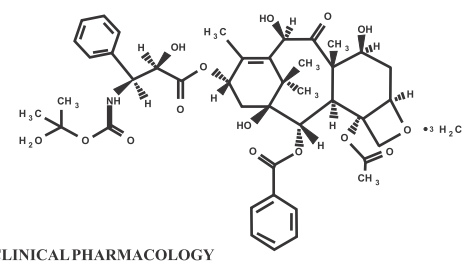
DONATAXEL
(Docetaxel) ڈوناٹاکسل
Concentrated Solution for Infusion

WARNING

DONATAXEL (docetaxel) for injection concentrate should be administered under the supervision or a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. 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 receive docetaxel at a dose of 100mg/m^2. Docetaxel should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase 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 isolated elevations of transaminase >1.5 x 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 DONATAXEL therapy and reviewed by the treating physician. DONATAXEL 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 DONATAXEL. 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. 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)

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. Docetaxel has the following structural formula:



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 diseassembly. 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

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115mg/m^2 in Phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70-115mg/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 alpha, beta, and gamma phases of 4 min, 36 min, and 11.1 hr, respectively. 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 values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese Patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

INDICATIONS AND USAGE

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

Non-Small Cell Lung Cancer: DONATAXEL is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Prostate Cancer: DONATAXEL in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

CONTRAINDICATIONS

DONATAXEL is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. DONATAXEL should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS

DONATAXEL should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Toxic Deaths: *Breast Cancer:* Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2% (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 (SGOT and/or SGPT > 1, times ULN together with AP > 2, 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-reated 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 a PS of 2 at study entry.

Premediacation Regimen: All patients should be premedicated with oral corticosteriods such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to DONATAXEL to reduce the severity of fluid retention and hypersensitivity reactions. This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given docetaxel at a dose of 100 mg/m^2 every 3 weeks.

Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3-day corticosteroids. Hypersensitivity reactions requiring discontinuation of the docetaxel infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3-day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hemotologic Effects: Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of docetaxel and grade 4 neutropenia (<500 cell/mm3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils < 1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related. Three breast cancer patients with severe liver impairment (bilirubin > 1,7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

Pregnancy: Docetaxel can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses >/=0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity. There are no adequate and well-controlled studies in pregnant women using docetaxel. If DONATAXEL 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 or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with DONATAXEL.

PRECAUTIONS

General: Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

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 DONATAXEL 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 DONATAXEL 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 DONATAXEL cycle.

Hypersensitivity Reactions: 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, interrruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of DONATAXEL and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of DONATAXEL.

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. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.

Fluid Retention: Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each DONATAXEL administration to reduce the incidence and severity of fluid retention. Patients with pre-exisiting effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. When fluid retention occurs, peripheral odema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg. Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. 9,8% (9/92) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of docetaxel to resolution (range: 0 to 42 + weeks). Patients developing peripheral edema may be treated with standard measures, e.g., Salt restriction, oral diuretic(s).

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%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

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.

Drug Interactions: There have been no formal clinical studies to evaluate the drug interactions of docetaxel with othermedications. 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.

Carcinogenicity, Mutagenicity, Impairment of Fertility: No studies have been conducted to assess the carcinogenic potential of docetaxel. Docetaxel has been shown to be clastogenic in the in vitro chromosome aberration test in CHO-K1 cells and in the in vivo micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. Docetaxel produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5mg/kg in rats and 0.375mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy: Pregnancy Category D. Positive evidence of human fetal risk based on adverse reaction from investigational or marketing exeriences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

Nursing 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, mothers should discontinue nursing prior to taking the drug. **Pediatric Use:** The safety and effectiveness of DONATAXEL in pediatric patients have not been established.

