®
(docetaxel)
for Injection Concentrate

WARNING

TAXOTERE® (docetaxel) for Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with TAXOTERE® therapy is increased in patients with abnormal liver function and in patients receiving higher doses (see **WARNINGS**).

TAXOTERE® should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of TAXOTERE® therapy and reviewed by the treating physician.

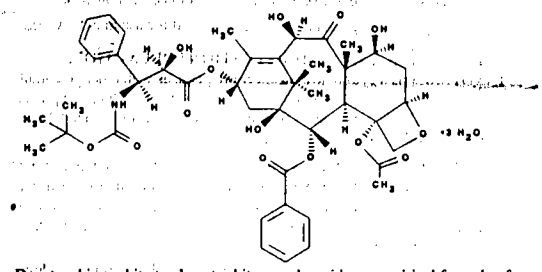
TAXOTERE® therapy should not be given to patients with neutrophil counts of < 1500 cells/mm³. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE®.

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 0.9% of patients who received the recommended dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the TAXOTERE® infusion were reported in five patients who did not receive premedication. These reactions 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.

Severe fluid retention occurred in 6% of patients despite use of a 5-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (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. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14} \cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE® (docetaxel) for Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE® is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE® for Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE® contains 13% ethanol in Water for Injection, and is supplied in 1.5 mL (to be used with 20 mg TAXOTERE® for Injection Concentrate) and 6.0 mL (to be used with 80 mg TAXOTERE® for Injection Concentrate) vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. 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.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 - 115 mg/m² in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70 - 115 mg/m² with infusion times of one to two hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m² and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10 - 90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within seven days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as one major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Based on *in vitro* studies, isoenzymes of the cytochrome P4503A (CYP 3A) subfamily appear to be involved in docetaxel metabolism.

A population pharmacokinetic analysis was carried out after TAXOTERE® treatment of 535 patients dosed at 100 mg/m². Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal (ULN) concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with TAXOTERE®.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

CLINICAL STUDIES

The efficacy and safety of TAXOTERE® has been evaluated in advanced breast carcinoma patients in independent clinical studies at doses of 100, 75, and 60 mg/m².

Safety and Efficacy at 100 mg/m²: The safety and efficacy of TAXOTERE® have been evaluated in three phase II studies which were conducted in a total of 134 patients with anthracycline-resistant, locally advanced or metastatic breast carcinoma. Anthracycline resistance was defined as progressive disease on anthracyclines for advanced disease or relapse on anthracycline adjuvant therapy. In these studies, TAXOTERE® was administered at a 100 mg/m² dose given as a one-hour infusion every 3 weeks.

The overall response rate (ORR) considering all patients (intent-to-treat) was 41% and the complete response (CR) was 2%. The median survival time was 43 weeks. In the evaluable patients (see table), the ORR was 47% and the CR was 2.8%. Overall response rates (ORR), duration of response, and time to progression are shown in the following table:

Efficacy Of TAXOTERE® In Anthracycline-Resistant Breast Cancer Patients Treated At 100 mg/m²

Overall Response Rates		(95% C.I.)
Intent-to-Treat Patients (n=134)	41%	(33 - 49)
Evaluable Patients (n=106)*	47%	(38 - 57)
Response Rate in Patients with Visceral Involvement		
Intent-to-Treat Patients (n=95)	37%	
Evaluable Patients (n=76)*	43%	
Median Response Duration**	6 months	(2.1 - 17.5)
Median Time to Progression**	4 months	(0.2 - 17.5)
Median Survival**	10 months	(0.2 - 24.6+)
1 Year Survival**	43%	

*Evaluable patients include those meeting the study eligibility requirements and having received at least two cycles of TAXOTERE® unless disease progression occurred earlier.

