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FULL PRESCRIBING INFORMATION

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, AND FLUID RETENTION

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 as a single agent at a dose of 100 mg/m^2 *[see Warnings and Precautions (5.1)]*.

Docetaxel Injection should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >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, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel Injection therapy *[see Warnings and Precautions (5.2)]*.
Docetaxel Injection therapy should not be given to patients with neutrophil counts of <1500 cells/mm^3. 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 Injection *[see Warnings and Precautions (5.3)]*.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and administration of appropriate therapy *[see Warnings and Precautions (5.5)]*. Docetaxel Injection must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.

2.6 Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to Docetaxel Injection administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.5)]*.

For metastatic castration-resistant prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the Docetaxel Injection infusion *[see Warnings and Precautions (5.5)]*.

2.7 Dosage Adjustments 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 Docetaxel Injection 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 Docetaxel Injection therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination Therapy with Docetaxel Injection in the Adjuvant Treatment of Breast Cancer

Docetaxel Injection in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel Injection dose reduced to 60 mg/ m^2. Patients who experience grade 3 or 4 stomatitis should have their Docetaxel Injection dose decreased to 60 mg/ m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel Injection therapy should have their dosage of Docetaxel Injection reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/ m^2, treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with Docetaxel Injection for NSCLC treatment after failure of prior platinum-based chemotherapy

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 week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during Docetaxel Injection treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination therapy with Docetaxel Injection for chemotherapy-naive NSCLC

Thoroughly mix the infusion bag or bottle manually by gentle inversion and rotation in a controlled manner and avoid foaming. Shaking or vigorous agitation should be avoided during preparation and transportation to the patient for administration.

As with all parenteral products, Docetaxel Injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection vial or diluted solution is not clear or appears to have precipitation, these should be discarded.

The Docetaxel Injection diluted solution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature below 25°C (77°F) and lighting conditions.

2.10 Stability

Docetaxel Injection infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours in either 0.9% Sodium Chloride solution or 5% Dextrose solution. Use within 4 hours including storage and administration. Do not freeze infusion solution.

3. DOSAGE FORMS AND STRENGTHS

- 20 mg/2 mL multiple-dose vial
- 80 mg/8 mL multiple-dose vial
- 160 mg/16 mL multiple-dose vial

4. CONTRAINDICATIONS

Docetaxel Injection is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm^3 *[see Warnings and Precautions (5.3)]*.
- a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.5)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

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 *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

5.2 Hepatic Impairment

Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection *[see Boxed Warning, Use in Specific Populations (8.6), Clinical Studies (14)]*.

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.

Avoid docetaxel in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN *[see Warnings and Precautions (5.1)]*.

For patients with isolated elevations of transaminase >1.5 x ULN, consider docetaxel dose modifications *[see Dosage and Administration (2.7)]*.

Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of docetaxel therapy.

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving Docetaxel Injection. Patients should not be retreated with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1500 cells/mm^3 *[see Contraindications (4)]* and platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of Docetaxel Injection 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 Injection cycle *[see Dosage and Administration (2.7)]*.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of docetaxel and grade 4 neutropenia (<500 cells/mm^3) 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 Injection 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 *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection *[see Dosage and Administration (2.7) Adverse Reactions (6)]*.

5.4 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 coadministration 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 *[see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)]*.

5.5 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 premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be re-challenged with Docetaxel Injection [*see Contraindications (4)]*.

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 Injection 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 Injection *[see Dosage and Administration (2.6)]*.

5.6 Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel Injection administration to reduce the incidence and severity of fluid retention *[see Dosage and Administration (2.6)]*. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema 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. Nine of 92 patients (9.8%) 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).

5.7 Second Primary Malignancies

Second primary malignancies, notably acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), Non-Hodgkin's Lymphoma (NHL), and renal cancer, have been reported in patients treated with docetaxel-containing regimens. These adverse reactions may occur several months or years after docetaxel-containing therapy.

Treatment-related AML or MDS has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (*TAX316*) AML occurred in 3 of 744 patients who received docetaxel, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide *[see Clinical Studies (14.2)]*. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies *[see Adverse Reactions (6.1)]*.

5.8 Cutaneous Reactions

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 *[see Dosage and Administration (2.7)]*. 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.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Permanent treatment discontinuation should be considered in patients who experience SCARs.

