# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: NDA 20262/S031

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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number: NDA 20262/S031**

**Trade Name: Taxol Injection**

**Generic Name: (paclitaxel)**

**Sponsor: Bristol-Myers Squibb Company**

**Approval Date: January 8, 1999**

**Indication: Provides for changes in the package insert only.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: NDA 20262/S031**

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-262/S-014, S-016, S-021, S-031
S-013 (FA), S-024 (FA)

Bristol-Myers Squibb Company
5 Research Parkway - P.O. Box 5100
Wallingford, CT 06492-7660

JAN 8 1999

Attention: Susan H. Behling
Director, U.S. Liaison
Worldwide Regulatory Affairs

Dear Ms. Behling:

Please refer to your supplemental new drug applications dated June 17, received June 19; July 1, received July 2; and December 20, 1996, received December 23, 1996; and December 18, 1998, received December 21, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxol (paclitaxel) Injection.

We acknowledge receipt of your amendment to S-016 dated September 4, 1996.

We have reviewed the final printed labeling (package insert only) submitted in accordance with our April 3, 1996 approval letter for S-013 and have determined that it is acceptable but has been superseded.

The supplemental application S-014, a Special Supplement-Changes Being Effected, provides for changes in the package insert only. The approximate volume size of 17 ml for the 100mg vial is changed to 16.7 ml to provide a more accurate description. This revision appears in the DESCRIPTION and HOW SUPPLIED sections.

The supplemental application S-016, a Special Supplement-Changes Being Effected provides for a revision in the product name to Taxol (paclitaxel) Injection. In addition a new precautionary statement has been added concerning potential drug interactions with drugs which act as substrates or inhibitors of the relevant cytochrome P450 isoenzymes and is accompanied by a corresponding change to the CLINICAL PHARMACOLOGY section. Also additional precautionary statements and adverse reaction information based upon information received from on-going clinical research and from postmarketing experience have been added.

The supplemental application S-021, a Special Supplement-Changes Being Effected, provides a revision to the PRECAUTIONS section, Nursing Mothers subsection that addresses the results of a rat lactation study.

The supplemental application S-031 with final printed labeling provides revisions to the label for S-024 approved June 30, 1998 and has not previously been launched for this new indication.

We have completed the review of these supplemental applications and they are approved effective on the date of this letter.

Please note that S-031 final printed labeling (submitted also as S-024 FA) supersedes all previous labeling.

Should a letter communicating important information about this drug product (i.e., a "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 Leslie Vaccari, Project Manager, at (301) 594-5784.

Sincerely yours,

/S/ 1/8/99

Robert L. Justice, M.D.
Acting 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 20262/S-031

## FINAL PRINTED LABELING

Mead Johnson
ONCOLOGY PRODUCTS

APPROVED

347630DIM-05
51-006186-04

F.P.O.

# TAXOL®
(paclitaxel)
INJECTION

Rx only


# TAXOL®
(paclitaxel)
INJECTION


**WARNING**

TAXOL® (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2–4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and $H_2$ antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

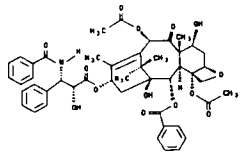
TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm³ and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

**DESCRIPTION**

TAXOL (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β,20-Epoxy-1, 2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217° C.

**CLINICAL PHARMACOLOGY**

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of TAXOL, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of TAXOL at dose levels of 135 and 175 mg/m² were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

**TABLE 1**
SUMMARY OF PHARMACOKINETIC PARAMETERS—MEAN VALUES

| Dose (mg/m²) | Infusion Duration (h) | N (patients) | $C_{MAX}$ (ng/mL) | AUC(0–∞) (ng h/mL) | T-HALF (h) | $CL_T$ (L/h/m²) |
|---|---|---|---|---|---|---|
| 135 | 24 | 2 | 195 | 6300 | 52.7 | 21.7 |
| 175 | 24 | 4 | 365 | 7993 | 15.7 | 23.8 |
| 135 | 3 | 7 | 2170 | 7952 | 13.1 | 17.7 |
| 175 | 3 | 5 | 3650 | 15007 | 20.2 | 12.2 |

$C_{MAX}$ = Maximum plasma concentration
AUC(0–∞) = Area under the plasma concentration-time curve from time 0 to infinity
$CL_T$ = Total body clearance

It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m² versus 175 mg/m²) increased the $C_{MAX}$ by 87%, whereas the AUC(0–∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the $C_{MAX}$ and AUC(0–∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15–135 mg/m² given by 1-hour infusions (n=15), 30–275 mg/m² given by 6-hour infusions (n=36), and 200–275 mg/m² given by 24-hour infusions (n=54) in Phase 1 & 2 studies. Values for $CL_T$ and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of TAXOL in patients with AIDS-related Kaposi's sarcoma have not been studied.

*In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89–98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15–275 mg/m² doses of TAXOL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m² dose of radiolabeled TAXOL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions** section.) The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

**CLINICAL STUDIES**

**Ovarian Carcinoma**

*First-Line Data*: The safety and efficacy of TAXOL (135 mg/m² over 24 hours) in combination with cisplatin (75 mg/m²) in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in a Phase 3 multicenter, randomized, controlled (vs. cyclophosphamide 750 mg/m²/cisplatin 75 mg/m²) clinical trial conducted by the Gynecology Oncology Group [illegible] or distant metastases) were randomized. Patients treated with TAXOL in combi-

$C_{MAX}$ = maximum plasma concentration
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It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m² versus 175 mg/m²) increased the $C_{MAX}$ by 87%, whereas the $AUC(0-\infty)$ remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the $C_{MAX}$ and $AUC(0-\infty)$ were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

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Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

## CLINICAL STUDIES

### Ovarian Carcinoma

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**TABLE 2**
EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDY

| | TAXOL/Cisplatin (n=196) | | Cyclophosphamide/Cisplatin (n=214) |
|---|---|---|---|
| • ***Clinical Response***[a] | (n=113) | | (n=127) |
| —rate (percent) | 62 | | 48 |
| —p-value | | 0.04 | |
| • ***Pathological Response***[b] | | | |
| —rate (percent) | 34 | | 20 |
| —p-value | | 0.001 | |
| • ***Pathological Complete Response*** | | | |
| —rate (percent) | 21 | | 16 |
| —p-value | | 0.20 | |
| • ***Time to Progression*** | | | |
| —median (months) | 16.6 | | 13.0 |
| —p-value | | 0.0008 | |
| • ***Survival*** | | | |
| —median (months) | 35.5 | | 24.2 |
| —p-value | | 0.0002 | |

[a] Among evaluable patients only.
[b] Includes patients with pathological complete response plus patients with microscopic residual disease.

