Ontaxel

Injection

DRUG INTERNATIONAL LTD.

Composition:

Ontaxel 30 IV Injection: Each vial contains 5ml solution containing Paclitaxel USP 30 mg (6 mg/ml).

Ontaxel 100 IV Injection: Each vial contains 16.7ml solution containing Paclitaxel USP 100 mg (6 mg/ml).

Ontaxel 300 IV Injection: Each vial contains 50ml solution containing Paclitaxel USP 300 mg (6 mg/ml).

PHARMACOLOGICAL INFORMATION : Ontaxel (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.

Mechanism of action : Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

PHARMACOKINETIC PROPERTIES

Distribution: Widely distributed into body fluids and tissues; affected by dose and duration of infusion one average, 89% of drugs is bound to serum protiens and the men apparant volume of distribution at steady state,with 1 to 6 hours infusion: 67.1 Lm^2 and with the 24 hours infusion of Ontaxel 30, ranged from 227-&;8 Lm^2

Protein binding : 89% to 98%.

Metabolism : Hepatic v/a CYP2C8/9 and 3A4; forms metabolites

Half-life elimination : 1- to 6-hour infusion: Mean (beta) : 6.4 hours

3-hour infusion: Mean (terminal): 13.1-20.2 hours

24-hour infusion: Mean (terminal): 15.7-52.7 hours

Excretion : Feces (~70%, ≤5% as unchanged drug); urine (14%)

Clearance : Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 Uhour/m^2; After 24-hour infusions: 14.2-17.2 L/hour/m^2

CLINICAL INFORMATION : Therapeutic Indications

Ovarian Carcinoma : Ontaxel is indicated as first line and subsequent therapy for the treatment of advanced carcinoma of the ovary.As first line therapy,Ontaxel is indicated in combination with cisplatin. **Breast carcinoma :** Ontaxel is indicated for the adjuvant treatment of node positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. Ontaxel 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 anthracline unless clinically contraindicated. Ontaxel is indicated for the first line therapy of advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracline therapy is suitable or in combination with trastuzumab in patients who over express HER-2 at a 2+ or 3+ level as determined by immunohistochemistry. Gemoxen, in combination of Ontaxel .is indicated in the treatment of patients with unresectable,locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated. Ontaxel is indicated for the treatment of metastatic cancer of the breast,in combination with trastuzumab (Herceptin), in patients who have tumors that over-express HER-2 and who have not received previous chemotherapy for their metastatic disease. **Non Small Cell Lung Carcinoma :** Ontaxel, in combination with cisplatin, is indicated for the first line treatment of non small cell lung cancer in patients who are not candidates for potential curative surgery and/or radiation therapy. **Kaposi's Saocoma :** Ontaxel is indicated for the second line treatment of AIDS related Kaposi's Sarcoma. **Gastric Carcinoma :** Ontaxel is indicated for the treatment of Gastric Carcinoma

Dosage & 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 Ontaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Nonpolyvinyl (non-PVC) administration sets (which are polyethylene-lined) should be used. Paclitaxel should be administered through IV tubing containing an in-line filter (with a microporous membrane NOT >0.22u). Use of filter devices such as IVEX-2 filters (which incorporate short inlet and outlet polyvinyl chloride-coated tubing) has not resulted in significant leaching of DEHP.

Premedication : All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of: - Dexamethasone 20 mg PO or 8 mg IV administered approximately 12 and 6 hours prior. Diphenhydramine 50 mg (or its equivalent-Promethazine HCl 25 mg) IV. 30 - 60 minutes prior. Cimetidine (300 mg) or ranitidine (50 mg) IV 30 - 60 minutes prior.

Special Instruction for Uses, Handling and Disposal : Ontaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Ontaxel. The use of gloves is recommended. If Ontaxel 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 Ontaxel 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 extravasations, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. All broken containers must be treated with the same precautions and regarded as contaminated waste. Contaminated waste is to be disposed of by incineration in rigid containers labeled for this purpose or must be destroyed as per the government rule.