**Intent-to-treat population

For the 134 anthracycline-resistant breast cancer patients who received TAXOTERE®, 127 had normal LFTs (see table for definition) at baseline, and 7 had elevated LFTs at baseline. Patients with elevated LFTs at baseline had an increased incidence of thrombocytopenia, infection, febrile neutropenia, and death considered at least possibly treatment related. The following table shows the incidence of important hematologic adverse events during the study:

Hematologic Adverse Events In Anthracycline-Resistant Breast Cancer Patients Treated At 100 mg/m² With Normal Or Elevated Baseline Liver Function Tests

Adverse Event		Normal LFTs* at Baseline n = 127 %	Elevated LFTs at Baseline n = 7 %
Neutropenia			
Any	<2000 cells/mm³	99.2	100
Grade 4	<500 cells/mm³	94.5	100
Thrombocytopenia			
Any	<100,000 cells/mm³	11.8	71.4
Grade 4	<20,000 cells/mm³	0	14.3
Anemia	<11 g/dL	98.4	85.7
Infection***			
Any		25.2	71.4
Grade 3 and 4		7.1	57.1
Febrile Neutropenia****			
By Patient		22.0	42.9
By Course		4.0	14.3
Septic Death		0.8	14.3
Non-Septic Death		0	14.3

*Normal LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.

**Elevated LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.

***Incidence of infection requiring hospitalization and/or intravenous antibiotics was 13.4% (n=17) among the 127 patients with normal LFTs at baseline. There were two patients with grade 2, one with grade 3, and fourteen with grade 4 neutropenia.

****Febrile Neutropenia: ANC grade 4 with fever > 38° C with IV antibiotics and/or hospitalization.

The following table shows important non-hematologic adverse events in the anthracycline-resistant breast cancer patients with normal and elevated LFTs at baseline:

Non-Hematologic Adverse Events In Anthracycline-Resistant Breast Cancer Patients Treated At 100 mg/m² With Normal Or Elevated Baseline Liver Function Tests

Adverse Event	Normal LFTs* at Baseline n = 127 %	Elevated LFTs at Baseline n = 7 %
Acute Hypersensitivity Reaction		
Regardless of Premedication		
Any	11.8	0
Severe	0	0
Fluid Retention***		
Regardless of Type of Premedication		
Any	56.7	57.1
Severe	9.4	14.3
With Recommended Premedication	n = 29	n = 3
Any	41.4	66.6
Severe	3.4	33.3
Neurosensory		
Any	66.1	42.9
Severe	7.1	0
Myalgia	35.4	57.1
Cutaneous		
Any	62.2	57.1
Severe	10.2	14.3
Asthenia		
Any	80.3	42.9
Severe	22.8	28.6
Stomatitis		
Any	55.9	71.4
Severe	8.7	57.1

*Normal LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline ph

phatase up to 5 times ULN.

** Elevated Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.

*** Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites).

Safety at 75 mg/m²: TAXOTERE® at a dose of 75 mg/m² every 3 weeks has been evaluated in two phase II studies in 55 previously untreated patients with normal liver function and locally advanced or metastatic breast carcinoma. The following table shows the important hematologic adverse events in these studies:

Hematologic Adverse Events In 55 Breast Cancer Patients Treated With 75 mg/m²

Adverse Event		%
Neutropenia		
Any	<2000 cells/mm³	98.1
Grade 4	<500 cells/mm³	80.0
Thrombocytopenia		
Any	<100,000 cells/mm³	5.5
Grade 4	<20,000 cells/mm³	0
Anemia	<11 g/dL	89.1
Infection		
Any		21.8
Grade 3 and 4		0
Febrile Neutropenia*		
By Patient		1.8
Septic Death		0
Non-Septic Death		0

* Febrile Neutropenia: ANC grade 4 with fever >38° C with IV antibiotics and/or hospitalization.

The following table shows the important non-hematologic adverse events at 75 mg/m².

Non-Hematologic Adverse Events In 55 Breast Cancer Patients Treated With 75 mg/m²

Adverse Event	%
Acute Hypersensitivity Reaction*	
Any	29.1
Severe	1.8
Fluid Retention**	
Any	69.1
Severe	10.9
Neurosensory	
Any	38.2
Severe	1.8
Myalgia	
Any	12.7
Severe	1.8
Cutaneous	
Any	47.3
Severe	1.8
Asthenia	
Any	63.6
Severe	7.3
Stomatitis	
Any	30.9
Severe	3.6

* Regardless of premedication

* Without recommended premedication

Safety and Efficacy at 60 mg/m²: The safety and efficacy of TAXOTERE® have been evaluated in three phase II Japanese studies in 174 patients (3 patients had elevated LFTs) who had received prior chemotherapy for locally advanced or metastatic breast carcinoma; 26 patients had progression of disease as best response to prior anthracycline treatment. In the 26 patients who had progression of disease as best response to prior anthracycline treatment, the ORR was 34.6% (95% C.I.: 20.2, 55.7) and the CR was 3.8%. The median duration of response was 4 months.