The adverse event profile for patients receiving TAXOL in combination with cisplatin in this study was generally consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 9) and narrative form.

*Second-Line Data:* Data from five Phase 1 & 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of TAXOL in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m² in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% CI: 11 to 37%) and 30% (95% CI: 18 to 46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these two studies measured from the first day of treatment was 7.2 months (range: 3.5–15.8 months) and 7.5 months (range: 5.3–17.4 months), respectively. The median survival was 8.1 months (range: 0.2–36.7 months) and 15.9 months (range: 1.8–34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of TAXOL, administered at two different doses (135 or 175 mg/m²) and schedules (3- or 24-hour infusion). The overall response rate for the 407 patients was 16.2% (95% CI: 12.8 to 20.2%), with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range: 3.2–21.6 months). Median time to progression was 3.7 months (range 0.1+ – 25.1+ months). Median survival was 11.5 months (range: 0.2–26.3+ months).

Response rates, median survival and median time to progression for the 4 arms are given in the following table.

**TABLE 3**
EFFICACY IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

| | 175/3 (n=96) | 175/24 (n=106) | 135/3 (n=99) | 135/24 (n=106) |
|---|---|---|---|---|
| • ***Response*** | | | | |
| —rate (percent) | 14.6 | 21.7 | 15.2 | 13.2 |
| —95% Confidence Interval | (8.5–23.6) | (14.5–31.0) | (9.0–24.1) | (7.7–21.5) |
| • ***Time to Progression*** | | | | |
| —median (months) | 4.4 | 4.2 | 3.4 | 2.8 |
| —95% Confidence Interval | (3.0–5.6) | (3.5–5.1) | (2.8–4.2) | (1.9–4.0) |
| • ***Survival*** | | | | |
| —median (months) | 11.5 | 11.8 | 13.1 | 10.7 |
| —95% Confidence Interval | (8.4–14.4) | (8.9–14.6) | (9.1–14.6) | (8.1–13.6) |

Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the two doses (135 or 175 mg/m²) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m² dose had a response rate similar to that for those receiving the 135 mg/m² dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m² dose of TAXOL had a longer time to progression than those receiving the 135 mg/m² dose: median 4.2 vs. 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour vs. the 24-hour infusion was 4.0 months vs. 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 175 mg/m² dose of TAXOL and 11.0 months in patients receiving the 135 mg/m² dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of TAXOL and 11.2 months for patients receiving the 24-hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

TAXOL remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, a platinum containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 & 2 clinical studies.

The adverse event profile in this Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 10) and narrative form.

The results of this randomized study support the use of TAXOL at doses of 135 to 175 mg/m², administered by a 3-hour intravenous infusion. The same doses administered by 24-hour infusion were more toxic. However, the study had insufficient power to determine whether a particular dose and schedule produced superior efficacy.

**Breast Carcinoma:** Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of TAXOL in patients with metastatic breast carcinoma.

*Phase 2 open label studies:* Two studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. TAXOL was administered in these two trials as a 24-hour infusion at initial doses of 250 mg/m² (with G-CSF support) or 200 mg/m². The response rates were 57% (95% CI: 37 to 75%) and 52% (95% CI: 32 to 72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of two chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL was 200 mg/m² as a 24-hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, for a response rate of 30% (95% CI: 15 to 50%).

*Phase 3 randomized study:* This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive TAXOL (paclitaxel) at a dose of either 175 mg/m² or 135 mg/m² given as a 3-hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% CI: 22 to 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4–18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03–17.1 months). Median survival was 11.7 months (range: 0–18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table.

**TABLE 4**
EFFICACY IN BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

| | 175/3 (n=235) | | 135/3 (n=236) |
|---|---|---|---|
| • ***Response*** | | | |
| —rate (percent) | 28 | | 22 |
| —p-value | | 0.135 | |
| • ***Time to Progression*** | | | |
| —median (months) | 4.2 | | 3.0 |
| —p-value | | 0.027 | |
| • ***Survival*** | | | |
| —median (months) | 11.7 | | 10.5 |
| —p-value | | 0.321 | |

The adverse event profile of the patients who received single-agent TAXOL in the Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 11) and narrative form.

**Non-Small Cell Lung Carcinoma (NSCLC):** In a Phase 3 open label randomized study conducted by the Eastern Cooperative Oncology Group (ECOG), 599 patients were randomized to either TAXOL (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2, and 3 (control).

Response rates, median time to progression, median survival, and one-year survival rates are given in the following table. The reported p-values have not been adjusted for multiple comparisons. There were statistically significant differences favoring each of the TAXOL plus cisplatin arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either TAXOL plus cisplatin arm and the cisplatin plus etoposide arm.

**TABLE 5**
EFFICACY PARAMETERS IN THE PHASE 3 FIRST-LINE NSCLC STUDY

| | T135/24 c75 (n=198) | T250/24 c75 (n=201) | VP100[a] c75 (n=200) |
|---|---|---|---|
| • ***Response*** | | | |
| —rate (percent) | 25 | 23 | 12 |
| —p-value[b] | 0.001 | <0.001 | |
| • ***Time to Progression*** | | | |
| —median (months) | 4.3 | 4.9 | 2.7 |
| —p-value[b] | 0.05 | 0.004 | |
| • ***Survival*** | | | |
| —median (months) | | | |

| | | | |
|---|---|---|---|
| • *Survival* | | | |
| —median (months) | 11.7 | | 10.5 |
| —p-value | | 0.321 | |

The adverse event profile of the patients who received single-agent TAXOL in the Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 11) and narrative form.