Preparation for Intravenous Administration : Ontaxel must be diluted prior to infusion. Ontaxel 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. Ontaxel 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. Ontaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

Intravenous infusion and dosage : Ovarian Cancer First line treatment in combination with cisplatin : Ontaxel administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2 every 3 weeks Ontaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2 every 3 weeks In patients previously treated with chemotherapy for carcinoma of the ovary, Ontaxel has been use at several doses and schedules; however, the optimal regimem is not yet clear. The recommended regimen is Ontaxel (paclitaxel) 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks. **Breast Cancer :** - 175 mg/m^2 administered IV 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. **AIDS-related Kaposi's sarcoma :** - 135 mg/m^2 given IV over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given IV. over 3 hours every 2 weeks is recommended (dose intensity 45-50 mg/ m^2 /week) **Lung cancer :** - For the first-line treatment of NSCLC, in combination with cisplatin, in patients who are not candidates for potentially curative surgery and/or radiation therapy. -135 mg/m^2 IV administered over 24 hours followed by cisplatin. The regimen to be repeated every 3 weeks based on the clinical status of the patient. **Gastric Cancer :** - Once daily 210 mg/m^2 (Body surface area) by 3 hours intravenous infusion for adults. At least 3 week of dosing interval is of absolute necessity.

Dosage modification for toxicity (solid tumors, including ovary, breast, and lung carcinoma) : Courses of Paclitaxel should not be repeated until the neutrophil count is> 1500 cells/mm^3 and the platelet count is> 100,000 cells/mm^3; reduce dosage by 20% for patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer).

Dosage modification for immuno suppression in advanced HIV disease : Paclitaxel should not be given to patients with HIV if the baseline or subsequent neutrophil count is < 1000 cells/mm^3. Additional modifications include: Reduce dosage of dexamethasone in premedication to 10 mg orally; reduce dosage by 20% in patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); initiate concurrent hematopoietic growth factor (G-CSF) as clinically indicated.

Dosage adjustment in hepatic impairment : These recommendations are based upon the patient's first course of therapy where the usual dose would be 135 mg/m^2 dose over 24 hours or the 175 mg/m^2 dose over 3 hours in patients with normal hepatic function. Dosage in subsequent courses should be based upon individual tolerance. Adjustments for other regimens are not available.

Stability : Unopened vials of Ontaxel 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 Ontaxel 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.

Side effects : The frequency and severity of adverse events have been generally similar for patients receiving Paclitaxel for the treatment with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, febrile neutropenia and GI toxicities. Patients require a lower dose intensity and supportive care. **Hematology :** Bone marrow suppression is the major dose-limiting toxicity of Paclitaxel. Neutropenia, the most important hematologic toxicity, is dose and schedule dependent and is generally rapidly reversible. Neutropenia does not appear to increase with cumulative exposure and is neither more frequent nor more severe for patients previously treated with radiation therapy. The use of supportive therapy, including G-CSF, is recommended in case of severe neutropenia.12% of all treatment courses report fever. Thrombocytopenia is uncommon. Anemia (Hb<11 g/dl) is observed in 78% of all patients and is severe (Hb<8 g/dl) in 165 of the cases. No consistent relationship between dose or schedule and the frequency of anemia is observed. **Hypersensitivity Reactions (HSR) :** The frequency and severity of HSRS1S1Wraffected by t~hedule of Paclitaxel administration. These are conserved in 20% of all courses and in 41 % of all patients. The most frequent symptoms observed are dyspnea, Flushing, chest patnllmttachycardia. Rare reports of chills and reports of back pain associated with HSRs have been received. **Cardiovascular :** Hypotension, during the first 3 hours of inclusion, occurs in 12% of all patients and 3% of all courses administered. The frequency of hypotension and bradycardia are not influenced by prior anthracycline therapy, nor by the dose or the schedule. Significant cardiovascular events possibly related to Paclitaxel occur in approximately 1 % of all patients. These events include syncope, rhythm abnormalities, hypertension and venous thrombosis. the arrhythmias include asymptomatic ventricular tachycardia bigeminy and complete AV block requiring pacemaker placements. ECG abnormalities are noted in 23% of the patients. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. **Central Nervous System :** The frequency and severity of neurologic manifestations are dose -dependent, but are not influenced by infusion duration. Peripheral neuropathy is observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency increases with cumulative dose. Neurologic symptoms arte observed in 27% patients after the first course of treatment and in 34-51% from course 2 to 109. Sensory symptoms usually improve or resolve within several months of Paclitaxel discontinuation. The incidence of neurologic symptoms does not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for Paclitaxel therapy. Other serious neurologic events have been rare (>1%) and include grand mal seizures, syncope, ataxia and neuroencephalopathy. Rare reports of reversible autonomic neuropathy resulting in paralytic ileus have also been observed. **Gastrointestinal :** Mild to moderate nausea/vomiting, diarrhea and mucositis are reported by 52%,38% and 31 % of all patients, respectively. Mucositis is schedule dependent and occurs more frequently with the 24-hour than with 3 -hour infusion. Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received. **Kidney/Genitourinary :** Urinary tract infections are frequently reported infectious complications. Among The patients treated for Kaposi's sarcoma with Paclitaxel, renal toxicity of-grade III and IV severity has-been reported. **Liver :** No relationship is observed between liver function abnormalities and either dose or schedule of Paclitaxel 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 Paclitaxel is not associated with cumulative hepatic encephalopathy leading to death have been documented. **Respiratory :** Upper respiratory tract infections do occur. Rare reports of intestinal pneumonia, lung fibrosis and pulmonary embolism have been received. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy. **Musculo-skeletal :** There is no consistent relationship between dose or schedule of Paclitaxel and the frequency or severity of arthralgia/myalgia. 60% of all patients treated experience arthalgia/myalgia, 8% experience severe symptoms. The symptoms are usually transient, occur 2-3 day after Paclitaxel administration and resolve within a few days.The frequently and severity of musculoskeletal symptoms remain unchanged throughout the treatment period. **Injection site reactions :** These include reactions secondary to extravasations, are usually mild and consist of erythema, tenderness, skin discoloration, or swelling at the injection site. These are observed more frequently with the 24-hour infusion than with the 3-hour infusion. Rare reports of more severe events such as phlebitis, cellulitis, indurations, skin exfoliation, necrosis and fibrosis have been documented. It is advisable to closely monitor the infusion site for possible infiltration during drug administration. **Other Clinical Events :** Alopecia is observed in almost all (87%) of the patients. Nail changes are uncommon (2%). Edema has been reported in 21% of all patients. Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash and pruritus have been documented.