The following table shows important hematologic adverse events for the Japanese breast cancer trials:

Hematologic Adverse Events In 174 Breast Cancer Patients Treated With 60 mg/m² Who Had Received Prior Chemotherapy In Trials Conducted In Japan

Adverse Event		%
Neutropenia		
Any	<2000 cells/mm³	95.4
Grade 4	<500 cells/mm³	74.9
Thrombocytopenia		
Any	<100,000 cells/mm³	14.4
Grade 4	<20,000 cells/mm³	1.1
Anemia	<11 g/dL	64.9
Infection		
Any		1.1
Grade 3 and 4		0
Febrile Neutropenia*		
By Patient		0
Septic Death		1.1
Non-Septic Death		0

* Febrile Neutropenia: ANC grade 3/4 concomitant with fever > 38.1° C.

The following table shows important non-hematologic adverse events for the Japanese breast cancer trials; the incidence of severe non-hematologic toxicity in patients dosed at 60 mg/m² is negligible:

Non-Hematologic Adverse Events In 174 Breast Cancer Patients Treated With 60 mg/m² Who Had Received Prior Chemotherapy In Trials Conducted In Japan

Adverse Event	%
Acute Hypersensitivity Reaction	
Any	0.6
Severe	0
Fluid Retention*	
Any	12.6
Severe	0
Neurosensory	
Any	19.5
Severe	0
Cutaneous	
Any	30.5
Severe	0
Myalgia	
Any	3.4
Severe	0
Asthenia	
Any	65.5
Severe	0
Stomatitis	
Any	19.0
Severe	0.6

* without premedication

INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

TAXOTERE® is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

TAXOTERE® should not be used in patients with neutrophil counts of <1500 cells/mm³.

WARNINGS

TAXOTERE® (docetaxel) for Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Toxic Deaths: TAXOTERE® administered at 100 mg/m² was associated with deaths considered possibly or probably related to treatment in 2.4% (34/1435) of patients with normal liver function and in 11% (6/55) of patients with abnormal liver function (SGOT and/or SGPT > 1.5 times ULN together with AP > 2.5 times ULN). 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. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Premedication Regimen: Although the optimal premedication regimen is not defined, all patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 5 days starting 1 day prior to TAXOTERE® to reduce the severity of fluid retention and hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 0.9% of patients who received the recommended premedication. Hypersensitivity reactions requiring discontinuation of the TAXOTERE® infusion were reported in 5 out of 1260 patients who did not receive premedication. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE®.

Hematologic Effects: Neutropenia (less than 2000 neutrophils/mm³) occurs in virtually all patients given 60 - 100 mg/m² of TAXOTERE® and grade 4 neutropenia (less than 500 cells/mm³) occurs in nearly all patients given 100 mg/m² and 75 - 80% of patients given 60 - 75 mg/m². Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE® should not be administered to patients with neutrophils < 1500 cells/mm³.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m² but was very uncommon in patients given 60 - 75 mg/m². Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in **CLINICAL STUDIES.**

Three breast cancer patients with severe liver impairment (bilirubin > 1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

Hepatic Impairment: (see BOXED WARNING).

Fluid Retention: (see BOXED WARNING).

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 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m² 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). The doses indicated above also caused 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®.

PRECAUTIONS

General: Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy and treatment-related side effects has not been established.

Hematologic Effects: 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% reduction in the dose of TAXOTERE® is recommended during subsequent cycles following severe neutropenia (< 500 cells/mm³) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE® (docetaxel) cycle (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions: Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE® infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of TAXOTERE® and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE® (see **WARNINGS: Premedication Regimen**).

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended (see **DOSAGE AND ADMINISTRATION** section). The discontinuation rate due to skin toxicity was 1.7%.