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Response rates, median time to progression, median survival, and one-year survival rates are given in the following table. The reported p-values have not been adjusted for multiple comparisons. There were statistically significant differences favoring each of the TAXOL plus cisplatin arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either TAXOL plus cisplatin arm and the cisplatin plus etoposide arm.

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| | T135/24 c75 (n=198) | T250/24 c75 (n=201) | VP100[a] c75 (n=200) |
|---|---|---|---|
| • ***Response*** | | | |
| —rate (percent) | 25 | 23 | 12 |
| —p-value[b] | 0.001 | <0.001 | |
| • ***Time to Progression*** | | | |
| —median (months) | 4.3 | 4.9 | 2.7 |
| —p-value[b] | 0.05 | 0.004 | |
| • ***Survival*** | | | |
| —median (months) | 9.3 | 10.0 | 7.4 |
| —p-value[b] | 0.12 | 0.08 | |
| • ***One-Year Survival*** | | | |
| —percent of patients | 36 | 40 | 32 |

[a] Etoposide (VP) 100 mg/m² was administered IV on days 1, 2, and 3.
[b] Compared to cisplatin/etoposide.

In the ECOG study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had seven subscales that measured subjective assessment of treatment. Of the seven, the Lung Cancer Specific Symptoms subscale favored the TAXOL 135 mg/m²/24 hour plus cisplatin arm compared to the cisplatin/etoposide arm. For all other factors, there was no difference in the treatment groups.

The adverse event profile for patients who received TAXOL in combination with cisplatin in this study was generally consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line NSCLC study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 12) and narrative form.

**AIDS-Related Kaposi's Sarcoma:** Data from two Phase 2 open label studies support the use of TAXOL as second-line therapy in patients with AIDS-related Kaposi's sarcoma. Fifty-nine of the 85 patients enrolled in these studies had previously received systemic therapy, including interferon alpha (32%), DaunoXome® (31%), DOXIL® (2%), and doxorubicin containing chemotherapy (42%), with 64% having received prior anthracyclines. Eighty-five percent of the pretreated patients had progressed on, or could not tolerate, prior systemic therapy.

In Study CA139-174 patients received TAXOL at 135 mg/m² as a 3-hour infusion every 3 weeks (intended dose intensity 45 mg/m²/week). If no dose-limiting toxicity was observed, patients were to receive 155 mg/m² and 175 mg/m² in subsequent courses. Hematopoietic growth factors were not to be used initially. In Study CA139-281 patients received TAXOL at 100 mg/m² as a 3-hour infusion every 2 weeks (intended dose intensity 50 mg/m²/week). In this study patients could be receiving hematopoietic growth factors before the start of TAXOL therapy, or this support was to be initiated as indicated; the dose of TAXOL was not increased. The dose intensity of TAXOL used in this patient population was lower than the dose intensity recommended for other solid tumors.

All patients had widespread and poor risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease ($T_1$), 88% had a CD4 count <200 cells/mm³ ($I_1$), and 97% had poor risk considering their systemic illness ($S_1$).

All patients in Study CA139-174 had a Karnofsky performance status of 80 or 90 at baseline; in Study CA139-281, there were 26 (46%) patients with a Karnofsky performance status of 70 or worse at baseline.

**TABLE 6**
EXTENT OF DISEASE AT STUDY ENTRY
Percent of Patients

| | Prior Systemic Therapy (n=59) |
|---|---|
| Visceral ± edema ±oral ± cutaneous | 42 |
| Edema or lymph nodes oral ± cutaneous | 41 |
| Oral ± cutaneous | 10 |
| Cutaneous Only | 7 |

Although the planned dose intensity in the two studies was slightly different (45 mg/m²/week in Study CA139-174 and 50 mg/m²/week in Study CA139-281), delivered dose intensity was 38–39 mg/m²/week in both studies, with a similar range (20–24 to 51–61).

*Efficacy:* The efficacy of TAXOL was evaluated by assessing cutaneous tumor response according to the amended ACTG criteria and by seeking evidence of clinical benefit in patients in six domains of symptoms and/or conditions that are commonly related to AIDS-related Kaposi's sarcoma.

*Cutaneous Tumor Response (Amended ACTG Criteria):* The objective response rate was 59% (95% CI: 46% to 72%) (35 of 59 patients) in patients with prior systemic therapy. Cutaneous responses were primarily defined as flattening of more than 50% of previously raised lesions.

**TABLE 7**
OVERALL BEST RESPONSE (AMENDED ACTG CRITERIA)
Percent of Patients

| | Prior Systemic Therapy (n=59) |
|---|---|
| Complete response | 3 |
| Partial response | 56 |
| Stable disease | 29 |
| Progression | 8 |
| Early death/toxicity | 3 |

The median time to response was 8.1 weeks and the median duration of response measured from the first day of treatment was 10.4 months (95% CI: 7.0 to 11.0 months) for the patients who had previously received systemic therapy. The median time to progression was 6.2 months (95% CI: 4.6 to 8.7 months).

*Additional Clinical Benefit:* Most data on patient benefit were assessed retrospectively (plans for such analyses were not included in the study protocols). Nonetheless, clinical descriptions and photographs indicated clear benefit in some patients, including instances of improved pulmonary function in patients with pulmonary involvement, improved ambulation, resolution of ulcers, and decreased analgesic requirements in patients with KS involving the feet and resolution of facial lesions and edema in patients with KS involving the face, extremities, and genitalia.

*Safety:* The adverse event profile of TAXOL administered to patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma was generally similar to that seen in the pooled analysis of data from 812 patients with solid tumors. These adverse events and adverse events from the Phase 2 second-line Kaposi's sarcoma studies are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 13) and narrative form. In this immunosuppressed patient population, however, a lower dose intensity of TAXOL and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors.

## INDICATIONS

TAXOL is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, TAXOL is indicated in combination with cisplatin.

TAXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

TAXOL, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

TAXOL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

## CONTRAINDICATIONS

TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

TAXOL should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm³ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm³.

## WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2–4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and $H_2$ antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. TAXOL should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³ (<1000 cells/mm³ for patients with KS). Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ (>1000 cells/mm³ for patients with KS) and platelets recover to a level >100,000 cells/mm³.

