DoceXan

Docetaxel USP 20 mg & 80 mg Injection

Ready to add to infusion solution

COMPOSITION

Docexan 20 Injection: Each vial contains 1 mL solution containing Docetaxel USP 20 mg.

Docexan 80 Injection: Each vial contains 4 mL solution containing Docetaxel USP 80 mg.

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 $C_{43}H_{53}NO_{14}.3H_2O$ and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Docexan (Docetaxel) Injection concentrate is a clear yellow to brownish-yellow viscous solution. Docexan is sterile, non-pyrogenic, and is available in single dose vials containing Docetaxel USP 20 mg or 80 mg.

CLINICAL PHARMACOLOGY

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 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

The pharmacokinetics of Docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m² in phase I studies. The AUC was dose proportional following doses of 70-115 mg/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 ab, and g phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late phase is due , in part, to a relatively slow efflux of Docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m² and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m² was similar to that of European/American populations dosed at 100 mg/m², suggesting no significant difference in the elimination of Docetaxel in the two populations.

A study of ^{14}C-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.

A population pharmacokinetic analysis was carried out after Docetaxel treatment of 535 patients dosed at 100 mg/m². Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of Docetaxel were not influenced by age or gender and Docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT > 1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase > 2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with Docexan.

In vitro studies showed that Docetaxel is about 94% protein bound, mainly to a1-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. In vitro drug interaction studies revealed that Docetaxel is metabolized by the CYP3A4 isozyme, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on in vitro findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in Docetaxel blood concentrations.

INDICATIONS

Breast Cancer: Docexan is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Non-small cell lung Cancer: Docexan 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.

Docexan 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: Docexan in combination with prednisolone is indicated for the treatment of patients with androgen independent (hormonal refractory) metastatic prostate cancer.

DOSAGE AND ADMINISTRATION

Administer under supervision of qualified physicians experienced in using antineoplastic agents. Facilities to manage possible complications must be available.

Breast Cancer: The recommended dose of Docexan is 60-100 mg/m² administered intravenously over 1 hour every 3 weeks.

Non Small cell Lung Cancer: The recommended dose of Docexan is 75 mg/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials.

Prostate Cancer: When used in combination with Cisplatin, the recommended dose of Docexan is 75 mg/m² administered intravenously over 1 hour immediately followed by Cisplatin 75 mg/m² over 30-60 minutes every week.

For hormone refractory metastatic prostate cancer, the recommended dose of Docexan is 75 mg/m² every 3 weeks as a 1 hour infusion. Prednisolone 5 mg orally twice daily is administered continuously.

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as Dexamethasone 16 mg per day (e.g. 8 mg BID) for 4-5 days starting 1 day prior to Docexan administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Dosage Adjustments During Treatment

Breast Cancer:

Patients who are dose initially at 100 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than 1 week, or severe or cumulative cutaneous reactions during Docexan therapy should have the dosage adjusted from 100 mg/m² to 75 mg/m². If the patient continues to experience these reactions, the dosage should either be decreased form 75 mg/m² to 55 mg/m² or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m² and who do not experience febrile neutropenia, neutrophils <500 cells/mm³ for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during Docexan therapy may tolerate higher doses. Patients who develop grade 3 peripheral neuropathy should have Docexan treatment discontinued entirely.

Non small cell Lung Cancer:

Monotherapy with Docexan for NSCLC treatment after failure of prior Platinum Based Chemotherapy

Patients who are dosed initially at 75 mg/m² and who experience either febrile neutropenia, neutrophils <500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions, or other grade ¾ non-hematological toxicities during Docexan treatment should have treatment with held until resolution of the toxicity and then resumed at 55 mg/m². Patients who develop grade 3 peripheral neuropathy should have Docexan treatment discontinued entirely.

Combination Therapy of Docexan & Cisplatin in Non Small cell Lung Cancer

For patients who are given initial dose of Docexan 75 mg/m² in combination with cisplatin whose nadir & platelet count during the previous course of therapy is <25,000 cell/mm³, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the Docexan dosage in subsequent cycles should be reduced to 65 mg/m². In patients who require a further dose reduction, a dose of 50 mg/m² is recommended.

Special Populations

Hepatic impairment: Patients with bilirubin > ULN should generally not receive Docexan. Also, patients with SGOT and/or SGPT >1.5 ×ULN concomitant with alkaline phosphatase> 2.5 × ULN should generally not receive Docexan.

Children: The safety and effectiveness of Docexan in pediatric patients below the age of 16 years have not been established.

Elderly: No dosage adjustments are required for use in elderly.

PREPARATION AND ADMINISTRATION

Administration Precautions

Docexan is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docexan solutions. The use of gloves is recommended. If Docexan solution, for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Preparation and Administration

Preparation of Docetaxel injection, solution, concentrate -Docetaxel 20 mg/mL and 80 mg/4mL :

One-vial Docetaxel (Injection Concentrate):

Docetaxel Injection Concentrate (20 mg/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 (e.g., 18 and 19 gauge) may cause stopper coring and rubber particulates.

1. Docetaxel vials should be stored between 2°C to 8°C (36°F to 46°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.

2. Using only a 21 gauge needle, aseptically withdraw the required amount of Docetaxel injection concentrate (20 mg Docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle (Non DEHP cont of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded.

3. Thoroughly mix the infusion by gentle manual rotation.

4. As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

5. Docetaxel infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The Docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

Stability: Unopened vials of Docexan are stable until the expiration date indicated on the package when stored refrigerated, 2°C to 8°C (36°F to 46°F), and protected from bright light. Freezing does adversely affect the product.