Fluid Retention: Severe fluid retention has been reported following TAXOTERE® therapy (see **BOXED WARNING** and **ADVERSE REACTIONS**). Patients should be premedicated with oral corticosteroids prior to each TAXOTERE® administration to reduce the incidence and severity of fluid retention (see **DOSAGE AND ADMINISTRATION** section). Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

In patients who received the recommended premedication, moderate fluid retention occurred in 17.4% with severe fluid retention in 6% and a 1.7% discontinuation rate. Fluid retention was completely, but sometimes slowly, reversible following discontinuation of TAXOTERE® (median of 29 weeks). The median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m² in patients receiving premedication. Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed among 7% of 134 patients with anthracycline-resistant breast cancer. When these occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued (see **DOSAGE AND ADMINISTRATION** section). Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms within a median of 9 weeks from onset (range: 0 to 106 weeks) and only about 3.8% of patients required discontinuation due to neurotoxicity. Peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 13.4% (7.1% severe) of the 127 anthracycline-resistant breast cancer patients with normal LFTs. No neuromotor toxicity was reported in the 7 patients with elevated LFTs.

Asthenia: Severe asthenia has been reported in 11.1% of the patients but has led to treatment discontinuation in only 2.6% of the patients. Severe asthenia was reported in 23% of 134 patients with anthracycline-resistant breast cancer and 5.5% of the 786 cycles received. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Information for Patients: For additional information, see the accompanying Patient Information Leaflet.

Drug Interactions: There have been no formal clinical studies to evaluate the drug interactions of TAXOTERE® with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving TAXOTERE® as there is a potential for a significant interaction.

Carcinogenicity, Mutagenicity, 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-K_1 cells and in the *in vivo* micronucleus test in the mouse, but 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 i.v. doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m² basis), but decreased 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 1/3 and 1/15 the recommended human dose on a mg/m² basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy: Pregnancy Category D (see **WARNINGS** section).

Nursing Mothers: 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 in nursing infants from TAXOTERE®, mothers should discontinue nursing prior to taking the drug.

Pediatric Use: The safety and effectiveness of TAXOTERE® in pediatric patients have not been established.

ADVERSE REACTIONS

There were 1495 patients enrolled in 37 clinical trials conducted in North America and Europe (624 breast carcinoma patients and 866 patients with other tumor types) who received TAXOTERE® at an initial dose of 100 mg/m² every 3 weeks. Five patients were not evaluable for toxicity since they discontinued TAXOTERE® treatment due to acute hypersensitiyity reactions with the first infusion. At least 95% of these patients did not receive hematopoietic support. The following table lists adverse reactions that occurred in at least 5% of 1435 patients with normal liver function tests at baseline (Normal LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN) as well as all deaths and adverse reactions in patients with abnormal liver function tests. These reactions were considered possibly or probably related to TAXOTERE®. The safety profile is generally similar in patients receiving TAXOTERE® for the treatment of breast carcinoma or for other tumor types.

Summary Of Adverse Events In Patients Receiving TAXOTERE® At 100 mg/m²

Adverse Event		Normal LFTs* at Baseline n=1435 %	Elevated LFTs** at Baseline n=55 %
Hematologic			
Neutropenia	<2000 cells/mm³	96.3	96.0
	<500 cells/mm³	76.0	86.0
Leukopenia	<4000 cells/mm³	96.5	98.1
	<1000 cells/mm³	31.0	44.2
Thrombocytopenia	<100,000 cells/mm³	7.5	27.3
Anemia	<11 g/dL	89.5	92.7
	<8 g/dL	8.4	30.9
Febrile Neutropenia		11.8	26.4
Septic Death		1.8	3.6
Non-Septic Death		0.6	7.3
Infections			
Any		21.7	32.7
Severe		5.6	16.4
Fever in absence of Infection			
Any		30.2	50.9
Severe		1.7	9.1
Hypersensitivity Reactions			
with recommended premedication		n=229	n=6
Any		15.7	0
Severe		0.9	0
Fluid Retention			
with recommended premedication		n=229	n=6
Any		48.5	66.7
Severe		5.2	33.3
Neurosensory			
Any		53.7	41.8
Severe		3.9	0
Neuromotor (principally distal extremity weakness)			
Any		13.4	5.5
Severe		3.7	1.8
Cutaneous			
Any		58.5	61.8
Severe		5.6	10.9
Nail Changes			
Any		28.2	18.2
Severe		2.6	4.6
Gastrointestinal			
Nausea		40.4	40.0
Diarrhea		40.4	32.7
Vomiting		24.0	25.5
Alopecia		80.0	61.8
Asthenia			
Any		61.5	54.5
Severe		11.1	23.6
Stomatitis			
Any		42.3	47.3
Severe		5.3	14.5
Myalgia			
Any		19.4	18.2
Severe		1.4	1.9
Arthralgia		8.6	7.3
Infusion Site Reactions		5.6	3.6

* Normal LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.

