Summary of Product Characteristics

1. Name of the Medical Product

Drug Product	**:**	ADOXI
Generic Name	**:**	Docetaxel Injection USP (80 mg/ 2.0 mL)
Strength	**:**	40 mg per mL**.** Each mL of sterile nonpyrogenic non aqueous pale yellow colour viscous oily solution contains 40 mg of Docetaxel (anhydrous), and 1080 mg of Polysorbate 80 USNF.

2. Quality and Quantitative Composition

Docetaxel Injection USP (80 mg /2.0 mL) [Injection Concentrate]

Each single dose vial contains:

Docetaxel (As Trihydrate) USP	
eq. to Anhydrous Docetaxel	80 mg
Polysorbate 80 USNF	qs. to 2.0 mL

Solvent for Docetaxel Injection USP (80 mg / 2.0 mL)

Alcohol (96 % v/v) BP	13 % w/v
Water for Injection USP	qs. to 6.0 mL

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile parenteral preparation for intravenous infusion after dilution

4. Clinical Particulars

4.1 Therapeutic Indications

Breast Cancer

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant

treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer

Docetaxel as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer

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

Gastric Adenocarcinoma

Docetaxel in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Head and Neck Cancer

Docetaxel in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

4.2 Posology and method of administration

Posology

Docetaxel Injection Concentrate 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.

Breast Cancer

The recommended dose of Docetaxel is 60-100 mg/m^2 administered intravenously over 1 hour every

3 weeks.

In the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel dose is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses.

Non-Small Cell Lung Cancer

For treatment after failure of prior platinum-based chemotherapy, Docetaxel was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials.

For chemotherapy-naïve patients, Docetaxel was evaluated in combination with cisplatin. The recommended dose of Docetaxel is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Prostate cancer

For hormone-refractory metastatic prostate cancer, the recommended dose of Docetaxel is 75 mg/m^2 every 3 weeks as a 1 hour intravenous 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 Docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions

For hormone-refractory metastatic 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 infusion.

Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of Docetaxel is 75 mg/m^2 as a 1 hour

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

Method of administration

Docetaxel Injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel solutions. The use of gloves is recommended.

If Docetaxel Injection 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 Docetaxel Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

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-2-ethylhexyl 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 polyethylene-lined administration sets.

Two-vial formulation (Injection Concentrate and Solvent)

Docetaxel Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Docetaxel Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with theentire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/ docetaxel.

Preparation and Administration

Donot use the two-vial formulation (Injection Concentrate and diluent) with the one-vial formulation.

Initial Diluted Solution

Docetaxel vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.

Aseptically withdraw the entire contents of the appropriate diluent vial into a syringe by partially inverting the vial, and transfer it to the appropriate vial of Docetaxel Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/ will result.
Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

The initial diluted Docetaxel solution (10 mg docetaxel/) 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.

Final Dilution for Infusion:

Aseptically withdraw the required amount of initial diluted Docetaxel solution (10 mg docetaxel) with a calibrated syringe and inject into a 250 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/.
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/ Docetaxel is not exceeded.Thoroughly mix the infusion by manual rotation.

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 initial diluted solution or final dilution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.

The final Docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

4.3 Contraindications

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred.

Docetaxel Injection should not be used in patients with neutrophil counts of <1500 cells/mm^3.

Occasionally, serious allergic reactions have occurred with this medicine. If you have any allergies, tell your doctor before receiving this medicine.

If you are using any other medicines, tell your doctor before receiving your infusions of Docetaxel.

Docetaxel can interact with other medicines. Use only medicines that are prescribed for you by your doctor and be sure to tell your doctor all the medicines that you use, including nonprescription drugs.

There is an increased risk of serious (possibly fatal) reactions in patients using docetaxel who have liver problems, patients receiving higher doses, and patients with non-small cell lung cancer who have received certain other chemotherapy drugs known as "platinums."

Paediatric trials of docetaxel have been limited and so safety of use in patients under 16 years has not been established

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Docetaxel can cause fatal harm when administered to a pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

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.

4.4 Special warning and precautions for use.

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

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

Docetaxel 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 dose reduced to 60 mg/m^2. Patients who experience Grade 3 or 4 stomatitis should have their Docetaxel dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel therapy should have their dosage of Docetaxel reduced from 75 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 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 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 treatment discontinued entirely.

Combination therapy with Docetaxel for chemotherapy-naïve NSCLC:

For patients who are dosed initially at Docetaxel 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the Docetaxel dosage in subsequent cycles should be reduced to 65 mg/m^2.
In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended.

