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The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA has also observed that accepted medical practice includes drug use that is not reflected in approved drug labeling. For products that do not have official package circulars, the publisher has emphasized the necessity of describing such products comprehensively, so that physicians can have access to all information essential for intelligent and informed decision making.

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**Key Efficacy Parameters in the Phase 3 Ovarian Carcinoma Study**

- **Response rate** (percent): 19.0% (18.0 - 20.1%)
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- **Median time to progression** (months): 7.6 (1.8 - 34.5)
- **Median time to severe hypersensitivity reactions (HSRs)**: 3.4 (2.8 - 4.2) months
- **Overall survival rate** (patients receiving ≥3 courses): 81.0% (68.2 - 89.1%)
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**CLINICAL STUDIES**

**Ovarian Carcinoma**

- Data from five Phase 1 and 2 clinical studies (189 patients) with 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 to support the use of TAXOL in patients with ovarian carcinoma. The overall response rate for four arms was 16.2% (95% CI: 12.8 - 20.2%), with 6 complete and 6 partial responses. Duration of response, measured from the first day of treatment, was 8.1 months (range: 3.5 - 14.6 months).

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a phase 3 randomized study were available to support the use of TAxOL in patients with metastatic breast cancers.

Phase 3 randomized studies were conducted in 53 patients previously treated with a maximum of 1 prior chemotherapy regimen. TAxOL was administered in these studies at a dose of 135 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response rates were 57% (95% CI: 37-75%) and 52% (95% CI: 32-72%), respectively. The third phase 2 study evaluated quality of life changes and was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 3 chemotherapy regimens for the treatment of metastatic disease. The dose of TAxOL was 200 mg/m^2 as a 24-hour infusion with G-CSF support. Nine of the 50 patients randomized to re-dosen received symptomatic disease with impaired performance status setting. Tbe overall response rate for the study was 87%.

Response rates, median survival and median time to progression for the 2 arms are given in the following table. The arms are listed by dose and schedule (mg/m^2/hours). [See second table at right.]

For the 458 patients who received TAxOL (paclitaxel) for Injection Concentrate in the Phase 3 study, the following table shows the incidence of some key adverse events by treatment arm (each arm was administered by a 3-hour infusion). [See third table at right.]

Myelosuppression and peripheral neuropathy were dose related. TAxOL was shown to be a severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

INDICATIONS
TAXOL is indicated, after failure of first-line or subsequent chemotherapy, for the treatment of metastatic carcinoma of the ovary.

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.

CONTRAINDICATIONS
TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor® EL (polyoxylated castor oil). TAXOL should not be used in patients with baseline neutropenia of <1,500 cells/mm^3.

WARNINGs
Patients should be pretreated with corticosteroids (such as dexamethasone), diphenhydramine and H<sub>2</sub> antagonists (such as cimetidine or ranitidine) before receiving TAxOL. [See "DOSEAGE AND ADMINISTRATION" section.] Severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and general edematous urticaria have occurred in 2% of patients receiving TAxOL. These reactions are probably histamine-mediated. One of these reactions occurred in a patient with pulmonary metastases who was a participant in a Phase I trial. This patient received no premedication; the dose of TAxOL, which was administered at 150 mg/m^2 infused over three hours. Within a few minutes from the beginning of a second course of TAxOL, the patient developed dyspnea, wheezing, and died. 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 1,500 cells/mm^3. 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 > 5,000 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. 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.

TAXOL may cause fetal harm when administered to a pregnant woman. TAxOL has been shown to be embryotoxic and fetotoxic in rats and rabbits and to decrease fertility in rats. TAxOL, when administered in the first trimester of pregnancy, has been shown to induce abortions, decrease body weight, increase fetal resorptions and decrease fetal body weight. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with TAxOL.

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 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 interaction: In a Phase I trial using escalating doses of TAxOL (110-200 mg/m^2) and cisplatin (50 or 75 mg/m^2) 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 38% when TAxOL was administered following cisplatin.

Based on in vitro data, there is the possibility of an inhibition of TAxOL metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with TAxOL when they are receiving ketoconazole as concomitant therapy.

Hematology: TAxOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelosuppression, it is recommended that frequent peripheral blood cell
Counts were performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophil recover to a level > 1,500 cells/mm³, and platelet 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.

Hypersensitivity reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g., cyclosporin for injection concentrate and thalidomide 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 pretreated with corticosteroids (such as prednisolone or prednisone). Minor symptoms such as flushing, skin reaction, urticaria or bronchospasm do not require interruption of therapy. However, severe reactions, such as hypodermic requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with TAXOL.

Cardiovascular: Hypotension and bradycardia have been observed during administration of TAXOL, but generally do not require treatment. Frequent vital sign monitoring, particularly during the first 3 hours 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 sympotmology is unusual and requires a dose reduction of 20% for all subsequent courses of TAXOL.

Hepatic: There is no evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes, but no data are available for patients with severe baseline cholestasis. However, evidence suggests that the liver plays an important role in the metabolism of TAXOL. As a result, since there are no data available from patients with severe liver disease, caution should be exercised when administering TAXOL to patients with severe hepatic impairment.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of TAXOL has not been studied. TAXOL has been shown to be mutagenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micro-nucleus test in mice); mammalian test systems, however, did not induce mutagenicity in the Ames test or the CHO/HPRT gene mutation assay. TAXOL at an iv. dose of 1 mg/kg produced low fertility and fetal toxicity in rats. TAXOL has also been shown to be maternal and embryotoxic in rabbits receiving the drug at an iv. dose of 3 mg/kg (33 mg/m²) during organogenesis. Some aberrations in human lymphocytes have also been noted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Caution should be exercised when administering TAXOL to patients with serious conduction abnormalities. (See "WARNINGS" section.)