** Elevated LFTs: SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of TAXOTERE®. Neutropenia is reversible and not cumulative. The median day to nadir was 8 days, while the median duration of severe neutropenia (<500 cells/mm³) was 7 days. Among patients with normal liver

n treated with TAXOTERE®, severe neutropenia occurred in 76% ted for more than 7 days in 4.3% of cycles. Anemia was reported in of patients, with severe cases being reported in 8.4% of the patients ARNINGS section).

neutropenia (<500 cells/mm³ with fever > 38°C with IV antibiotics hospitalization) occurred in 11.8% of the patients with normal liver n (3% of the cycles). Infectious episodes occurred in 21.7% of the s (6.2% of the cycles) and were fatal in 1.6% of those treated with TERE® (1.4% in breast cancer patients).

bocytopenia (<100,000 cells/mm³) occurred in 7.5% of the patients rmal liver function. Bleeding episodes were reported in 2.3% of the s. A fatal gastrointestinal hemorrhage associated with thrombocy- was reported in one patient. Three breast cancer patients with liver impairment (bilirubin > 1.7 times ULN) developed fatal gas- tinal bleeding associated with severe drug-induced thrombocytope-

sensitivity Reactions: Hypersensitivity reactions requiring discon- n of the TAXOTERE® infusion were reported in 5 patients of 1260 d not receive premedication. Severe hypersensitivity reactions char- ed by hypotension and/or bronchospasm, or generalized rash/ery- have been observed in only 0.9% of patients with normal liver n receiving the recommended premedication regimen and none of atients had to discontinue therapy.

events, including flushing, rash with or without pruritus, chest tight- ack pain, dyspnea, drug fever, or chills, have been reported and d after discontinuing the infusion and appropriate therapy (see NINGS section).

Retention (see BOXED WARNING): Events such as edema and gain and, less frequently, pleural effusion, pericardial effusion or have been described. Among 229 patients with normal liver func- ceiving the recommended pretreatment, severe fluid retention was ed in 6%, causing treatment discontinuation in 1.7%. When it peripheral edema usually starts at the lower extremities and may e generalized with a median weight gain of 2 kg. Fluid retention is ative in incidence and severity. The median cumulative dose to onset derate or severe fluid retention was 705 mg/m². Fluid retention was ctely reversible, resolving a median of 29 weeks (range: 0 to 42+) from the last TAXOTERE® infusion.

neous: Reversible cutaneous reactions characterized by a rash includ- calized eruptions, mainly on the feet and/or hands, but also on the face or thorax, usually associated with pruritus, have been observed. ons generally occurred within one week after TAXOTERE® infu- recovered before the next infusion and were not disabling. Severe ions, such as eruptions followed by desquamation, occurred in 5.6% e patients and rarely led to interruption or discontinuation of OTERE® treatment. Alopecia occurred in 80% of patients, and it was e in 61.8% of patients.

e nail disorders occurred in 2.6% of the patients. These reactions characterized by hypo- or hyperpigmentation, and occasionally by olysis (in 0.8% of patients) and pain.

ologic: Neurosensory symptoms characterized by paresthesia, dyses- or pain (including burning sensation) have been reported in patients ving TAXOTERE®. Severe reactions were observed in 3.9%.

omotor events characterized mainly by weakness have been reported vere severe in 3.7% of the patients.

rointestinal: Gastrointestinal reactions (nausea, and/or vomiting, r diarrhea) were generally mild to moderate and severe reactions red in 8.2% of the patients. Stomatitis was reported in 42.3% of nts receiving TAXOTERE®. Severe reactions were observed in 5.3% tients.

liovascular: Hypotension occurred in 3.6% of the patients; 3.4% red treatment. Clinically meaningful events such as heart failure, sinus cardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, ypertension occurred rarely.

sion Site Reactions: Infusion site reactions were generally mild and sted of hyperpigmentation, inflammation, redness or dryness of the phlebitis, extravasation, or swelling of the vein.