Severe conduction abnormalities have been documented in <1% of patients during TAXOL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during TAXOL infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL.

### Pregnancy

TAXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m² basis), teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If TAXOL 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. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (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 TAXOL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

**Drug Interactions:** In a Phase 1 trial using escalating doses of TAXOL (110–200 mg/m²) and cisplatin (50 or 75 mg/m²) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (i.e. TAXOL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when TAXOL was administered following cisplatin.

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering TAXOL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See **CLINICAL PHARMACOLOGY** section.)

Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

**Hematology:** TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, TAXOL, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm³.

**Hypersensitivity Reactions:** Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g. cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and $H_2$ antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have [illegible]

*Safety.* The adverse event profile of TAXOL administered to patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma was generally consistent with pooled analysis of data from 812 patients with solid tumors. These adverse events and adverse events from the Phase 2 second-line Kaposi's sarcoma studies are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 13) and narrative form. In this immunosuppressed patient population, however, a lower dose intensity of TAXOL and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors.

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**Cardiovascular:** Hypotension, bradycardia, and hypertension have been observed during administration of TAXOL, but generally do not require treatment. Occasionally TAXOL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of TAXOL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See **WARNINGS** section.)

**Nervous System:** Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of TAXOL.

TAXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **PRECAUTIONS: Pediatric Use** section.)

**Hepatic:** There is evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering TAXOL to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

**Injection Site Reaction:** Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of TAXOL (paclitaxel) has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m² basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See **WARNINGS** section.)

**Pregnancy:** Pregnancy "Category D." (See **WARNINGS** section.)

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled TAXOL to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving TAXOL therapy.

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

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

**ADVERSE REACTIONS**

**Pooled Analysis of Adverse Event Experiences from Single-Agent Studies**

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent TAXOL. Two hundred and seventy-five patients were treated in eight Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m² administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m²) and two schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m²) administered over 3 hours in a controlled study.

**TABLE 8**
SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT TAXOL

| | Percent of Patients (n=812) |
|---|---|
| • ***Bone Marrow*** | |
| —Neutropenia <2000/mm³ | 90 |
| < 500/mm³ | 52 |
| —Leukopenia <4000/mm³ | 90 |
| <1000/mm³ | 17 |
| —Thrombocytopenia <100,000/mm³ | 20 |
| < 50,000/mm³ | 7 |
| —Anemia <11 g/dL | 78 |
| < 8 g/dL | 16 |
| —Infections | 30 |
| —Bleeding | 14 |
| —Red Cell Transfusions | 25 |
| —Platelet Transfusions | 2 |
| • ***Hypersensitivity Reaction***[b] | |
| —All | 41 |
| —Severe[†] | 2 |
| • ***Cardiovascular*** | |
| —Vital Sign Changes[c] | |
| —Bradycardia (n=537) | 3 |
| —Hypotension (n=532) | 12 |
| —Significant Cardiovascular Events | 1 |
| • ***Abnormal ECG*** | |
| —All Pts | 23 |
| —Pts with normal baseline (n=559) | 14 |
| • ***Peripheral Neuropathy*** | |
| —Any symptoms | 60 |
| —Severe symptoms[†] | 3 |
| • ***Myalgia/Arthralgia*** | |
| —Any symptoms | 60 |
| —Severe symptoms[†] | 8 |
| • ***Gastrointestinal*** | |
| —Nausea and vomiting | 52 |
| —Diarrhea | 38 |
| —Mucositis | 31 |
| • ***Alopecia*** | 87 |
| • ***Hepatic*** (Pts with normal baseline and on study data) | |
| —Bilirubin elevations (n=765) | 7 |
| —Alkaline phosphatase elevations (n=575) | 22 |
| —AST (SGOT) elevations (n=591) | 19 |
| • ***Injection Site Reaction*** | 13 |

[a] Based on worst course analysis.
[b] All patients received premedication.
[c] Over the first 2 hours of infusion.

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TAXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **PRECAUTIONS: Pediatric Use** section.)

**Hepatic:** There is evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering TAXOL to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

**Injection Site Reaction:** Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of TAXOL (paclitaxel) has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m² basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See **WARNINGS** section.)

**Pregnancy:** Pregnancy "Category D." (See **WARNINGS** section.)

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled TAXOL to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving TAXOL therapy.

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

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

**ADVERSE REACTIONS**

**Pooled Analysis of Adverse Event Experiences from Single-Agent Studies**

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent TAXOL. Two hundred and seventy-five patients were treated in eight Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m² administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m²) and two schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m²) administered over 3 hours in a controlled study.

**TABLE 8**

SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT TAXOL

| | Percent of Patients (n=812) |
|---|---|
| • ***Bone Marrow*** | |
| —Neutropenia <2000/mm³ | 90 |
| < 500/mm³ | 52 |
| —Leukopenia <4000/mm³ | 90 |
| <1000/mm³ | 17 |
| —Thrombocytopenia <100,000/mm³ | 20 |
| < 50,000/mm³ | 7 |
| —Anemia <11 g/dL | 78 |
| < 8 g/dL | 16 |
| —Infections | 30 |
| —Bleeding | 14 |
| —Red Cell Transfusions | 25 |
| —Platelet Transfusions | 2 |
| • ***Hypersensitivity Reaction***[b] | |
| —All | 41 |
| —Severe[†] | 2 |
| • ***Cardiovascular*** | |
| —Vital Sign Changes[c] | |
| —Bradycardia (n=537) | 3 |
| —Hypotension (n=532) | 12 |
| —Significant Cardiovascular Events | 1 |
| • ***Abnormal ECG*** | |
| —All Pts | 23 |
| —Pts with normal baseline (n=559) | 14 |
| • ***Peripheral Neuropathy*** | |
| —Any symptoms | 60 |
| —Severe symptoms[†] | 3 |
| • ***Myalgia/Arthralgia*** | |
| —Any symptoms | 60 |
| —Severe symptoms[†] | 8 |
| • ***Gastrointestinal*** | |
| —Nausea and vomiting | 52 |
| —Diarrhea | 38 |
| —Mucositis | 31 |
| • ***Alopecia*** | 87 |
| • ***Hepatic*** (Pts with normal baseline and on study data) | |
| —Bilirubin elevations (n=765) | 7 |
| —Alkaline phosphatase elevations (n=575) | 22 |
| —AST (SGOT) elevations (n=591) | 19 |
| • ***Injection Site Reaction*** | 13 |

[a] Based on worst course analysis.
[b] All patients received premedication.
[c] During the first 3 hours of infusion.
[†] Severe events are defined as at least Grade III toxicity.