Prostate Cancer:

Combination therapy with Docetaxel for hormone-refractory metastatic prostate cancer:

Docetaxel should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel therapy should have the dosage of Docetaxel reduced from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Gastric or Head and Neck Cancer:

Docetaxel in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer:

Patients treated with Docetaxel in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the Docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the Docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the Docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm3. Discontinue treatment if these toxicities persist.

Liver dysfunction:

In case of AST/ALT > 2.5 to ≤5 x UNL and AP ≤2.5 x UNL, or AST/ALT > 1.5 to ≤5 x UNL and AP > 2.5 to ≤5 x UNL, Docetaxel should be reduced by 20%.
In case of AST/ALT > 5 x UNL and/or AP > 5 x UNL Docetaxel should be stopped.

Pregnancy:

Pregnancy Category D:

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 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 or potential risk for loss of the pregnancy. 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 safety and effectiveness of docetaxel in pediatric patients have not been established.

Hepatic Impairment:

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

Geriatric Use:

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

4.5 Interaction with other medicinal products and other form of interactions

Drug interactions may be the result of altered pharmacokinetics or pharmacodynamics due to one of the drugs involved. Cisplatin, dexamethasone, doxorubicin, etoposide and vinblastine are all potentially co-administered with docetaxel and did not modify docetaxel plasma binding in phase II studies. Cisplatin is known to have a complex interaction with some CYPs and has in some events been shown to reduce docetaxel clearance by up to 25%. Anticonvulsants induce some metabolic pathways relevant to docetaxel. CYP450 and CYP3A show increased expression in response to the use of anticonvulsants and the metabolism of docetaxel metabolite M4 is processed by these CYPs. A corresponding increase in clearance of M4 by 25% is observed in patients taking phenytoin and phenobarbital, common anticonvulsants.

Common and/or likely drug-drug combinations and known side effects from drug interactions

Drug Interacting with Docetaxel	Adverse Effects from Interaction
Cisplatin	Increased risk of delayed neuropathy
Cyclosporine, Dalfopristin, Erythromycin, Itraconazole, Ketoconazole, Quinupristin, Terfenadine, Troleandomycin	Increased risk of docetaxel toxicity including some or all of; anaemia, leucopoenia, thrombocytopenia, fever, diarrhoea
Doxorubicin Hydrochloride	cholestatic jaundice and pseudomembranous colitis
Doxorubicin Hydrochloride Liposome	Increased doxorubicin exposure
Vaccinations for; Bacillus of Calmette and Guerin, Measles, Mumps, Poliovirus, Rotavirus, Rubella, Smallpox, Typhoid, Varicella, Yellow Fever	Increased risk of infection by live vaccine
Thalidomide	Increased risk of venous thromboembolism

Erythromycin, ketoconazole and cyclosporine are CYP3A4 inhibitors and therefore inhibit the

metabolic pathway of docetaxel. When used with anticonvulsants, which induce CYP3A4, an increased dose of docetaxel may be required.

Pre-treatment with corticosteroids has been used to decrease hypersensitivity reactions and oedema in response to docetaxel and has shown no effect on the pharmacokinetics of docetaxel. The efficacy of docetaxel was improved by treatment with oral capecitabine and after more than 27 months follow-up, the survival benefit has been confirmed. Doxorubicin was combined with docetaxel in one study of 24 patients and resulted in an increased AUC of docetaxel by 50 to 70%, indicating doxorubicin may affect the disposition of docetaxel. Etoposide has also been shown to decrease docetaxel clearance; thought patient numbers for this observation have been low.

Prednisone given with docetaxel led to improved survival, quality of life and pain management in patients with hormone-refractory prostate cancer.

4.6 Pregnancy and lactation

Pregnancy Category D

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 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 or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

Lactating 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

4.7 Effects on ability to drive and use machine

Since Solvent for Docetaxel Injection contains Alcohol, which may cause dizziness. So driving and operation of machinery is not recommended

4.8 Undesirable effects

Some people receiving a docetaxel injection have had a reaction to the infusion (when the medicine is injected into the vein). Tell your caregiver right away if you feel dizzy, light-headed, warm, or itchy, or if you have chest tightness or trouble breathing during the injection.

Get emergency medical help if any of these signs of an allergic reaction

Hives; Difficulty breathing; Swelling of your face, lips, tongue, or throat.

Call the doctor at once if you have any of these serious side effects

Easy bruising or bleeding,

Unusual weakness; Feeling like you might pass out;

Fever, chills, body aches, flu symptoms; severe diarrhea;

Skin changes or bruising where the IV was placed;

Nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools,

Jaundice (yellowing of the skin or eyes);

Feeling short of breath, even with mild exertion;

Swelling of your ankles or feet, weight gain; A red, blistering, peeling skin rash; or

Numbness, burning, pain, or tingly feeling.

