PRODUCT IDENTIFICATION GUIDE

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A phase 3 randomized study were available to support the use of TAXOL in patients with metastatic breast carcinoma. Phase 3 open label studies: Two studies were conducted in 33 patients previously treated with a maximum of one prior chemotherapy regimen. TAXOL was administered in these trials as a 24 hour infusion at initial doses of 225 mg/m² (with G-CSF support) or 200 mg/m². The response rate was 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 2 chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL, 200 mg/m² as a 24-hour infusion with G-CSF support. None of the 30 patients achieved a partial response, for a response rate of 30% (95% CI: 15-50%).

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 at a dose of either 150 mg/m² or 200 mg/m² given as a 3-hour infusion. In the 471 patients enrolled, 66% had symptomatic disease with impaired performance status. At study entry, 75% had visceral disease. Thirty-seven percent of the 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 22% (95% CI: 22-30%), with 17 complete and 89 partial responses. The median duration of response, measured from the first day of treatment, was 4.1 months (range: 1.4-18.1 + 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. The arms were listed by dose and schedule (mg/m²/hours). (See second table at right.) For the 458 patients who received TAXOL (paclitaxel) for the treatment arm (each arm was administered by a 3-hour infusion). (See third table at right.) Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

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 (polyoxyethylated castor oil). TAXOL should not be used in patients with baseline neutropenia of <1,500 cells/mm³.

WARNINGS
Patients should be pretreated with corticosteroids (such as cimetidine or ranitidine) before receiving TAXOL. These reactions are probably histamine-mediated. Patients should be pretreated with corticosteroids (such as cimetidine or ranitidine) before receiving TAXOL. There was one severe hypersensitivity reaction to TAXOL.
counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophil recovery to a level > 1,500 cells/mm³ and platelet recovery 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) should not receive TAXOL. Patients previously treated with TAXOL should be premedicated with corticosteroids (such as desamethasone), diphenhydramine and H₂ antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require treatment. Therapy with TAXOL may be resumed. Severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of TAXOL and gavenous symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged 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 infusion, should be 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.

**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 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 (micronucleus test in bone marrow). However, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. TAXOL at an I.V. dose of 1 mg/kg (6 mg/m²) produced low fertility and fetal toxicity in rats. TAXOL has also been shown to be maternal and embryofetal toxic to rabbits receiving the drug at an I.V. dose of 3 mg/kg (18 mg/m²) during organogenesis. (See "WARNINGS," section.)

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

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued during 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 (483 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies. Two hundred and seventy-five patients were treated in 8 Phase 2 studies with TAXOL doses ranging from 135 to 500 mg/m² administered over 24 hours in 4 of these studies, G-CSF was administered as hematopoietic support. The Phase 3 system, however, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. TAXOL at an I.V. dose of 1 mg/kg (6 mg/m²) produced low fertility and fetal toxicity in rats. TAXOL has also been shown to be maternal and embryofetal toxic to rabbits receiving the drug at an I.V. dose of 3 mg/kg (18 mg/m²) during organogenesis. (See "WARNINGS," section.)

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

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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 administration. IV 5% dextrose in 0.9% saline IV at a dose of 175 mg/m2 administered intravenously over 3 hours every three weeks. Courses of TAXOL should have dose reductions 20% for subsequent courses of TAXOL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: TAXOL is a cytotoxic anticancer drug and, as with other potentially toxic substances, 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. If TAXOL contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation for Intravenous Administration: TAXOL for Injection Concentrate must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection USP, 5% Dextrose Injection USP, or 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 solution is 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 coloration 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 IV 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 solutions are prepared in PVC or polyolefin. Complete information is not available for all containers and administration sets. TAXOL solutions should be prepared and stored in glass, plastic or polyolefin containers. The preparation of polyolefin containers and administration sets, such as those which are polyethylene lined, should be used.

TAXOL is to be administered through an in-line filter with a microcopolous membrane not greater than 0.22 micron. Use of filter devices such as IVEX 200 filters which incorporate short inlet and outlet filters has not resulted in significant leaching of DEHP.

Stability: Unopened vials of TAXOL (pamlaxel) for injection Concentrate are stable until the date indicated on the package when stored under refrigeration, 2°C–8°C (36°F–46°F), in the original package. Freezing does not adversely affect the product. Upon refrigeration concentrations in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on drug activity. This does not affect the expiration date. The vial remains cloudy if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended above should be stable at refrigerator temperature (approximately 5°C–10°C) and light conditions for up to 24 hours.

HOW SUPPLIED

NDC 0013-3456-20 30 mg/mL single-dose vial individually packaged in a carton.

NDC 0013-3456-99 30 mg/5 mL single-dose vial individually packaged on a roll. TAXOL should be administered to patients who have not previously been treated with this regimen. TAXOL solutions should be prepared in the manner recommended in the guidelines are necessary or indicated. In the event of extravasation, it is recommended to refill the vial of TAXOL, and/or change the administration set. This product does not meet USP requirements. Testolactone exceeds USP Organic Volatile Impurities (OV) Limit for Methylene Chloride. The USP limit for Methylene Chloride is 105 ppm. Testolactone normally contains 1,000 ppm.

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. Dose alteration in patients previously exposed to the plasticizer DEHP [di(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, dilute to 1:1000 with 0.9% saline (physiologic saline, polypropylene) or plastic bags (polypropylene, polyethylene) and administered through polyethylene-lined administration sets.

REFERENCES


4. National Study Commission on Cytotoxic Exposure—Recommendations for handling cytotoxic agents. Available by post from Mr. Louis P. Ferraro, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences. 179 Longwood Avenue, Boston, MA 02215.