None of the observed toxicities were clearly influenced by age.

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of important adverse events.

**TABLE 9**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDY**

| | Percent of Patients | |
|---|---|---|
| | TAXOL (135/24)[b] /Cisplatin (75)[c] (n=196) | Cyclophosphamide (750)[c] /Cisplatin (75)[c] (n=213) |
| • ***Bone Marrow*** | | |
| —Neutropenia < 2000/mm³ | 96 | 92 |
| < 500/mm³ | 81[d] | 58[d] |
| —Thrombocytopenia < 100,000/mm³ | 26 | 30 |
| < 50,000/mm³ | 10 | 9 |
| —Anemia <11 g/dL | 88 | 86 |
| < 8 g/dL | 13 | 9 |
| —Infections | 21 | 15 |
| —Febrile Neutropenia | 15[d] | 4[d] |
| • ***Hypersensitivity Reaction[e]*** | | |
| —All | 8[d] | 1[d] |
| —Severe[†] | 3[d] | —[d] |
| • ***Peripheral Neuropathy*** | | |
| —Any symptoms | 25 | 20 |
| —Severe symptoms[†] | 3[d] | —[d] |
| • ***Nausea and Vomiting*** | | |
| —Any symptoms | 65 | 69 |
| —Severe symptoms[†] | 10 | 11 |
| • ***Myalgia/Arthralgia*** | | |
| —Any symptoms | 9[d] | 2[d] |
| —Severe symptoms[†] | 1 | — |
| • ***Diarrhea*** | | |
| —Any symptoms | 16[d] | 8[d] |
| —Severe symptoms[†] | 4 | 1 |
| • ***Asthenia*** | | |
| —Any symptoms | 17[d] | 10[d] |
| —Severe symptoms[†] | 1 | 1 |
| • ***Alopecia*** | | |
| —Any symptoms | 55[d] | 37[d] |
| —Severe symptoms[†] | 6 | 8 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours.
[c]Dose in mg/m².
[d]p<0.05 by Fisher exact test.
[e]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

**Second-Line Ovary:** For the 403 patients who received single-agent TAXOL in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

**TABLE 10**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY**

| | Percent of Patients | | | |
|---|---|---|---|---|
| | 175/3[b] (n=95) | 175/24[b] (n=105) | 135/3[b] (n=98) | 135/24[b] (n=105) |
| • ***Bone Marrow*** | | | | |
| —Neutropenia <2000/mm³ | 78 | 98 | 78 | 98 |
| < 500/mm³ | 27 | 75 | 14 | 67 |
| —Thrombocytopenia <100,000/mm³ | 4 | 18 | 8 | 6 |
| < 50,000/mm³ | 1 | 7 | 2 | 1 |
| —Anemia <11 g/dL | 84 | 90 | 68 | 88 |
| < 8 g/dL | 11 | 12 | 6 | 10 |
| —Infections | 26 | 29 | 20 | 18 |
| • ***Hypersensitivity Reaction[c]*** | | | | |
| —All | 41 | 45 | 38 | 45 |
| —Severe[†] | 2 | 0 | 2 | 1 |
| • ***Peripheral Neuropathy*** | | | | |
| —Any symptoms | 63 | 60 | 55 | 42 |
| —Severe symptoms[†] | 1 | 2 | 0 | 0 |
| • ***Mucositis*** | | | | |
| —Any symptoms | 17 | 35 | 21 | 25 |
| —Severe symptoms[†] | 0 | 3 | 0 | 2 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours.
[c]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

**Breast:** For the 458 patients who received single-agent TAXOL in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a 3-hour infusion).

**TABLE 11**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 BREAST CARCINOMA STUDY**

| | Percent of Patients | |
|---|---|---|
| | 175/3[b] (n=229) | 135/3[b] (n=229) |
| • ***Bone Marrow*** | | |
| —Neutropenia <2000/mm³ | 90 | 81 |
| < 500/mm³ | 28 | 19 |
| —Thrombocytopenia <100,000/mm³ | 11 | 7 |
| < 50,000/mm³ | 3 | 2 |
| —Anemia <11 g/dL | 55 | 47 |
| < 8 g/dL | 4 | 2 |
| —Infections | 23 | 15 |
| —Febrile Neutropenia | 2 | 2 |
| • ***Hypersensitivity Reaction[c]*** | | |
| —All | 36 | 31 |
| —Severe[†] | 0 | <1 |
| • ***Peripheral Neuropathy*** | | |
| —Any symptoms | 70 | 46 |
| —Severe symptoms[†] | 7 | 3 |
| • ***Mucositis*** | | |
| —Any symptoms | 23 | 17 |
| —Severe symptoms[†] | 3 | <1 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours.
[c]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

**First-Line NSCLC in Combination:** In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either TAXOL (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2, and 3 (control).

The following table shows the incidence of important adverse events.

