DOCETAXEL LIPID SUSPENSION FOR INJECTION 20mg & 80mg/vial

DOCISOL® 20/80

Injection

COMPOSITION

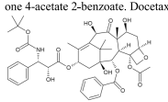
DOCETAXEL LIPID SUSPENSION FOR INJECTION 20 mg/vial	
Each vial contains:	
Docetaxel Anhydrous IP	20 mg
Excipients	q.s.

COMPOSITION

DOCETAXEL LIPID SUSPENSION FOR INJECTION 80 mg/vial	
Each vial contains:	
Docetaxel Anhydrous IP	80 mg
Excipients	q.s.

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.

This formulation is a sterile lyophilized powder containing Soy phosphatidylcholine and Sodium Cholesteryl Sulfate with 20 mg Docetaxel (anhydrous) per vial. Each 20 mg vial is first reconstituted by adding 9 ml of sterile water to yield 2 mg/ml of docetaxel lipid suspension. Similarly, 80 mg vial is first reconstituted by adding 36 ml of sterile water to yield 2 mg/ml of docetaxel lipid suspension. The reconstituted suspension can further be diluted with 5% dextrose Injection or 0.9% sodium chloride Injection prior to administration.

CLINICAL PHARMACOLOGY

Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

Pharmacokinetics

In vitro drug interaction studies conducted by investigators have shown 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 CYP3A4.

An open label, balanced, randomized, two periods, two treatment, two sequences, crossover, multicentric study was conducted to evaluate safety and pharmacokinetic comparison of intravenous infusion of docetaxel lipid suspension (test) and polysorbate based Docetaxel Injection Concentrate (reference), innovator's product in advanced solid tumor patients.

INDICATIONS

Docetaxel lipid suspension for injection is indicated for:

- For the treatment of patients with advanced gastric adenocarcinoma
- For the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck
- For the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer
- For the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy
- For the treatment of patients with non-small cell lung cancer

DOSAGE AND ADMINISTRATION

Docetaxel lipid suspension for injection is a sterile lyophilized powder containing 20 mg/vial Docetaxel (anhydrous). Each 20 mg vial is first reconstituted by adding 9 ml of sterile water to yield 2 mg/ml of docetaxel lipid suspension. Similarly, 80 mg vial is first reconstituted by adding 36 ml of sterile water to yield 2 mg/ml of docetaxel lipid suspension. The reconstituted suspension can further be diluted with 5% dextrose Injection or 0.9% sodium chloride Injection prior to administration. Dosage and procedure of administration can vary based on the cancer types as following.

Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of docetaxel lipid suspension is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration.

Head and Neck Cancer

Induction chemotherapy followed by radiotherapy

For the induction treatment of locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel lipid suspension is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles.

Following chemotherapy, patients should receive radiotherapy.

Induction chemotherapy followed by chemoradiotherapy

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel lipid suspension is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemo-radiotherapy.

Prostate cancer

For hormone-refractory metastatic prostate cancer, the recommended dose of Docetaxel lipid suspension is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

Breast cancer

For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of docetaxel lipid suspension is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks for maximum of 6 cycles.

Non-small cell lung cancer

For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks.

For chemotherapy-naïve patients, the recommended dose is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes *every* 3 weeks.

Preparation Guide for Use of Docetaxel Lipid Suspension

Pre Reconstitution steps:

- Use the Sterile surgical hand glove only for reconstitution.
- Perform the Reconstitution only in biosafety cabinet.
- Mop the outer surface of Docisol pack + Sterile infusion bags/bottle and Expose to UV light for 15 min. or as per SOP of Biosafety cabinet.

Initial dilution

The docetaxel lipid suspension available as lyophilized powder in a vial should be reconstituted using Sterile Water for Injection (WFI). Initial dilution should be prepared as follows:

- Add 9 ml of Sterile WFI to vial of Docetaxel lipid suspension for injection 20 mg to yield a preparation containing 2mg/ml. For vial of Docetaxel lipid suspension for injection 80 mg, add 36 ml of Sterile WFI to the vial to yield a preparation containing 2 mg/ml.
- Slowly inject the WFI through the inner wall of the vial. Do not inject WFI directly onto the lyophilized cake.
- After adding WFI, gently swirl the vial until the drug dissolves completely. Do not agitate or shake the vial as foaming can occur.
- If foaming /clumping occurs, keep the solution aside till the foam settle down.
- Aseptically withdraw the required amount of reconstituted Docisol solution with a calibrated syringe using fresh 20 Gauge needle.
- After complete extraction of the solution replace the 20 Gauge needle with a "5 Micron" filter needle.

