

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 paclitaxel 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 paclitaxel related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel 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 paclitaxel safety. Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.

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 ONXOL overdose. The primary anticipated complications of overdose 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 ONXOL 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 ONXOL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before ONXOL, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to ONXOL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before ONXOL.

For patients with **carcinoma of the ovary**, the following regimen is recommended: In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel 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 paclitaxel 135 mg/m² or 175 mg/m² administered intravenously over three hours every three weeks.

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

For the therapy of patients with solid tumors (ovary and breast), courses of ONXOL should not be repeated until the neutrophil count is at least 1,500 cells/mm³ and the platelet count is at least 100,000 cells/mm³. Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe peripheral neuropathy during ONXOL (paclitaxel) Injection therapy should have dosage reduced by 20% for subsequent courses of ONXOL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: ONXOL is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling ONXOL. The use of gloves is recommended. If ONXOL 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 ONXOL 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: ONXOL must be diluted prior to infusion. ONXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, 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 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 dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. ONXOL 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.

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.

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

Stability: Unopened vials of ONXOL (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 ONXOL 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 0172-3754-73 ONXOL (paclitaxel) Injection is available as a 30 mg/5 mL multi-dose vial individually packaged in a carton.

NDC 0172-3756-75 ONXOL (paclitaxel) Injection is available as a 150 mg/25 mL multi-dose vial individually packaged in a carton.

NDC 0172-3753-77 ONXOL (paclitaxel) Injection is available as a 300 mg/50 mL multi-dose 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 published¹⁻⁷. 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 of Hazardous Drugs (OSHA WORK-PRACTICE GUIDELINES). Am J Health -Syst-Pharm 1996; 53:1669-1685.

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ovarian cancer and non-small cell lung cancer. It has also been approved for use in head and neck cancer patients undergoing radiation therapy. In this patient population, Ethyol has been demonstrated to limit the degree of xerostomia (dry mouth), an often severe and irreversible side effect of radiation therapy caused by damage to the salivary glands. MedImmune has also dedicated additional research and clinical resources to evaluate new opportunities for the product, including subcutaneous administration and the reduction of mucositis in lung cancer patients.

MedImmune, Inc. is a biotechnology company focused on developing and marketing products that address medical needs in areas such as infectious disease, immune regulation and cancer. Headquartered in Gaithersburg, Maryland, MedImmune has manufacturing facilities in Frederick, Maryland and Nijmegen, the Netherlands.



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