ADVERSE REACTIONS

Summary of Adverse Events in Patients Receiving DONATAXEL at 100 mg/m^2

Adverse Event	All Tumour Types Normal LFTs* n = 2045 %	All Tumor Types Elevated LFTs** n = 61 %	Breast Cancer Normal LFTs* n = 965 %
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5	96.4	98.5
<500 cells/mm^3	75.4	87.5	85.9
Leukopenia			98.6
			43.7
<4000 cells/mm^3	95.6	98.3	98.6
<1000 cells/mm^3	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm^3	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
With 3-day Premedication	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5
Neurosensory			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
Cutaneous			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
Nail Changes			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
Gastrointestinal			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
Stomatitis			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
Alopecia	75.8	62.3	74.2
Asthenia			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
Myalgia			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8
Arthralgia	9.2	6.6	8.2
Infusion Site Reactions	4.4	3.3	4.0

* 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.

** Elevated Baseline LFTs: SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN.

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

Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administrated at 100 mg/m^2 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/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFT's, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles. Febrile neutropneia (<500 cells/mm^3 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 premedicated with 3-day corticosteroids.
Severe 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 92 breast cancer patients premedicated with 3-day corticosteroids. Thrombocytopenia (<100.000 cells/mm3) associated with fatal gastrointestinal hemorrhage has been reported. Hypersensitivity Reactions: 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: Reversible cutaneous reactions characterized by a rash including localized eruptions, 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. Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.
Gastrointestinal: Gastrointestinal reactions(nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Severe 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-daycorticosteroids. 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 ccorticosteroids.
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, dyshythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8,1% (7/86) of metastatic breast cancer patients receiving docetaxel 100 mg/m^2 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 consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, 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.)

DOSAGE AND ADMINISTRATION

Breast Cancer: The recommended dose of DONATAXEL is 60-100mg/m^2 administered intravenously over 1 hour every 3 weeks.
Non-Small Cell Lung Cancer: The recommended dose of DONATAXEL 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.
Prostate cancer: For hormone-refractory metastatic prostate cancer, the recommended dose of DONATAXEL is 75 mg/m^2 every 3 weeks as a 1 hour infusion. Prednisone 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 3 days starting 1 day prior to DONATAXEL administration in order to reduce the incidence and severity of fluid retention as well as the severity of hyper sensitivity reactions.
Dosage Adjustment During Treatment: Breast Cancer: Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during DONATAXEL therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during DONATAXEL therapy may tolerate higher doses. Patients who develop >/= grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely. Non-Small Cell Lung Cancer: Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one wek, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicity during docetaxel treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/ m^2. Patients who develop >/= grade 3 peripheral neutropathy should have DONATAXEL treatment discontinued entirely.
Special Populations: *Hepatic Impairment:* Bilirubin > ULN should generally not receive DONATAXEL. Also, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should generally not receive DONATAXEL.
Children: The safety and effectiveness of docetaxel 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 PRECAUTIONS

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, cation should be exercised when handling and preparing DONATAXEL solutions. The use of gloves is recommended. If DONATAXEL concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If DONATAXEL concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water. Docetaxel requires two dilutions prior to administration. Please follow the preparation instructions provided below. Preparation of the Intial Diluted Solution
Remove the appropriate number of vials of DONATAXEL and diluent (13% ethanol in water for injection) from the refrigerator. Allow the vials to stand at room temperature for approxiamely 5 minutes. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of DONATAXEL. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/ml will result. Gently rotate the initial diluted solution for approximately 15 seconds to assure full mixture of the concentrate and diluent. The initial diluted DONATAXEL solution (10 mg docetaxel/ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.
The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.
Preparation of the Final Dilution for Infusion
Aseptically withdraw the required amount of initial diluted DONATAXEL solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a 250 ml infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 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. Thoroughly mix the infusion by manual rotation. As with all parenteral products, DONATAXEL should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the DONATAXEL for injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.
The final DONATAXEL dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions. Contact of the docetaxel 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-2ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylenelined administration sets.

HOW SUPPLIED

Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenie, diluent (13% ethanol in Water for Injection) vial. The following strength is available; 20 mg & 80mg.

PHARMACEUTICAL PRECAUTIONS

Store between 2 and 8°C. Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Keep all medicines away from the reach of children.

DONATAXEL Inj. 20mg Pak. Regn. No. 030836
DONATAXEL 80 Inj. 80mg Pak. Regn. No. 060360

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Size of Literature: 290 x 206mm