Hepatic: In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT ≥ 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, were observed in 18.1% and 7.6% of patients, respectively. During the study, increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 4.5% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established.)

Ongoing Evaluation: The following serious adverse events of uncertain relationship to TAXOTERE® have been reported:

Body as a whole: abdominal pain, diffuse pain, chest pain

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction

Digestive: constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, intestinal obstruction, ileus, gastrointestinal perforation, neutropenic enterocolitis

Nervous: confusion

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome

Urogenital: renal insufficiency

OVERDOSAGE

There is no known antidote for TAXOTERE® overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis.

There were two reports of overdose. One patient received 150 mg/m² and the other received 200 mg/m² as one-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single i.v. doses that were ≥154 mg/kg (about 4.5 times the recommended human dose on a mg/m² basis); neurotoxicity associated with paralysis, non-extension of hind limbs and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the recommended human dose on a mg/m² basis). In male and female rats, lethality was observed at a dose of 20 mg/kg, (comparable to the recommended human dose on a mg/m² basis) and was associated with abnormal mitosis and necrosis of multiple organs.

DOSAGE AND ADMINISTRATION

For treatment of patients with locally advanced or metastatic carcinoma of the breast after progression during anthracycline-based therapy for metastatic disease or relapse during anthracycline-based adjuvant therapy, the recommended dose of TAXOTERE® is 60 - 100 mg/m² administered intravenously over 1 hour every three weeks.

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 5 days starting 1 day prior to TAXOTERE® administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **WARNINGS** and **PRECAUTIONS** sections).

Dosage Adjustments During Treatment: Patients who are dosed initially at 100 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE® therapy should have the dosage adjusted from 100 mg/m² to 75 mg/m². If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m² to 55 mg/m² or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m² and who do not experience febrile neutropenia, neutrophils <500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE® therapy may tolerate higher doses.

Special Populations:

Hepatic Impairment: Patients with bilirubin > ULN should generally not receive TAXOTERE®. Also, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should generally not receive TAXOTERE®.

Children: The safety and effectiveness of docetaxel in pediatric patients below the age of 16 years have not been established.

Elderly: No dosage adjustments are required for use in elderly.

PREPARATION AND ADMINISTRATION PRECAUTIONS

TAXOTERE® is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE® solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE® concentrate, premix solution, or infusion solution should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE® concentrate, premix solution, or infusion solution should come into contact with mucosa, immediately and thoroughly wash with water.

TAXOTERE® for Injection Concentrate requires dilution prior to administration. Please follow the preparation instructions provided below. Note: Both the TAXOTERE® for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Premix Solution

1. Remove the appropriate number of vials of TAXOTERE® for Injection Concentrate and diluent from the refrigerator. Allow the vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the entire contents of the diluent vial into a syringe and transfer it to the vial of TAXOTERE® for Injection Concentrate.

   Information regarding fill volumes is listed below:

Strength	Vial Content	Diluent Vial
TAXOTERE® 20 mg	23.6 mg / 0.59 mL	1.83 mL
TAXOTERE® 80 mg	94.4 mg / 2.36 mL	7.33 mL

   This will assure a final premix concentration of 10 mg docetaxel/mL.
3. Gently rotate each premix solution vial for approximately 15 seconds to assure full mixture of the concentrate and diluent.
4. The TAXOTERE® premix solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the premix solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

B. Preparation of the Infusion Solution

1. Aseptically withdraw the required amount of TAXOTERE® premix solution (10 mg docetaxel/mL) with a calibrated syringe and inject the required volume of premix solution into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.9 mg/mL.

   If a dose greater than 240 mg of TAXOTERE® is required, use a larger volume of the infusion vehicle so that a concentration of 0.9 mg/mL TAXOTERE® is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE® for Injection premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

TAXOTERE® infusion solution should be administered intravenously as a one-hour infusion under ambient room temperature and lighting conditions.

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, diluted TAXOTERE® solution should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Stability: Unopened vials of TAXOTERE® are stable until the expiration date indicated on the package when stored refrigerated, 2° to 8°C (36° to 46°F), and protected from bright light. Freezing does not adversely affect the product.

