Daxotel Injection

DRUG INTERNATIONAL LTD.

Composition: **Daxotel-20:** Each vial contains Docetaxel Anhydrous USP 20mg/ml.
Daxotel-80: Each vial contains Docetaxel Anhydrous USP 80mg/4ml.

Pharmacology: **Mechanism of Action:** Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use. **Pharmacokinetics: Absorption:** The pharmacokinetics of Docetaxel has been evaluated in cancer patients after administration of 20mg/m2 to 115mg/m2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70mg/m2 to 115mg/m2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the a, b, and g phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m2. **Distribution:** The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of Docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to a 1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of Docetaxel. Metabolism: In vitro drug interaction studies revealed that Docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. **Elimination:** A study of Docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major & 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Indications: **Breast Cancer (BC):** Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Docetaxel in combination with Doxorubicin and Cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer. **Non-small Cell Lung Cancer (NSCLC):** Docetaxel as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Docetaxel in combination with Cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition. **Castration-Resistant Prostate Cancer (CRPC):** Docetaxel in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer. **Gastric Adenocarcinoma (GC):** Docetaxel in combination with Cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. Squamous Cell Carcinoma of the Head and Neck (SCCHN): Docetaxel in combination with Cisplatin & Fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head & neck (SCCHN).

Dosage and Administration: **Breast Cancer:** For locally advanced or metastatic breast cancer after failure of prior chemo therapy, the recommended dose of Docetaxel is 60mg/m2 to 100mg/m2 administered intra venously over 1 hour every 3 weeks. • For the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel dose is 75mg/m2 administered 1 hour after Doxorubicin 50mg/m2 and Cyclophosphamide 500mg/m2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. **Non-small Cell Lung Cancer:** For treatment after failure of prior platinum-based chemotherapy, Docetaxel was evaluated as monotherapy and the recommended dose is 75mg/m2 administered intravenously over 1 hour every 3 weeks. A dose of 100mg/m2 in patients previously treated with chemothera- py was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized controlled trials. • For chemotherapy-naive patients, Docetaxel was evaluated in combination with Cisplatin. The recommended dose of Docetaxel is 75mg/m2 administered intravenously over 1 hour immediately followed by Cisplatin 75mg/m2 over 30-60 minutes every 3 weeks. **Prostate Cancer:** For metastatic castration-resistant prostate cancer, the recommended dose of Docetaxel is 75mg/m2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5mg orally twice daily is administered continuously. **Gastric Adenocarcinoma:** For gastric adenocarcinoma, the recommended dose of Docetaxel is 75mg/m2 as a 1 hour intravenous infusion, followed by Cisplatin 75mg/m2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the Cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for Cisplatin administration. **Head and Neck Cancer:**

• 75mg/m2 followed by Cisplatin 75mg/m2 IV (Day 1), followed by Fluorouracil 750mg/m2 per day as a 24-hr IV (Days 1-5), starting at end of Cisplatin infusion; for 4 cycles, • 75mg/m2 followed by Cisplatin 100mg/m2 IV (Day 1), followed by Fluorouracil 1000mg/m2 per day as a 24-hr IV (Days 1-4); for 3 cycles. Or, as directed by the registered physicians. **Premedication Regimen:** All patients should be premedicated with oral corticosteroids such as Dexamethasone 16mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to Docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivi- ty reactions. For metastatic castration-resistant prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral Dexamethasone 8mg at 12 hours, 3 hours, and 1 hour before the Docetaxel infusion.

Administration Precautions: Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel solutions. The use of gloves is recommended. If Docetaxel Injection initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

Preparation and Administration: Docetaxel Injection (20mg/mL) requires no prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw Docetaxel from the vial because larger bore needles.

Contraindications: Docetaxel is contraindicated in patients with: • neutrophil counts of «1500 cells/mm3. • a history of severe hypersensitivity reactions to Docetaxel or to other drugs formulated with Polysorbate 80. Severe reactions, including anaphylaxis, have occurred. **Warning:** • Docetaxel should not be used in patients with bilirubin upper limit of normal (ULN), or to patients with AST and/or ALT .5 x ULN concomitant with alkaline phosphatase x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase. 5 x ULN also had a higher rate of febrile neutropenia. Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of Docetaxel.