**TABLE 12**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY FOR FIRST-LINE NSCLC**

| | Percent of Patients | | |
|---|---|---|---|
| | T135/24[b] c75 (n=195) | T250/24[c] c75 (n=197) | VP100[d] c75 (n=196) |
| • ***Bone Marrow*** | | | |
| —Neutropenia | | | |
| < 2000/mm³ | 89 | 86 | 84 |
| < 500/mm³ | 74[e] | 65 | 55 |
| —Thrombocytopenia | | | |
| < normal | 48 | 68 | 62 |
| < 50,000/mm³ | 6 | 12 | 16 |
| —Anemia | | | |
| < normal | 94 | 96 | 95 |
| < 8 g/dL | 22 | 19 | 28 |

[illegible] diarrhea [illegible] any grade, was [illegible] of any grade was reported more frequently (16%) compared to the control arm (8%)

| | | | |
|---|---|---|---|
| —Thrombocytopenia | < 100,000/mm³ | 11 | 2 |
| —Anemia | < 50,000/mm³ | 3 | 2 |
| | <11 g/dL | 55 | 47 |
| | < 8 g/dL | 4 | 2 |
| —Infections | | 23 | 15 |
| —Febrile Neutropenia | | 2 | 2 |
| • ***Hypersensitivity Reaction***[c] | | | |
| —All | | 36 | 31 |
| —Severe[†] | | 0 | <1 |
| • ***Peripheral Neuropathy*** | | | |
| —Any symptoms | | 70 | 46 |
| —Severe symptoms[†] | | 7 | 3 |
| • ***Mucositis*** | | | |
| —Any symptoms | | 23 | 17 |
| —Severe symptoms[†] | | 3 | <1 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours.
[c]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

**First-Line NSCLC in Combination:** In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either TAXOL (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2, and 3 (control).

The following table shows the incidence of important adverse events.

**TABLE 12**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY FOR FIRST-LINE NSCLC**

| | Percent of Patients | | |
|---|---|---|---|
| | T135/24[b] c75, (n=195) | T250/24[c] c75 (n=197) | VP100[d] c75 (n=196) |
| • ***Bone Marrow*** | | | |
| —Neutropenia | | | |
| < 2000/mm³ | 89 | 86 | 84 |
| < 500/mm³ | 74[e] | 65 | 55 |
| —Thrombocytopenia | | | |
| < normal | 48 | 68 | 62 |
| < 50,000/mm³ | 6 | 12 | 16 |
| —Anemia | | | |
| < normal | 94 | 96 | 95 |
| < 8 g/dL | 22 | 19 | 28 |
| —Infections | 38 | 31 | 35 |
| • ***Hypersensitivity Reaction***[f] | | | |
| —All | 16 | 27 | 13 |
| —Severe[†] | 1 | 4[e] | 1 |
| • ***Arthralgia/Myalgia*** | | | |
| —Any symptoms | 21[e] | 42[e] | 9 |
| —Severe symptoms[†] | 3 | 11 | 1 |
| • ***Nausea/Vomiting*** | | | |
| —Any symptoms | 85 | 87 | 81 |
| —Severe symptoms[†] | 27 | 29 | 22 |
| • ***Mucositis*** | | | |
| —Any symptoms | 18 | 28 | 16 |
| —Severe symptoms[†] | 1 | 4 | 2 |
| • ***Neuromotor Toxicity*** | | | |
| —Any symptoms | 37 | 47 | 44 |
| —Severe symptoms[†] | 6 | 12 | 7 |
| • ***Neurosensory Toxicity*** | | | |
| —Any symptoms | 48 | 61 | 25 |
| —Severe symptoms[†] | 13 | 28[e] | 8 |
| • ***Cardiovascular Events*** | | | |
| —Any symptoms | 33 | 39 | 24 |
| —Severe symptoms[†] | 13 | 12 | 8 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours; cisplatin dose in mg/m².
[c]TAXOL dose in mg/m²/infusion duration in hours with G-CSF support; cisplatin dose in mg/m².
[d]Etoposide (VP) dose in mg/m² was administered IV on days 1, 2, and 3; cisplatin dose in mg/m².
[e]p<0.05.
[f]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

Toxicity was generally more severe in the high-dose TAXOL treatment arm (T250/c75) than in the low-dose TAXOL arm (T135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose TAXOL arm experienced more arthralgia/myalgia of any grade and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

**Kaposi's Sarcoma:** The following table shows the frequency of important adverse events in the 85 patients with KS treated with two different single-agent TAXOL regimens.

**TABLE 13**
**FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE AIDS-RELATED KAPOSI'S SARCOMA STUDIES**

| | Percent of Patients | |
|---|---|---|
| | Study CA139-174 TAXOL 135/3[b] q 3 wk (n=29) | Study CA139-281 TAXOL 100/3[b] q 2 wk (n=56) |
| • ***Bone Marrow*** | | |
| —Neutropenia | | |
| < 2000/mm³ | 100 | 95 |
| < 500/mm³ | 76 | 35 |
| —Thrombocytopenia | | |
| <100,000/mm³ | 52 | 27 |
| < 50,000/mm³ | 17 | 5 |
| —Anemia | | |
| <11 g/dL | 86 | 73 |
| < 8 g/dL | 34 | 25 |
| —Febrile Neutropenia | 55 | 9 |
| • ***Opportunistic Infection*** | | |
| —Any | 76 | 54 |
| —Cytomegalovirus | 45 | 27 |
| —Herpes Simplex | 38 | 11 |
| —*Pneumocystis carinii* | 14 | 21 |
| —*M. avium-intracellulare* | 24 | 4 |
| —Candidiasis, esophageal | 7 | 9 |
| —Cryptosporidiosis | 7 | 7 |
| —Cryptococcal meningitis | 3 | 2 |
| —Leukoencephalopathy | — | 2 |
| • ***Hypersensitivity Reaction***[c] | | |
| —All | 14 | 9 |
| • ***Cardiovascular*** | | |
| —Hypotension | 17 | 9 |
| —Bradycardia | 3 | — |
| • ***Peripheral Neuropathy*** | | |
| —Any | 79 | 46 |
| —Severe[†] | 10 | 2 |
| • ***Myalgia/Arthralgia*** | | |
| —Any | 93 | 48 |
| —Severe[†] | 14 | 16 |
| • ***Gastrointestinal*** | | |
| —Nausea and Vomiting | 69 | 70 |
| —Diarrhea | 90 | 73 |
| —Mucositis | 45 | 20 |
| • ***Renal (creatinine elevation)*** | | |
| —Any | 34 | 18 |
| —Severe[†] | 7 | 5 |
| • ***Discontinuation for drug toxicity*** | 7 | 16 |

[a]Based on worst course analysis.
[b]TAXOL dose in mg/m²/infusion duration in hours.
[c]All patients received premedication.
[†]Severe events are defined as at least Grade III toxicity.