HOW SUPPLIED

TAXOTERE® for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE® 80 MG (NDC 0075-8001-80)
TAXOTERE® (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 (Fill: 94.4 mg docetaxel in 2.36 mL polysorbate 80) and diluent for TAXOTERE® 80 mg. 13% (w/w) ethanol in Water for Injection (Fill: 7.33 mL). Both items are in a blister pack in one carton.

TAXOTERE® 20 MG (NDC 0075-8001-20)
TAXOTERE® (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 (Fill: 23.6 mg docetaxel in 0.59 mL polysorbate 80) and diluent for TAXOTERE® 20 mg. 13% (w/w) ethanol in Water for Injection (Fill: 1.83 mL). Both items are in a blister pack in one carton.

Storage: Store refrigerated, 2° to 8°C (36° to 46°F). Retain in the original package to protect from bright light.

TAXOTERE® premix solution (10 mg TAXOTERE®/mL) and fully prepared TAXOTERE® infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used as soon as possible after preparation. However, the premix solution is stable for 8 hours either at room temperature, 15° to 25°C (59° to 77°F), or stored refrigerated, 2° to 8°C (36° to 46°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-4]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm.* 1986; 43(5): 1193-1204.
2. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990; 47(95): 1033-1049.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA.* 1985; 253 (11): 1590-1592.
4. Oncology Nursing Society Clinical Practice Committee. Cancer Chemotherapy Guidelines. Module II – Recommendations of Nursing Practice in the Acute Care Setting. *ONS.* 1988; 2-14.

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

IN-5493C Rev. 7/97

Patient Information Leaflet

Questions and Answers About Taxotere® for Injection Concentrate

(generic name = docetaxel)

(pronounced as TAX-O-TEER)

[illegible]at is Taxotere?

[illegible]tere is a medication to treat breast cancer. It has [illegible] side effects in some patients. This leaflet is [illegible] to help you understand how to use Taxotere and [illegible] its side effects to the fullest extent possible. The [illegible] you understand your treatment, the better you will [illegible] able to participate in your care. If you have questions [illegible] concerns, be sure to ask your doctor or nurse. They are [illegible]ys your best source of information about your condi[illegible] and treatment.

Patient Information Leaflet
Detach and give to Patient

What is the most important information about Taxotere?

- Since this drug, like many other cancer drugs, affects your blood cells, your doctor will ask for routine blood tests. These will include regular checks of your white blood cell counts. Rarely, people with low blood counts have developed life-threatening infections. The earliest sign of infection may be fever, so if you experience a fever, tell your doctor right away.
- Rare, but sometimes serious, allergic reactions have occurred with this medicine. If you have any allergies, tell your doctor before receiving this medicine.
- A small number of people who take Taxotere have severe fluid retention, which can be life-threatening. To help avoid this problem, you must take another medication called dexamethasone (DECKS-A-METH-A-SONE) prior to each Taxotere treatment. You must follow the schedule and take the exact dose of dexamethasone prescribed (see schedule at end of brochure). If you forget to take a dose or do not take it on schedule you must tell the doctor or nurse prior to your Taxotere treatment.
- If you are using any other medicines, tell your [illegible] before receiving your infusions of Taxotere.

How does Taxotere work?

Taxotere works by attacking cancer cells in your [illegible] Different cancer medications attack cancer cells in [illegible] ent ways.

Here is how Taxotere works: Every cell in your body [illegible]tains a supporting structure (like a skeleton). If this [illegible] is damaged, it can not grow or reproduce. Tax[illegible] makes this "skeleton" in cancer cells very stiff, so th[illegible] cells can no longer grow.

How will I receive Taxotere?

Taxotere is given by an infusion directly into your [illegible] Your treatment will take about 1 hour. Generally, p[illegible] receive Taxotere every 3 weeks. The amount of Tax[illegible] and the frequency of your infusions will be determin[illegible] your doctor.