Nursing Mothers: It is not known whether the drug is excreted in breast milk. 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 while receiving TAXOL therapy.

Pediatric Use: The safety and effectiveness of TAXOL in children have not been established.

ADVERSE REACTIONS

Data in the following table are based on the experience of 812 patients (603 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies. Two hundred and seventy-five patients were treated in 8 Phase II studies with TAXOL, ranging from 135 to 300 mg/m² administered over 24 hours in 4 of these studies; G-CSF was administered as hematologic support. Three hundred and one patients were treated in the randomized Phase III 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 either 3 or 24 hours in a controlled study. [See table above.]

The following table relates to the overall safety database of 812 patients treated in clinical studies. In addition, relevant events have been reported from the postmarketing experience of other courses of TAXOL.

The frequency and severity of adverse events are generally similar between patients receiving TAXOL for the treatment of ovarian or breast carcinoma. The frequency and severity of key adverse events for the Phase 3 ovarian and breast carcinoma studies are tabulated in tabular form by treatment arm in "CLINICAL PHARMACOLOGY", "Clinical Studies" section.

Hematologic: Bone marrow suppression was the most frequent 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 Phase 3 ovarian study with a 3-hour infusion, neutrophil counts decline below 500 cells/mm³ in 13% of the patients treated with a dose of 135mg/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 or more severe for patients previously treated with radiation therapy.

In Phase 3 ovarian study, infectious episodes were reported in 19% of the patients given either 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. Thrombocytopenia was uncommon, and almost never severe. 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. Among the 812 patients, 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 ovarian study, bleeding episodes were reported in 10% of patients and 20% of the patients receiving either the 135 or 175 mg/m² dose given by a 3-hour infusion; no patients treated with the 3-hour infusion received platelet transfusions. Anemia (Hb < 10 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 and 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 2% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSR): All patients received predemedication prior to TAXOL. (See "WARNINGS" and "WARNINGS, Hypersensitivity Reactions" sections). The frequency and severity of HSRs were not affected by the dose or schedule of TAXOL administration. In the Phase 3 ovarian study the 3-hour infusion was not associated with a greater increase in HSRe 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 3% 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 (paclitaxel) for injection Concentrate infusion. The most frequent symptoms observed during these severe reactions were dyspnea, 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.

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 Phase 3 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 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.

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 25% 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 ECG at baseline,
therapy with anthracyclines did not influence the frequency of BOC abnormalities.

The number and severity of neurologic mani-
sf ections were dose-dependent, but were not influenced by duration. Peripheral neuropathy was observed in 30% of patients (8%), and 2% in 50% of patients without pre-existing neuropathy.

The frequency of peripheral neuropathy increased with cu-
lcumulative dose and the number of courses of neurologic symptoms did increase in the subset of patients previously treated with taxol. Pre-existing neuropathies resulting from prior therapy are not a contraindication for TAXOL therapy.

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

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of TAXOL safety.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of TAXOL and the frequency or severity of arthralgia/myalgia. Arthralgia/myalgia is a common complication of therapy with anthracyclines and did not increase with dose. Arthralgia/myalgia was noted more frequently in patients without pre-existing neuropathy. Arthralgia/myalgia, seen in 30% of patients (12%), and 3% in 50% of patients without pre-existing neuropathy.

Skin Abnormalities: Skin reactions secondary to extravasation, were usually mild and may be resolved more frequently with 3-hour than with 24-hour infusion bags or sets, only 1% had severe edema and 1% of the patients. Transient skin changes due to TAXOL were observed in 87% of the patients. Transient skin changes due to TAXOL no other skin toxicities were significantly associated with TAXOL. These reactions have been served more frequently with 3-hour than with 24-hour bags or sets. Only 1% had severe edema and 1% of the patients.

TAXOL should not be repeated until the neutrophil count is at least 1,500 cells/mm³ and the platelet count remains 50,000 cells/mm³.

Preparation for Intravenous Administration: TAXOL for Injections Concentrate must be diluted prior to infusion. The solutions are physically and chemically stable for up to 27 hours.

REFERENCES


34560DM-O7


TAXOL®

Inactive ingredients: calcium stearate, cornstarch, gelatin, and lactose. Testolactone is a white, odorless, crystalline solid, soluble in ethanol and slightly soluble in water.

CLINICAL PHARMACOLOGY

The precise mechanism by which testolactone produces its clinical antineoplastic effects has not been established. Its principal action is reported to be the inhibition of tubular reabsoption of calcium but to have no effect on serum calcium concentration. The mechanism of the hypocalcic effect is unknown. No clinical effects of testolactone on renal adenaleens have been observed in in vitro studies, and the aromatic inhibition may be noncompetitive and irreversible. This phenomenon may account for the persistence of testolactone's effect on estrogen synthesis after drug withdrawal.

Despite some similarity to testosterone, testolactone has no in vivo anabolic effect. No clinical effects of testolactone have been reported in clinical studies in patients receiving testolactone. In a study, testolactone administered orally (1000 mg) was reported to inhibit renal tubular reabsoption of calcium and some unmetabolized drug, are excreted in the urine. Based on in vitro studies, the aromatase inhibition may be noncompetitive and irreversible. This phenomenon may account for the persistence of testolactone's effect on estrogen synthesis after drug withdrawal.

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