

# ONXOL™

(paclitaxel) Injection  
Rx only

## WARNING

ONXOL™ (paclitaxel) Injection 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.

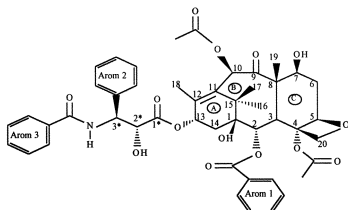
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients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

ONXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup> and should not be used in patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1,000 cells/mm<sup>3</sup>. 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 ONXOL.

## DESCRIPTION

ONXOL™ (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. ONXOL is available in 30 mg (5mL), 150 mg (25mL) and 300 mg (50mL) multiple dose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of polyoxyl 35 castor oil, NF, 2 mg citric acid anhydrous and 49.7% (w/v) dehydrated alcohol, USP.

Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via an extractive process from *Taxus brevifolia* or *Taxus yunnanensis*. The chemical name for paclitaxel is (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclohexa [3,4] benz [1,2-c] oxet-5-one-6,12b-diacetate, 12-benzoate, 9-ester with (2R,3S)-N-benzyloxy-3-phenylisoserine. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula C<sub>47</sub>H<sub>53</sub>NO<sub>14</sub> and a molecular weight of 853.93. 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 paclitaxel, 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 paclitaxel at dose levels of 135 and 175 mg/m<sup>2</sup> were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

DOSE (mg/m <sup>2</sup> )	INFUSION DURATION (h)	N (patients)	C <sub>MAX</sub> (ng/mL)	AUC (0-∞) (ng·h/mL)	T-HALF (h)	CL <sub>T</sub> (L/h/m <sup>2</sup> )
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.1	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C<sub>MAX</sub> = Maximum plasma concentration  
AUC (0-∞) = Area under the plasma concentration - time curve from time 0 to infinity  
CL<sub>T</sub> = Total body clearance

It appeared that with the 24 hour infusion of paclitaxel, a 30% increase in dose (135 mg/m<sup>2</sup> versus 175 mg/m<sup>2</sup>) increased the C<sub>MAX</sub> by 87%, whereas the AUC(0-∞) remained proportional. However, with a 3 hour infusion, for a 30% increase in dose, the C<sub>MAX</sub> 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 paclitaxel, ranged from 227 to 688 L/m<sup>2</sup>, 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 to 135 mg/m<sup>2</sup> given by 1 hour infusions (N=15), 30 to 275 mg/m<sup>2</sup> given by 6 hour infusions (N=36), and 200 to 275 mg/m<sup>2</sup> given by 24 hour infusions (N=54) in Phase 1 & 2 studies. Values for CL<sub>T</sub> and volume of distribution were consistent with the findings in the Phase 3 study.

*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 bound; the presence of cimetidine, ranitidine, dexmethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m<sup>2</sup> doses of paclitaxel 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 5 patients administered a 225 or 250 mg/m<sup>2</sup> dose of radio-labeled paclitaxel 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 6-oxo-, 3'-p-dihydroxypaclitaxel by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketorolac, verapamil, diazepam, quinidine, dexmethasone, 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: 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 paclitaxel 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/m<sup>2</sup> 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 six 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 to 15.8 months) and 7.5 months (range: 5.3 to 17.4 months), respectively. The median survival was 8.1 months (range: 0.2 to 36.7 months) and 15.9 months (range: 1.8 to 34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of paclitaxel, administered at two different doses (135 or 175 mg/m<sup>2</sup>) 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 to 21.6 months). Median time to progression was 3.7 months (range: 0.1+ to 25.1+ months). Median survival was 11.3 months (range: 0.2 to 26.3+ months).

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

	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)	(11.1 - 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/m<sup>2</sup>) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m<sup>2</sup> dose had a response rate similar to that of those receiving the 135 mg/m<sup>2</sup> 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/m<sup>2</sup> dose of paclitaxel had a longer time to progression than those receiving the 135 mg/m<sup>2</sup> 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/m<sup>2</sup> dose of paclitaxel and 11.0 months in patients receiving the 135 mg/m<sup>2</sup> dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of paclitaxel 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.

Paclitaxel 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 ten 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 4 & 5) and narrative form.

The results of the randomized study support the use of paclitaxel injection at doses of 135 to 175 mg/m<sup>2</sup>, 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: After Failure of Initial Chemotherapy:** 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 paclitaxel 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. Paclitaxel was administered in these 2 trials as a 24 hour infusion at initial doses of 250 mg/m<sup>2</sup> (with G-CSF support) or 200 mg/m<sup>2</sup>. The response rates were 57% (95% CI: 37% - 75%) and 52% (95% CI: 32% - 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 2 chemotherapy regimens for the treatment of metastatic disease. The dose of paclitaxel was 200 mg/m<sup>2</sup> 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% - 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 paclitaxel at a dose of either 175 mg/m<sup>2</sup> or 135 mg/m<sup>2</sup> 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% - 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: 0.1 - 18.9 months).

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

	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 paclitaxel 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 4 & 6) and narrative form.

## INDICATIONS AND USAGE

ONXOL is indicated as subsequent therapy for the treatment of advanced carcinoma of the ovary.

ONXOL 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

ONXOL is contraindicated in patients who have a history of hypersensitivity reactions to ONXOL or other drugs formulated in polyoxyl 35 castor oil.

ONXOL should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm<sup>3</sup> or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1,000 cells/mm<sup>3</sup>.

## 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 paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine and H<sub>2</sub> antagonists. (See "DOSAGE AND ADMINISTRATION" section). Patients who experience severe hypersensitivity reactions to ONXOL 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. ONXOL should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup> (<1,000 cells/mm<sup>3</sup> for patients with KS). Frequent monitoring of blood counts should be instituted during ONXOL treatment. Patients should not be re-treated with subsequent cycles of ONXOL until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> (>1,000 cells/mm<sup>3</sup> for patients with KS) and platelets recover to a level >100,000 cells/mm<sup>3</sup>.

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

**Pregnancy:** ONXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m<sup>2</sup> 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 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m<sup>2</sup> 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 ONXOL 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

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

ONXOL 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 1 trial using escalating doses of paclitaxel (110 to 200 mg/m<sup>2</sup>) and cisplatin (50 or 75 mg/m<sup>2</sup>) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e. paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel injection was administered following cisplatin.

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

Potential interactions between ONXOL, 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:** ONXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ONXOL. Patients should not be re-treated with subsequent cycles of ONXOL until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> and platelets recover to a level >100,000 cells/mm<sup>3</sup>. In the case of severe neutropenia (<500 cells/mm<sup>3</sup> for seven days or more) during a course of ONXOL 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 polyoxyl 35 castor oil, (e.g. cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with ONXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with ONXOL should be premedicated with corticosteroids (such as dexmethasone), diphenhydramine and H<sub>2</sub> 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 ONXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with ONXOL.

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