As part of your treatment, to reduce side effects you[illegible] [illegible]or will prescribe another medicine called dexam[illegible]sone. Your doctor will tell you how and when to tak[illegible] medicine. It is important that you take the dexametha[illegible]

neuropathy mainly manifested as distal extremity

Date Day 1	Date Day 2 Treatment Day	Date Day 3	Date Day 4	Date Day 5
Start Dexamethasone tablets 2 times per day AM/ PM	Take Dexamethasone tablets 2 times per day AM/ PM	Take Dexamethasone tablets 2 times per day AM/ PM	Take Dexamethasone tablets 2 times per day AM/ PM	Take Dexamethasone tablets 2 times per day AM/ PM

he infusion and the administration of appropriate therapy.

OTEREL must not be given to patients who have a history of

of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which dif

Overall Response Rates (95% C.I.)

Intent-to-Treat Patients (n=134) 41% (33-49)

n = 127

Hair [illegible] patients taking [illegible] hair on your [illegible] [illegible] eyebrows [illegible] may [illegible] off begin [illegible] ments and [illegible] from patient to patient. Once you have completed all your treatments, hair generally grows back.

Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.

Fatigue – A number of patients (about [illegible]%) receiving Taxotere feel very tired following their treatments. If you feel tired or weak, allow yourself extra rest before your next treatment. If it is bothersome or lasts for longer than one week, inform your doctor or nurse.

Muscle Pain – This happens about 20% of the time, but is rarely severe. You may feel [illegible] [illegible] [illegible] tell your doctor or nurse [illegible] They may suggest ways to make you more comfortable.

Rash – This side effect occurs commonly but is severe in about 5%. You may develop a rash that looks like a blotchy, hive-like reaction. This usually occurs on the hands and feet but may also appear on the arms, face, or body. Generally, it will appear between treatments and will go away before the next treatment. Inform your doctor or nurse if you experience a rash. They can help you avoid discomfort.

Odd Sensations – About half of patients getting Taxotere will feel numbness, tingling, or burning sensations in their hands and feet. If you do experience this, tell your doctor or nurse. Generally, these go away within a few weeks or months after your treatments are completed.

Nail Changes – Color changes to your fingernails or toenails may occur while taking Taxotere. In extreme, but rare, cases nails may fall off. After you have finished Taxotere treatments, your nails will generally grow back.

Other Possible Side Effects – Less severe side effects include nausea, vomiting, and diarrhea. If you experience these or any other unusual effects, tell your doctor or nurse.

If you are interested in learning more about this drug, ask your doctor for a copy of the package insert [illegible]

Rev. [illegible]

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
[illegible]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20449/S004

ADMINISTRATIVE DOCUMENTS

DEC 31 1997

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 20-449 /004

DATE OF SUBMISSION: SLR-004 **November 24, 1997 (Changes Being Effected)**
DATE OF REVIEW: December 19, 1997

DRUG: Taxotere® (docetaxel) for Injection Concentrate
SPONSOR: Rhone-Poulenc Rorer

This supplement provides for a revised package insert. In accordance with 21 CFR §314.70(c)(2)(i), as changes being effected, the package insert is modified to add certain adverse events which have been received through postmarketing surveillance.

I have reviewed the new labeling, comparing it with the previous labeling supplement (PA dated 5/14/96) and find it acceptable. The changes are as follows:

Changes in the package insert:

1. Per our request, the patient package insert is attached to the package insert and the patient package insert is referenced in the PRECAUTIONS section under Information for Patients to refer to attached patient package insert.

2. The established name appears on the first column, page two to satisfy labeling regulations.

3. Changes being effected are all in the ADVERSE REACTIONS section and are underlined below to indicated what was added:

   Ongoing Evaluation: The following serious adverse events of uncertain relationship to TAXOTERE® have been reported:

   Body as a whole: abdominal pain, diffuse pain, chest pain

   Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, <u>myocardial infarction</u>

   Digestive: constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, intestinal obstruction, ileus, <u>gastrointestinal perforation, neutropenic enterocolitis</u>

With the concurrence of the Medical Officer, these revisions are acceptable and the supplement should be approved.

/S/ 12/22/97

Ann M. Staten, Project Manager/ Date

/S/

Concurrence: 12/31/97

Donna Griebel, M.D., Medical Officer/ Date

CC: Original NDA 20-449
HFD-150/Div File
/DGriebel
/AStaten

R/D initialed by D. Pease/12-19-97
F/T PGuinn for DPease/ 12/22/97

CSO Labeling Review