Daxotel

Docetaxel Anhydrous USP Injection

DRUG INTERNATIONAL LTD.

COMPOSITION

Daxotel Injection: Each Vial Contains Docetaxel Anhydrous USP 80mg /2ml.

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is a white to almost-white powder with an empirical formula of C43H53N014.3H2O and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Docetaxel Injection concentrate is a clear alcoholic solution. Docetaxel is sterile.

Preparation : Ready to add to infusion solution.

CLINICAL 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.

HUMAN PHARMACOKINETICS

Absorption: The pharmacokinetics of Docetaxel has been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 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/m^2 .

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 and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

INDICATION

Breast Cancer: 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: 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.Prostate Cancer: Docetaxel in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer. Gastric Adenocarcinoma: 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. Head And Neck Cancer: Docetaxel in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Dosage and Administration:

Breast Cancer: For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of Docetaxel is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks. For the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel dose is 75 mg/m^2 administered 1 hour after Doxorubicin 50 mg/m^2 and Cyclophosphamide 500 mg/m^2 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 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy 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 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Prostate Cancer: For metastatic castration-resistant prostate cancer, the recommended dose of Docetaxel is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion.

Gastric Adenocarcinoma: For gastric adenocarcinoma, the recommended dose of Docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 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.

Head And Neck Cancer: For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of Docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days.

Side Effects:

The most serious adverse reactions from Docetaxel are: toxic deaths, hepatic impairment, hematologic effects, enterocolitis and neutropenic colitis, hypersensitivity reactions fluid retention, acute myeloid leukemia, cutaneous reactions, neurologic reactions eye disorders, asthenia, alcohol content.

Drug Interaction

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.

Contraindication

Continued use of Cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients with Known hypersensitivity to Cyclophosphamide, Severly impaired bone marrow function (particularly in patients who have been pretreated with cytotoxic agents and radiotherapy), inflammation of the bladder (Cystitis) and active infections.

Precautions

Patients being treated with Etoposide must be frequently observed for myelosuppression both during and after therapy. Patients with low serum albumin may be at an increased risk for Etoposide associated toxicities. In patients with renal impairment, dose adjustment is recommended.

Breast Cancer

Docetaxel administered at 100 mg/m^2 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 patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, 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 100 mg/m^2 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 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry

Hepatic Impairment

Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel.

Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving Docetaxel. Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel Cycle.

Enterocolitis And Neutropenic Colitis

Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with Docetaxel alone and in combination with other chemotherapeutic agents, despite the co-administration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new or worsening symptoms of gastrointestinal toxicity

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients pre-medicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel.

Pregnancy & Lactation

Docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.

Storage

Docetaxel should be stored between 2^o C and 25^o C in a dry place. Keep out of reach of children.

Packing

Each vial contains 1 vial of 2ml solution containing Docetaxel Anhydrous USP 80mg.