Docetaxel final dilution for infusion, if stored between 2°C to 8°C (36°F to 46°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C to 8°C (36°F to 46°F).

OVERDOSE

There is no known antidote for Docexan 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 150 mg/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.

CONTRAINDICATIONS

Docexan is contraindicated in patients who have a history of severe hypersensitivity reactions to Docetaxel or to other drugs formulated with polysorbate 80. Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm³.

WARNING

Docexan should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. The incidence of treatment-related mortality associated with Docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum based chemotherapy who received Docetaxel.

Docetaxel should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or with SGPT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN. Patients with elevations of bilirubin or abnormalities of trasaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with increased elevations of transaminase > 1.5 × ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel therapy and reviewed by the treating physician.

Docetaxel therapy should not be given to patients with neutrophil counts of <1500 cells/mm³. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving Docetaxel.

Hypersensitivity Reaction

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the Docetaxel infusion were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to Docetaxel or to other drugs formulated with polysorbate 80.

Fluid Retention

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. 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).

Pregnancy

Docetaxel can cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant woman using Docetaxel. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be appraised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Precautions

Hematologic Effects: In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Docetaxel. Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level > 1500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm³) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel injection cycle.

Hypersensitivity Reaction: 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.

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%.

Asthenia: Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Carcinogenicity, Mutagenicity, Impairment of Fertility: No studies have been conducted to assess the carcinogenic potential of Docetaxel.

Pediatric Use: The safety and effectiveness of Docetaxel in pediatric patients have not been established.

ADVERSE EFFECTS

The adverse reactions are described separately for Docetaxel 100 mg/m², the maximum dose approved for breast cancer, and 75 mg/m², the dose approved for advanced non-small cell lung carcinoma after prior platinum-based chemotherapy and in combination with cisplatin for treatment of patients with non-small cell lung carcinoma who have not previously received chemotherapy for this condition.

Docetaxel 100 mg/m²: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received Docetaxel administered at 100 mg/m² as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to Docetaxel. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving Docetaxel for the treatment of breast cancer and in patients with other tumor types.

Hematologic: Reversible marrow suppression was the major dose-limiting toxicity of Docetaxel. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm³) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cels/mm³ with fever > 38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premeditated with 3-day corticosteroids. Sever infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of Thrombocytopenia (<100,000 cells/mm³) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions: Severe hypersensitivity reactions are discussed in the Warnings and Precautions sections. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

Cutaneous: Severe skin toxicity is discussed in Precautions. Reversible cutaneous reactions characterized by a rash including localized eruption, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after Docetaxel infusion, recovered before the next infusion, and were not disabling.

Sever nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic: (See Precautions)

Gastrointestinal: Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Sever reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids. Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular: Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86) of metastatic breast cancer patients receiving Docetaxel 100 mg/m² in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF BY 10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions: Infusion site reactions were generally mild and considered of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitits, extravasation, or swelling of the vein.

Hepatic: In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on Docetaxel, increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established).

Docetaxel 75 mg/m²: Treatment emergent adverse drug reactions are shown below. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

Treatment Emergent Adverse Events Regardless of Relationship to Treatment in Patients Receiving Docetaxel as Monotherapy for Non-Small cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

*Normal Baseline LFTs: Transaminases 1.5 times ULN or alkaline phosphatase 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

Adverse Event	Docetaxel 75 mg/m² N = 176 %	Best Supportive Care N = 49 %	Vinorelbine/Ifosfamide N = 119 %
Neutropenia			
Any	84.1	14.3	83.2
Grade 3/4	65.3	12.2	57.1
Leukopenia			
Any	83.5	6.1	89.1
Grade 3/4	49.4	0	42.9
Thrombocytopenia			
Any	8.0	0	7.6
Grade 3/4	2.8	0	1.7
Anemia			
Any	91.0	55.1	90.8
Grade 3/4	9.1	12.2	14.3
Febrile Neutropenia**	6.3	NA+	0.8
Infection			
Any	33.5	28.6	30.3
Grade 3/4	10.2	6.1	9.2
Treatment Related Mortality	2.8	NA+	3.4
Hypersensitivity Reactions			
Any	5.7	0	0.8
Grade 3/4	2.8	0	0
Fluid Retention		ND++	
Any	33.5		22.7
Grade 3/4	2.8		3.4
Neurosensory			
Any	23.3	14.3	28.6
Grade 3/4	1.7	6.1	5.0
Neuromotor			
Any	15.9	8.2	10.1
Grade 3/4	4.5	6.1	3.4
Skin			
Any	19.9	6.1	16.8
Grade 3/4	0.6	2.0	0.8
Gastrointestinal			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4			

** Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization

*** COSTART term and grading system

+ Not applicable; ++ Not done

DRUG INTERACTIONS

There have been no formal clinical studies to evaluate the drug interactions of Docetaxel with other medications. 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, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin.

Caution should be exercised with these drugs when treating patients receiving Docetaxel as there is a potential for a significant interaction.

STORAGE

Store the vial in original carton at 2°C to 8°C (36°F to 46°F). Protect from light.

PACKAGING

Docexan 20 Injection: Each commercial box contains one vial of Docetaxel 20 mg injection.

Docexan 80 Injection: Each commercial box contains one vial of Docetaxel 80 mg injection.

Manufactured by
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

LF24901