Contraindications : Patients with a known hypersensitivity to Paclitaxel or other drugs formulated in Cremophor EL (polyoxyethylated castor oil) - Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of < 1500 cells/mm^3.or.in patients with AIDS- related Kaposi's sarcoma with baseline neutrophil counts of < 1000 cells/ mm^3.

Use in Pregnancy and Lactation: Pregnancy Category D. There is no adequate and well- controlled clinical studies in pregnant or breastfeeding women. It should only be used in pregnant women if the potential benefit justifies the potential risk to the foetus. Since it is not known if Paclitaxel is distributed into milk, the drug should be used with caution in nursing women.

Drug Interactions : Substrate (major) of CYP2C8/9, 3A4; **Induces** CYP3A4. Carboplatin, cisplatin (platinum derivatives): When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives to limit myelosuppression and to enhance efficacy. CYP2C8/9 inducers: May decrease the levels/effects of paditaxel. Example inducers indude carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, and secobarbital. CYP2C8/9 inhibitors: May increase the levels/effects of paditaxel. Example inhibitors indude delavirdine, fluconazole, gemfibrozil, ketoconazole, nicardipine, NSAIDs, pioglitazone, and sulfonamides. CYP3A4 inducers: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Example inducers indude aminoglutethimide, carbamazepine, nafcillin, nevi rapine, phenobarbital, phenytoin, and rifamycins. CYP3A4 inhibitors: May increase the levels/effects of paditaxel. Example inhibitors indude azole antifungals, ciprofloxacin, darithromycin, diclofenac, doxycycline, erythromycin, irnatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, and veraparnil. Doxorubicin: Paclitaxel may increase doxorubicin levels/toxicity.

Overdosage : There is no known antidote for Paclitaxel over dosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Storage: Product should be stored in original cartons between 20°C-25°C in the original package to protect from light.

Packaging:

Ontaxel 30 injection: Each box contains one vial of 5 ml solution containing Paclitaxel USP 30 mg.

Ontaxel 100 injection: Each box contains one vial of 16.7 ml solution containing Paclitaxel USP 100 mg.

Ontaxel 300 injection: Each box contains one vial of 50 ml solution containing Paclitaxel USP 300 mg.