5.9 Neurologic Reactions

Severe neurosensory symptoms (*e.g.* 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 *[see Dosage and Administration (2.7)]*. 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).

5.10 Eye Disorders

Cystoid macular edema (CME) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered.

5.11 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.

5.12 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, docetaxel can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of

major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating docetaxel. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of Docetaxel Injection. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Docetaxel Injection *[see Use in Specific Populations (8.1, 8.3)]*.

5.13 Alcohol Content

Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of Docetaxel Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Docetaxel Injection on the ability to drive or use machines immediately after the infusion. Each administration of Docetaxel Injection at 100 mg/m^2 delivers 2.65 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 5.3 grams of ethanol [*see Description (11)*]. Other docetaxel products may have a different amount of alcohol.

6. ADVERSE REACTIONS

The most serious adverse reactions from docetaxel are:

- Toxic Deaths *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hepatic Impairment *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Hematologic Effects *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Enterocolitis and Neutropenic Colitis *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see- Boxed Warning, Warnings and Precautions (5.5)]*
- Fluid Retention *[see- Boxed Warning, Warnings and Precautions (5.6)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.7)]*
- Cutaneous Reactions *[see Warnings and Precautions (5.8)]*
- Neurologic Reactions *[see Warnings and Precautions (5.9)]*
- Eye Disorders *[see Warnings and Precautions (5.10)]*
- Asthenia *[see Warnings and Precautions (5.11)]*
- Alcohol Content *[see Warnings and Precautions (5.13)]*

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication. Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

gastrointestinal perforation, intestinal obstruction, ileus, and dehydration as a consequence to gastrointestinal events have been reported.

Hearing: rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Hematologic: bleeding episodes. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported.

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication. Hypersensitivity reactions with potential fatal outcome have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and Nutrition Disorders: electrolyte imbalance, including cases of hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion. Cases of cystoid macular edema (CME) have been reported in patients treated with docetaxel.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis have rarely been reported and may be associated with fatal outcome. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure have been reported, the majority of these cases were associated with concomitant nephrotoxic drugs.

Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer, have been reported in patients treated with docetaxel-containing regimens *[see Warnings and Precautions (5.7)]*.

7. 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 co-administered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection close monitoring for toxicity and a Docetaxel Injection dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action, Docetaxel Injection can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Docetaxel Injection contains alcohol which can interfere with neurobehavioral development *[see Clinical Considerations]*. In animal reproductive studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused an increased incidence of embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively *[see Data]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Docetaxel Injection contains alcohol *[see Warnings and Precautions (5.13)]*. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Data

Animal data

Intravenous administration of ≥0.3 and 0.03 mg/kg/day docetaxel to pregnant rats and rabbits, respectively, during the period of organogenesis caused an increased incidence of intrauterine mortality, resorptions, reduced fetal weights, and fetal ossification delays. Maternal toxicity was also observed at these doses, which were approximately 0.02 and 0.003 times the daily maximum recommended human dose based on body surface area, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of docetaxel in human milk, or on its effects on milk production or the breastfed child. No lactation studies in animals have been conducted. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Docetaxel Injection and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Docetaxel Injection.

Contraception

Females

Among the 221 patients treated with docetaxel injection in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Head and Neck Cancer

Among the 174 and 251 patients who received the induction treatment with docetaxel injection in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.

These clinical studies of docetaxel injection in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

Patients with bilirubin >ULN should not receive Docetaxel Injection. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel Injection *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

The alcohol content of Docetaxel Injection should be taken into account when given to patients with hepatic impairment *[see Warnings and Precautions (5.13)]*.

