PACKAGE INSERT TEMPLATE FOR DOCETAXEL SOLUTION FOR INJECTION

Brand or Product Name
[Product name] 80mg/2ml Vial
[Product name] 20mg/0.5ml Vial

Name and Strength of Active Substance(s)
Docetaxel trihydrate…mg equivalent to …mg Docetaxel anhydrous

Product Description
[Visual description of the appearance of the product (eg colour etc)]
eg Clear colourless liquid

Pharmacodynamics
Docetaxel is a semisynthetic analogue of paclitaxel
Systemic: Docetaxel is an antimitotic agent. It binds to free tubulin, then promotes the polymerization of tubulin into stable microtubules and inhibits microtubule disassembly, resulting in blockade of cellular mitotic and interphase functions and, consequently, in inhibition of cell division. Unlike paclitaxel and other spindle poisons in clinical use, docetaxel does not alter the number of protofilaments in the bound microtubules.
The mechanisms by which resistance to docetaxel occurs are not completely understood. Studies have shown that docetaxel is active against several tumor cell lines overexpressing the multidrug resistance gene. Also, cross-resistance between docetaxel and paclitaxel does not occur consistently.
Several in vitro and in vivo studies have shown that docetaxel has only moderate immunosuppressive activity

Pharmacokinetics
The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Distribution
Intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins

Metabolism
It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A4

Excretion
Docetaxel is excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment

Indication
Breast Cancer:

- Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

- Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

- Docetaxel in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

- Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer in whom previous therapy has failed. Prior therapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer:

- Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer even after failure of 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, in patients who have not previously received chemotherapy for this condition.
- Docetaxel in combination with carboplatin represents a treatment option to cisplatin-based therapy.

Ovarian Cancer:

- Docetaxel is indicated for the treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.

Squamous Cell Carcinoma of the Head and Neck:

- Docetaxel is indicated as monotherapy in the treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck after failure of a previous chemotherapy regimen.

Prostate Cancer:

- Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostatic cancer

- The use of docetaxel should be confined to units specialized in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Gastric Adenocarcinoma:

- Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Head and neck cancer:

- Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Recommended Dosage

For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. For prostate cancer, given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion.

Docetaxel is administered as a one-hour infusion every three weeks.

Breast cancer

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel 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 cycles. For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dosage of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).

In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 twice daily (within 30 minutes after a meal)

for 2 weeks followed by 1- week rest period. For capecitabine dose calculation according to body surface area, see capecitabine summary of product characteristics.

Non-small cell lung cancer
In chemotherapy naive patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dosage is 75 mg/m^2 as a single agent.

Prostate cancer
The recommended dose of docetaxel is 75 mg/m2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

Gastric adenocarcinoma
The recommended dose of docetaxel is 75 mg/m^2as a 1 hour infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour infusion (both on day 1 only), and followed by 5-fluorouracil 750 mg /m2 per day given as a 24-hour continuous 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. Prophylactic G-CSF should be used to mitigate the risk of hematological toxicities.

Head and neck cancer
For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head neck (SCCHN), the recommended dose of Docetaxel is 75 mg/m^2as a 1 hour infusion followed by cisplatin 75 mg/m^2over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m^2per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. For cisplatin and 5-fluorouracil dose modifications, see manufacturer's summary of product characteristic.

Ovarian Cancer
The recommended dosage is 100mg/m2 administered as one hour infusion every three weeks. When use in combination, docetaxel is administered at the recommended dosage of 75 mg/m^2.

Squamous Cell Carcinoma of the Head and Neck
The recommended dosage is 100mg/m2 administered as one hour infusion every three weeks. When use in combination, docetaxel is administered at the recommended dosage of 75 mg/m^2.

Dosage adjustment during treatment

General

Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil < 500 cells /mm3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100mg/m^2 to 75mg/m^2 and/or from 75 to 60mg/m^2. If the patient continues to experience these reactions at 60mg/m^2, the treatment should be discontinued.

Adjuvant therapy for breast cancer

In patients who received adjuvant therapy for breast cancer and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg. Day 4 to 11) in all subsequent cycles. Patients who continued to experience this reaction should remain on G-CSF and have their docetaxel dose reduced to 60mg/m^2.