Less serious side effects may include

Feeling weak or tired;

White patches or sores inside your mouth or on your lips;

Mild nausea, vomiting, diarrhea, constipation, or loss of appetite;

Watery eyes;

Changes in menstrual periods;

Temporary hair loss; or Fingernail or toenail changes.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA)

4.9 Overdosage

There is no known antidote for Docetaxel 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 IV doses that were ≥ 154 mg/kg (about 4.5 times the recommended human dose 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 recommended human dose on a mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg / kg (comparable to the recommended human dose on a mg/m2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

5. Pharmacological properties

5.1 Pharmacodynamics Properties

Molecular target

Docetaxel binds to microtubules reversibly with high affinity and has a maximum stoichiometry of 1

mole docetaxel per mole tubulin in microtubules. This binding stabilises microtubules and prevents depolymerisation from calcium ions, decreased temperature and dilution, preferentially at the plus end of the microtubule. Docetaxel has been found to accumulate to higher concentration in ovarian adenocarcinoma cells than kidney carcinoma cells, which may contribute to the more effective treatment of ovarian cancer by docetaxel. It has also been found to lead to the phosphorylation of oncoprotein, which is apoptosis blocking in its oncoprotein form.

Modes of action:

The cytotoxic activity of docetaxel is exerted by promoting and stabilising microtubule assembly, while preventing physiological microtubule depolymerisation/disassembly in the absence of GTP. This leads to a significant decrease in free tubulin, needed for microtubule formation and results in inhibition of mitotic cell division between metaphase and anaphase, preventing further cancer cell progeny.

Because microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell and cause initiation of apoptosis. Apoptosis is also encouraged by the blocking of apoptosis-blocking bcl-2 oncoprotein. Both in vitro and in vivo analysis show the anti-neoplastic activity of docetaxel to be effective against a wide range of known cancer cells, cooperate with other anti-neoplastic agents activity, and have greater cytotoxicity than paclitaxel, possibly due to its more rapid intracellular uptake.

The main mode of therapeutic action of docetaxel is the suppression of microtubule dynamic assembly and disassembly, rather than microtubule bundling leading to apoptosis, or the blocking of bcl-2.

Cellular responses

Docetaxel exhibits cytotoxic activity on breast, colorectal, lung, ovarian, gastric, renal and prostate cancer cells. Docetaxel does not block disassembly of interphase microtubules and so does not prevent entry into the mitotic cycle, but does block mitosis by inhibiting mitotic spindle assembly. Resistance to paclitaxel or anthracycline doxorubicin does not necessarily indicate resistance to docetaxel. Microtubules formed in the presence of docetaxel are of a larger size than those formed in

the presence of paclitaxel, which may result in improved cytotoxic efficacy. Abundant formation of microtubules and the prevention to replicate caused by the presence of docetaxel leads to apoptosis of tumour cells and is the basis of docetaxel use as a cancer treatment. It is unknown if pathophysiological interactions with docetaxel exist at this stage, however tumour type has been shown to have efficacy on cellular activity. Docetaxel activity is significantly greater in ovarian and breast tumours than for lung tumours.

5.2 Pharmacokinetics Properties

Absorption and distribution

Intravenous administration of docetaxel results in 100% bioavailability and absorption is immediate. Oral bioavailability has been found to be 8% ±6% on its own and, when co-administered with cyclosporine, bioavailability increased to 90% ± 44%. In practice, docetaxel is administered intravenously only to increase dose precision. Evaluation of docetaxel pharmacokinetics in phase II and III clinical studies were with 100 mg/m² dosages given over one-hour infusions every three weeks.

Docetaxel was shown to be greater than 98% plasma protein bound independent of concentration at 37°C and pH 7.4 Docetaxel's plasma protein binding includes lipoproteins, alpha1 acid glycoprotein and albumin. Alpha1 acid glycoprotein is the most variable of these proteins inter-individually, especially in cancer patients and is therefore the main determinant of docetaxel's plasma binding variability. Docetaxel interacted little with erythrocytes and was unaffected by the polysorbate 80 in its storage medium.

The concentration-time profile of docetaxel was consistent with a three-compartment pharmacokinetic model. An initial, relatively rapid decline, with an α half-life of mean 4.5 minutes is representative of distribution to peripheral compartments from the systemic circulation. A β half-life of mean 38.3 minutes and a relatively slow γ half-life of mean 12.2 hours represent the slow efflux of docetaxel from the peripheral compartment.