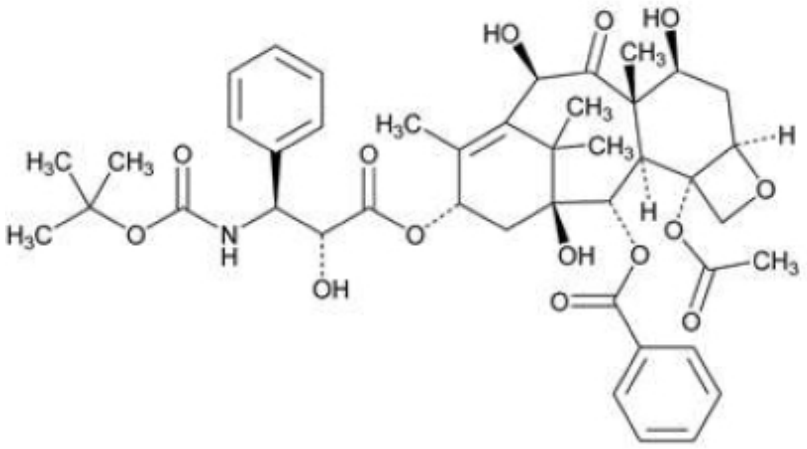
10. OVERDOSAGE

There is no known antidote for Docetaxel Injection over-dosage. In case of over-dosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of over-dosage 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/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident. In mice, lethality was observed following single intravenous doses that were ≥154 mg/kg (about 4.5 times the human dose of 100 mg/m^2 on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

11. DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semi-synthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water.

Docetaxel Injection is a clear, colorless to pale yellow solution. Docetaxel Injection is sterile, non-pyrogenic, and is available in multiple-dose vials, supplied as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.

Each mL of Docetaxel Injection contains 10 mg docetaxel, 275.9 mg alcohol 96% (v/v), 4 mg citric acid, 648 mg polyethylene glycol 300, and 80 mg polysorbate 80.

12. CLINICAL PHARMACOLOGY

12.1 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.

12.3 Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have 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 α, β, and γ 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 α_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 *[see Drug Interactions (7)]*.

Single Arm Studies

Docetaxel at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was 2.1%.

Docetaxel was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2 - 55.7), similar to the response rate in single arm studies of 100 mg/m^2.

14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of docetaxel for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1 - 3, 4+), 1491 patients were randomized to receive either docetaxel 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients (see Figure 1).

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90) (see Figure 2). There will be further analysis at the time survival data mature.

Figure 1 - TAX316 Disease Free Survival K-M Curve

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Docetaxel Injection is supplied in a multiple-dose vial as a sterile, pyrogen-free solution. Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution. The following strengths are available:

Strength	NDC Number	Volume
20 mg/2 mL	66758-050-01	Carton of one 2 mL Multiple-Dose Vial
80 mg/8 mL	66758-050-02	Carton of one 8 mL Multiple-Dose Vial
160 mg/16 mL	66758-050-03	Carton of one 16 mL Multiple-Dose Vial

16.2 Storage

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

After initial puncture, Docetaxel Injection multiple-dose vials are stable for 28 days when stored between 2ºC to 8ºC and at room temperature, with or without protection from light.

16.3 Handling and Disposal

Docetaxel Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Bone Marrow Suppression

Advise patients that periodic assessment of their blood count will be performed to detect neutropenia, thrombocytopenia, and/ or anemia *[see Contraindications (4), Warnings and Precautions (5.3)]*. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.

Enterocolitis and Neutropenic Colitis

Advise patients of the symptoms of colitis, such as abdominal pain or tenderness, and/or diarrhea, with or without fever, and instruct patients to promptly contact their healthcare provider if they experience these symptoms *[see Dosage and Administration (2.7) and Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Ask patients whether they have previously received paclitaxel therapy, and if they have experienced a hypersensitivity reaction to paclitaxel. Instruct patients to immediately report to their healthcare provider signs of a hypersensitivity reaction *[see Contraindications (4), Warnings and Precautions (5.5)]*.

Fluid Retention

Advise patients to report signs of fluid retention such as peripheral edema in the lower extremities, weight gain, and dyspnea immediately to their healthcare provider *[see Warnings and Precautions (5.6)]*.

3 months after the last dose of Docetaxel Injection *[see Warnings and Precautions (5.12), and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during Docetaxel Injection treatment and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that Docetaxel Injection may impair fertility *[see Nonclinical Toxicology (13.1)]*.

Alcohol Content in Docetaxel Injection

Explain to patients the possible effects of the alcohol content in Docetaxel Injection, including possible effects on the central nervous system *[see Warnings and Precautions (5.13)]*.

Ability to Drive or Operate Machines

Explain to patients that Docetaxel Injection may impair their ability to drive or operate machines due to its side effects *[see Adverse Reactions (6)]* or due to the alcohol content of Docetaxel Injection *[see Warnings and Precautions (5.13)]*. Advise them not to drive or use machines if they experience these side effects during treatment.

Drug Interactions

Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to their healthcare provider *[see Drug Interactions (7)]*.

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