As demonstrated in this table, toxicity was more pronounced in the study utilizing TAXOL at a dose of 135 mg/m² every 3 weeks than in the study utilizing TAXOL at a dose of 100 mg/m² every 2 weeks. Notably, severe neutropenia (76% versus 35%), febrile neutropenia (55% versus 9%), and opportunistic infections (76% versus 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.) Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

**Adverse Event Experiences by Body System**

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent TAXOL in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received TAXOL in combination with cisplatin and that occurred with a difference that was clinically significant in this population are also described. The frequency and severity of important adverse events for the Phase 3 first- and second-line ovarian, breast carcinoma, NSCLC, and Kaposi's sarcoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving TAXOL for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described.

**Hematologic:** Bone marrow suppression was the major dose-limiting toxicity of TAXOL. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm³ in 13% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (< 500 cells/mm³) was more frequent with the 24-hour infusion than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose [illegible]

[c] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

As demonstrated in this table, toxicity was more pronounced in the study utilizing TAXOL at a dose of 135 mg/m² every 3 weeks than in the study utilizing TAXOL at a dose of 100 mg/m² every 2 weeks. Notably, severe neutropenia (76% versus 35%), febrile neutropenia (55% versus 9%), and opportunistic infections (76% versus 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.) Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

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Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent TAXOL in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received TAXOL in combination with cisplatin and that occurred with a difference that was clinically significant in this population are also described. The frequency and severity of important adverse events for the Phase 3 first- and second-line ovarian, breast carcinoma, NSCLC, and Kaposi's sarcoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving TAXOL for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described.

**Hematologic:** Bone marrow suppression was the major dose-limiting toxicity of TAXOL. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm³ in 13% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (<500 cells/mm³) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

In the study where TAXOL was administered to patients with ovarian carcinoma at a dose of 135 mg/m²/24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the TAXOL plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the TAXOL plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the TAXOL/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When TAXOL followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (TAXOL 135 mg/m²/24 hours followed by cisplatin) and 65% (TAXOL 250 mg/m²/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 19% of the patients given either the 135 or 175 mg/m² dose by a 3-hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.) The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See **DOSAGE AND ADMINISTRATION** section.)

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm³). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no patients treated with the 3-hour infusion received platelet transfusions. In the Phase 3 NSCLC study, severe thrombocytopenia was experienced by 6% of the patients in the TAXOL 135 mg/m²/24 hours followed by cisplatin arm.

Anemia (Hb <11 g/dL) was observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

**Hypersensitivity Reactions (HSRs):** All patients received premedication prior to TAXOL (see **WARNINGS** and **PRECAUTIONS: Hypersensitivity Reactions** sections). The frequency and severity of HSRs were not affected by the dose or schedule of TAXOL administration. In the Phase 3 second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of TAXOL infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of TAXOL safety.

**Cardiovascular:** Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to single-agent TAXOL occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension, and venous thrombosis. One of the patients with syncope treated with TAXOL at 175 mg/m² over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy, and complete AV block requiring pacemaker placement. Among patients with NSCLC treated with TAXOL in combination with cisplatin in the Phase 3 study, significant cardiovascular events occurred in 12–13%. This apparent increase in cardiovascular events is possibly due to an increase in cardiovascular risk factors in patients with lung cancer.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See **PRECAUTIONS: Drug Interactions** section.)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of TAXOL safety.

**Respiratory:** Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as part of the continuing surveillance of TAXOL safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

**Neurologic:** The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy.

The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34–51% from course 2 to 10.

Peripheral neuropathy was the cause of TAXOL discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of TAXOL discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for TAXOL therapy. In patients with NSCLC, administration of TAXOL followed by cisplatin resulted in greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent TAXOL. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving TAXOL 135 mg/m² by 24-hour infusion followed by cisplatin 75 mg/m² and 8% of NSCLC patients receiving cisplatin/etoposide (see Table 12).

Other than peripheral neuropathy, serious neurologic events following TAXOL administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia and neuroencephalopathy.

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of TAXOL safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

**Arthralgia/Myalgia:** There was no consistent relationship between dose or schedule of TAXOL and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after TAXOL administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

**Hepatic:** No relationship was observed between liver function abnormalities and either dose or schedule of TAXOL administration. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to TAXOL was not associated with cumulative hepatic toxicity.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of TAXOL safety.

**Renal:** Among the patients treated for Kaposi's sarcoma with TAXOL, five patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other four patients had renal insufficiency with reversible elevations of serum creatinine.

**Gastrointestinal (GI):** Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

In patients with poor-risk AIDS-related Kaposi's sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79%, and 28% of patients, respectively. One third of patients with Kaposi's sarcoma complained of diarrhea prior to study start. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section.)

In the first-line Phase 3 ovarian carcinoma study, the incidence of nausea and vomiting when TAXOL was administered in combination with cisplatin appeared to be greater compared with the database for single-agent TAXOL in ovarian and breast carcinoma. In the same study, diarrhea of any grade was reported more frequently (16%) compared to the control arm (8%) (p=0.008), but there was no difference for severe diarrhea.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of TAXOL safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with TAXOL alone and in combination with other chemotherapeutic agents.

**Injection Site Reaction:** Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

**Other Clinical Events:** Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to TAXOL-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with TAXOL administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash and pruritus have been received as part of the continuing surveillance of TAXOL safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of TAXOL safety. In the Phase 3 trial of TAXOL 135 mg/m² over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/cisplatin.

**Accidental Exposure:** Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

## OVERDOSAGE

There is no known antidote for TAXOL overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (see **PRECAUTIONS: Pediatric Use** section).

## DOSAGE AND ADMINISTRATION

Note: 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 TAXOL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to TAXOL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before TAXOL, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to TAXOL, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before TAXOL.

For patients with **carcinoma of the ovary**, the following regimens are recommended:

1) For previously untreated patients with carcinoma of the ovary, the recommended regimen, given every 3 weeks, is TAXOL administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin at a dose of 75 mg/m².
2) In patients previously treated with chemotherapy for carcinoma of the ovary, TAXOL has been used at several doses and schedules; however, the optimal regimen is not yet clear (see **CLINICAL STUDIES: Ovarian Carcinoma** section). The recommended regimen is TAXOL 135 mg/m² or 175 mg/m² administered intravenously over 3 hours every 3 weeks.