Final Dilution for Infusion

- Inject the reconstituted solution through a 5-micron needle into 250 ml or 500 ml infusion bag or bottle of 0.9% normal saline or 5% Dextrose solution.
- Mix the infusion thoroughly by manual rotation.
- If the Docisol initial diluted solution or final diluted solution for intravenous infusion appeared to have particulate matter, the same should be discarded.
- Start the infusion using the Normal IV set.
- Use the solution within 8 hrs of initial reconstitution.

Post Reconstitution:

- Discard the Docisol empty bottle and pack in Chemotherapy disposal bin.
- Discard the hand glove in surgical waste disposal Bin.
- Wash your hands thoroughly with soap solution / Decontamination solution.

FRONT

CONTRAINDICATIONS

Polysorbate based Docetaxel Injection containing ethanol has been contraindicated in patients with hypersensitivity (anaphylactic/anaphylactoid reactions) to polysorbate 80. However, docetaxel lipid suspension is not contraindicated in patients with hypersensitivity to polysorbate 80. Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel. Severe reactions, including anaphylaxis, have occurred. Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS AND PRECAUTIONS

Toxic Deaths: The incidence of treatment-related mortality associated with Docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses of Docetaxel. Patients should be closed monitored for liver dysfunction.

Hepatic Impairment: The incidence of treatment-related mortality associated with Docetaxel therapy is increased in patients with abnormal liver function. Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel. Patients treated with docetaxel lipid suspension should be closed monitored for hepatic impairment.

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

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

Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel Injection.

Fluid Retention: Severe fluid retention has been reported following conventional polysorbate based Docetaxel therapy. Only one patient had fluid retention without premedication in docetaxel lipid suspension group. However, patients should be closely monitored and treated based on the severity of fluid retention.

Acute Myeloid Leukemia: Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients with polysorbate based Docetaxel Injection given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML has occurred who received Docetaxel, doxorubicin and cyclophosphamide in the clinical studies.

Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed with polysorbate based Docetaxel Injection. In case of severe skin toxicity with docetaxel lipid suspension is observed, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% for metastatic breast cancer patients.

Neurologic Reactions

Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) were observed with polysorbate based Docetaxel Injection in 5.5% of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1 %. When these symptoms occur with Docetaxel lipid suspension, dosage must be adjusted. If symptoms persist, treatment should be discontinued.

ADVERSE EFFECTS

The most serious adverse reactions from Docetaxel are:

Toxic Deaths

Polysorbate based Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% 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% 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. Cautions should be taken when treating patients with docetaxel lipid suspension and medical condition should be regularly monitored.

Hepatotoxicity

Similar to polysorbate based Docetaxel Injection, the docetaxel lipid suspension 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 offebrile neutropenia grade 4. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel therapy.

Neutropenia

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of polysorbate based 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 when treated with docetaxel lipid suspension. Docetaxel should not be administered to patients with neutrophils <1500 cells/mm^3.

Fluid Retention

Severe fluid retention has been reported following polysorbate 80 based Docetaxel therapy in earlier studies. Even though this was not observed in greater number of Patients treated with docetaxel lipid suspension without premedication but such condition should be monitored by medical Investigators.

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 CYP3A4.

USE IN SPECIFIC POPULATIONS

Pregnancy

Docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryo-fetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. There are no adequate and well-controlled studies in pregnant women using Docetaxel. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy of docetaxel lipid suspension in pediatric patients as monotherapy or in combination has not been established.

Hepatic Impairment

Patients with bilirubin >ULN should not receive Docetaxel. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel.

OVERDOSAGE

There is no known antidote for docetaxel overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored.

Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

STORAGE

Store at 2-8^{0}C. Do not freeze. Protect from light. Keep out of reach of children.

PACKAGING INFORMATION

Available as 20 mg and 80 mg in single vial individually packed in a carton.

Marketed by :

wembrace®

Wembrace Biopharma Pvt. Ltd.
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