Administration a 100 mg/m² dose over a one hour infusion gave a mean total body clearance of 21 L/h/m² and a mean steady state volume of distribution of 73.8 L/m² or 123 L based on the mean BSA (body surface area) of 1.68 m². Area under the plasma concentration-time curve had a mean value of 2.8 mg.h/L. The Cmax of docetaxel was found to be 4.15 ± 1.35 mg/L. Increased dose resulted in a

linear increase of the area under the concentration-time curve and so it is concluded that dose is directly proportional to plasma concentration

Metabolism and excretion

Docetaxel is mainly metabolised in the liver by the cytochrome P450 CYP3A4 and CYP3A5 subfamilies of isoenzymes. Metabolism is principally oxidative and at the tert-butylpropionate side chain, resulting first in an alcohol docetaxel (M2), which is then cyclised to three further metabolites (M1, M3 and M4). M1 and M3 are two diasteromeric hydroxyoxazolidinones and M4 is an oxazolidinedione. Phase II trials of 577 patients showed docetaxel clearance to be related to body surface area and; hepatic enzyme and alpha1 acid glycoprotein, plasma levels.

The following model is agreed to represent docetaxel clearance in humans:

$$CL = BSA \cdot (22.1 - 3.55 \cdot AAG - 0.095 \cdot AGE + 0.2245 \cdot ALB) \cdot (1 - 0.334 \cdot HEP12)$$

where CL is total body clearance (L/h), BSA is total body surface area (m^2), AAG and ALB represent alpha1 acid glycoprotein and albumin plasma concentrations (g/L) respectively, and AGE is the patients age (years). HEP12 represents a measure of hepatic dysfunction, affecting clearance of docetaxel. This final model accounted for a modest proportion of patients and identified most of the patients varying from the model (population median of CL = 35.6 L/h) as having hepatic dysfunction, indicating hepatic function as the most unpredictable factor with regards to clearance variability.

Patients with significant hepatic dysfunction had an approximately 30% decrease in clearance of docetaxel and were also at a higher risk of toxicity poisoning from docetaxel treatment. Clearance has been shown from population pharmacokinetic studies to decrease significantly with age, increased alpha1 acid glycoprotein and albumin concentrations and decreased body surface area.

Renal impairment is unlikely to affect metabolism or excretion of docetaxel as renal excretion contributes less than 5% of elimination. Limited data is available for docetaxel use in children with dosage between 55 and 75 mg/m^2. Two paediatric studies have taken place that show a mean clearance of 33 $L/h/m^2$ and concentration-time profiles best fitted by a two-compartmental model of distribution and elimination. Mean distribution half-life was 0.09 hours and mean elimination half-life was 1.4 hours in paediatric studies.

Biodistribution of 14C-labelled docetaxel in three patients showed the bulk of the drug to be metabolised and excreted in bile to the faeces. Of the radioactively labelled docetaxel administered,

80% was eliminated to the faeces with 5% in the urine over seven days, an indication that urinary excretion of docetaxel is minimal. Saliva contributed minimal excretion and no excretion was detected through pulmonary means. The terminal half-life of docetaxel was determined as approximately 86 hours, through prolonged plasma sampling, contrary to the clinically stated terminal half-life of 10–18 hours.

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

Docetaxel has been shown to be mutagenic in the in vitro micronucleus and chromosome aberration test in CHO-K1 cells and in the in vivo micronucleus test in the mouse. However, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. These results are consistent with the pharmacological activity of docetaxel.

Undesirable effects on the testis observed in rodent toxicity studies suggest that docetaxel may impair male fertility.

6. Pharmaceutical Particulars

6.1 List of excipients

Following excipients used during the manufacturing of Docetaxel Injection USP (Two vial formulation)

Following excipients used during the manufacturing of Docetaxel Injection USP

Polysorbate 80 USNF as solbulizer.

Ethanol 96 % BP

Water for Injection USP as vehicle.

6.2 Incompatibilities

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-2-ethylhexyl 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 polyethylene-lined administration sets.

6.3 Shelf life

24 months from the date of manufacturing, when retained in the original carton.

6.4 Special precautions for storage

Store protected from light at a temperature between 2 º to 8° (36º F and 46º F)

6.5 Special precautions for disposal and other handlings

Docetaxel is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel solutions. The use of gloves is recommended.

If Docetaxel concentrate or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Docetaxel concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

As with all parenteral products, Docetaxel infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.5. Nature and contents of container

10 mL Clear Glass Vial USP Type I [Injection Concentrate and Solvent]

20 mm Bromo butyl rubber plug

20 mm ALuminium flip off seal

7. Marketing authorisation holder

Beta Drugs Limited

Kharuni-Lodhimajra Road,

Vill: Nandpur, Baddi, Distt. Solan,

Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

07493/08900/NMR/2021

9. Date of first authorisation

02 Jun 2022

10. Date of revision of the text