For patients with **carcinoma of the breast**, TAXOL at a dose of 175 mg/m² administered intravenously over 3 hours every 3 weeks has been shown to be effective after failure of chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. (See **CLINICAL STUDIES: Breast Carcinoma** section.)

For patients with **non-small cell lung carcinoma**, the recommended regimen, given every 3 weeks, is TAXOL administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin, 75 mg/m².

For patients with **AIDS-related Kaposi's sarcoma**, TAXOL administered at a dose of 135 mg/m² given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m² given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m²/week). In the two clinical trials evaluating these schedules (see **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma** section), the former schedule (135 mg/m² every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m² every 2 weeks).

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

1) Reduce the dose of dexamethasone as one of the three premedication drugs to 10 mg PO (instead of 20 mg PO);
2) Initiate or repeat treatment with TAXOL only if the neutrophil count is at least 1000 cells/mm³;
3) Reduce the dose of subsequent courses of TAXOL by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer); and
4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of TAXOL should not be repeated until the neutrophil count is at least 1500 cells/mm³ and the platelet count is at least 100,000 cells/mm³. TAXOL should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm³. Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe peripheral neuropathy during TAXOL therapy should have dosage reduced by 20%

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### Preparation and Administration Precautions

TAXOL is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling TAXOL. The use of gloves is recommended. If TAXOL solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If TAXOL contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see **PRECAUTIONS: Injection Site Reaction** section).

### Preparation for Intravenous Administration

TAXOL (paclitaxel) injection must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through I.V. tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. TAXOL solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of TAXOL since they can cause the stopper to collapse resulting in loss of sterile integrity of the TAXOL solution.

### Stability

Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25°C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

## HOW SUPPLIED

| | |
|---|---|
| NDC 0015-3475-30 | 30 mg/5 mL multidose vial individually packaged in a carton. |
| NDC 0015-3476-30 | 100 mg/16.7 mL multidose vial individually packaged in a carton. |
| NDC 0015-3479-11 | 300 mg/50 mL multidose vial individually packaged in a carton. |

### Storage

Store the vials in original cartons between 20°–25° C (68°–77° F). Retain in the original package to protect from light.

### Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

## REFERENCES


1 Recommendations for the safe handling of parenteral antineoplastic drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2 AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253 (11): 1590-1592.
3 National Study Commission on Cytotoxic Exposure — Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4 Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983; 1:426-428.
5 Jones RB, et al: Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept./Oct. 258-263.
6 American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.
7 Controlling occupational exposure to hazardous drugs. (OSHA WORK-PRACTICE GUIDELINES.) Am J Health-Syst Pharm 1996; 53:1669-1685.


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IVEX-2® is the registered trademark of the Millipore Corporation.
Chemo Dispensing Pin™ is a trademark of B. Braun Medical Incorporated.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20262/S031

## CORRESPONDENCE

114.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-262/S-031

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

DEC 23 1998

Attention: Susan H. Behling, Director
Worldwide Regulatory Affairs

Dear Ms. Behling:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Taxol (paclitaxel) Injection

NDA Number: 20-262

Supplement Number: 031

Date of Supplement: December 18, 1998

Date of Receipt: December 21, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 19, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

/S/

12-23-98

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-262/031
HFD-150/Div. Files
HFD-150/CSO/Ms. Leslie Vaccari 12-23-98

filename: C:\WPWIN61\TEMPLATE\FDA\20262S31.WPD

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, 314 & 601)*

*Form Approved: OMB No. 0910-0338*
*Expiration Date: April 30, 2000*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Bristol-Myers Squibb Company | December 18, 1998 |
| **TELEPHONE NO.** *(Include Area Code)* 203-677-7593 | **FACSIMILE (FAX) Number** *(Include Area Code)* 203-677-7867 |

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

5 Research Parkway
Wallingford, CT 06492

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-262 - S-024

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Paclitaxel | Taxol® (paclitaxel) Injection |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 5ß,20-Epoxy-1,2alpha,4,7ß,10ß,13alpha-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine

CODE NAME *(If any)* NSC-125973, Taxol A BMS-181339-01, BMY-45622

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Nonaqueous solution for dilution | 30mg/5ml vials | I.V. Infusion |

(PROPOSED) INDICATION(S) FOR USE:

Treatment of advanced Non-small Cell Lung Cancer

## APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

BMS IND

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☒ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| | 7. Clinical Microbioblogy (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| | 12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| | 19. OTHER (Specify) |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Susan H Behling | Susan H. Behling, Director<br>Worldwide Regulatory Affairs | Dec. 18, 1998 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 5 Research Parkway, Wallingford, CT 06492 | (203 ) 677-7593 |

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**FORM FDA 356h (7/97)**

Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

ORIGINAL

NDA SUPP AMENDMENT
SE1-024 (FA)

NDA NO. 20-262 REF NO. 031
NDA SUPPL FOR SLR

December 18, 1998

FINAL PRINTED LABELING


TAXOL® NDA#20-262 (paclitaxel) Injection

Robert L. Justice, M.D., Acting Director
Division of Oncology Drug Products-HFD 150
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Dear Dr. Justice:

In reference to our supplemental new drug application (S-024) for TAXOL® for the treatment of patients with non-small cell lung cancer, enclosed please find final printed labeling (FPL) for your review and approval. This FPL reflects the revisions to the Division's June 30, 1998 draft labeling that were discussed and agreed upon during our meeting with Division personnel on October 6, 1998, as well as subsequent revisions included in the labeling submitted in Word format on November 16, 1998. The Division's acceptance of the November 16, 1998 proposal was communicated to BMS via facsimile on December 7, 1998. The two minor editorial changes noted in the December 7 correspondence have also been addressed in this FPL.

We look forward to your approval of this final labeling so that we may proceed with our plans to market this product for this indication. If you have any questions or concerns, please call me at 203-677-7593.

Sincerely,

Susan H. Behling

Susan H. Behling, Director
Worldwide Regulatory Affairs

/Enclosures (20 copies of FPL /10 of which are individually mounted)

Desk Copy: Ms. Leslie Vaccari, Special Assistant to the Director, Oncology Division