• Docetaxel should not be administered to patients with neutrophil counts of Kl 500 cells/mm3. Blood counts should be frequently monitored as neutropenia may be severe and result in infection. • Docetaxel should not be administered to patients who have a history of severe hypersensitivity reactions to Docetaxel or to other drugs formulated with Polysorbate 80. Severe hypersensitivity reactions have been reported in patients despite Dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and administration of appropriate therapy. • Severe fluid retention occurred in 6.5% (6/92) of patients despite use of Dexamethasone premedication. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

Precautions: **Breast Cancer:** Docetaxel administered at 100mg/m2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of 11 patients with various tumor types who had abnormal baseline liver function (AST and/or ALT .5 times ULN together with AP times ULN). Among patients dosed at 60mg/m2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths. **Non-small Cell Lung Cancer:** Docetaxel administered at a dose of 100mg/m2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75mg/m2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75mg/m2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry. **Hepatic Impairment:** Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Docetaxel should be avoided in patients with bilirubin upper limit of normal (ULN), or to patients with AST and/or ALT. 5 x ULN concomitant with alkaline phosphatase x ULN. Bilirubin, AST or ALT, and alkaline phosphatase should be measured prior to each cycle of Docetaxel therapy. **Hypersensitivity Reactions:** Patients who have previously experienced a hypersensitivity reaction to Paclitaxel may develop a hypersensitivity reaction to Docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to Paclitaxel closely during initiation of Docetaxel therapy. Hypersensitivity reactions may occur within a few minutes following initiation of a Docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of Docetaxel. **Fluid Retention:** Severe fluid retention has been reported following Docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel administration to reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

Side Effects: The most serious adverse reactions from Docetaxel are: • Toxic Deaths • Hepatic Impairment • Hematologic • Enterocolitis and Neutropenic Colitis Hypersensitivity Reactions • Fluid Retention • Second Primary Malignancies • Cutaneous Reactions • Neurologic Reactions • Eye Disorders • Asthenia • Alcohol Content.

Use in Pregnancy and Lactation: Docetaxel can cause fetal harm when administered to a pregnant woman. If Docetaxel 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 during therapy with Docetaxel. **Lactating Mothers:** It is not known whether Docetaxel 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 from Docetaxel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Females:** Docetaxel can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment and for 6 months after the last dose of Docetaxel. **Males:** Based on genetic toxicity findings, male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 3 months after the last dose of Docetaxel. **Infertility:** Based on findings in animal studies, Docetaxel may impair fertility in males of reproductive potential.

Pediatric Use: The alcohol content of Docetaxel Injection should be taken into account when given to pediatric patients. The efficacy of Docetaxel in pediatric patients as monotherapy or in combination has not been established. **Geriatric Use:** In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Drug Interactions: Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of Docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. In vivo studies showed that the exposure of Docetaxel increased 2.2-fold when it was coadministered with Ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly Ritonavir, may increase the exposure of Docetaxel. Concomitant use of Docetaxel and drugs that inhibit CYP3A4 may increase exposure to Docetaxel and should be avoided. In patients receiving treatment with Docetaxel, close monitoring for toxicity and a Docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Overdose: There is no known antidote for Docetaxel overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed. In two reports of overdose, one patient received 150mg/m2 and the other received 200mg/m2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

Storage: Store between 2°C-25°C in a dry place. If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection vials to stand at room temperature for approximately 5 minutes before use. Protect from light & moisture. Keep out of reach of children.

Packaging: **Daxotel-20:** Each box contains one vial of Docetaxel Anhydrous USP 20mg/ml solution for IV infusion.

Daxotel-80: Each box contains one vial of Docetaxel Anhydrous USP 80mg/4ml solution for IV infusion.