However, in clinical practice neutropenia could occur earlier. Thus the use of G-CSF should be considered function of the neutropenic risk of the patient and current recommendations. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m^2

In combination with cisplatin

For patients who are dosed initially at docetaxel 75mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is<25000 cells/mm^2, or in patients who experience febrile neutropenia, or in patients with serious non-hematologic toxicities, the docetaxel dosage in subsequent cycles should be reduced to 65mg/m^2. For cisplatin dosage adjustments, see manufacturer's summary of product characteristics.

In combination with capecitabine:

- For capecitabine dose modifications, see capecitabine summary of product characteristics
- For patients developing the first appearance of a Grade 2 toxicity, which persists at the time of the next docetaxel /capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100% of the original dose.
- For patients developing the second appearance of a Grade 2 toxicity, or the first appearance of a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with docetaxel 55mg/m^2.
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose.

In combination with cisplatin and 5-fluorouracil:

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/mm^3. Discontinue treatment if these toxicities persist.

Recommended dose modifications for gastrointestinal toxicities in patients treated with docetaxel in combination with cisplatin and 5-fluorouracil (5-FU):

Toxicity	Dosage adjustment
Diarrhoea grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.
Diarrhoea grade 4	First episode: reduce docetaxel and 5-FU doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce 5-FU dose by 20%. Second episode: stop 5-FU only, at all subsequent cycles. Third episode: reduce docetaxel dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%

For cisplatin and 5-fluorouracil dosage adjustments, see manufacturers' summary of product characteristics.

In patients who received an induction treatment with docetaxel for inoperable locally advanced squamous SCCHN and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg, day 6-15) in all subsequent cycles.

Special populations

Patients with hepatic impairment: Based on pharmacokinetic data with docetaxel at 100mg/m^2 as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75mg/m^2 .For those patients with serum bilirubin>ULN and/or ALT and AST.3.5 times the ULN associated with alkaline phosphatase > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination.

Children: The safety and effectiveness of docetaxel in children have not been established.

Elderly: Based on population pharmacokinetic analysis, there are no special instructions for use in the elderly. In combination with capecitabine, for patients 60 years of age or more, a starting dose reduction of capecitabine to 75% is recommended

Mode of Administration

Intravenous Administration

Contraindications

- Hypersensitivity reactions to the active substance or to any of the excipients
- Docetaxel should not be used in patients with baseline neutrophil counts of < 1,500 cells/mm^3
- Docetaxel must not be used in pregnant or breast-feeding women
- Docetaxel should not be used in patients with severe liver impairment since there is no data available
- Contraindications for other medicinal products also apply, when combined with docetaxel

Warnings and Precautions

- Treatment-related mortality has been reported; increased risk in patients with abnormal liver function, receiving higher doses, and 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)

- Concomitant use with CYP3A4 inhibitors should be avoided; if coadministration with a potent CYP3A4 inhibitor is necessary, closely monitor patients for toxicity and consider a docetaxel dosage adjustment

- Severe thrombocytopenia has occurred; monitor blood cell counts frequently; do not retreat with subsequent cycles until the platelet count is greater than 100,000 cells/mm(3)

- Severe (grade 4) neutropenia has been reported, with some cases associated with infection; monitor blood cell counts frequently and for signs of febrile neutropenia or neutropenic infections; dose reduction or therapy discontinuation may be warranted; do not retreat with subsequent cycles until the neutrophil count is greater than 1500 cells/mm(3)

- In patients treated with docetaxel in combination with cisplatin and 5-fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic GCSF. Patients treated with TCF should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TCF should be closely monitored.

- Observe patients closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel. Flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

- Cutaneous toxicity (eg, localized erythema of the extremities with edema followed by desquamation) has occurred; dose reduction or therapy discontinuation may be warranted if severe skin toxicity develops

- Severe fluid retention (eg, peripheral edema, generalized edema, pleural effusion, ascites) has occurred; pretreatment with oral corticosteroids recommended prior to each dose

- Elderly patients (aged 65 yr or older); higher incidence of serious adverse events compared with younger patients

- Hepatic impairment; increased risk of severe or life-threatening toxicities; do not use in patients in patients with a bilirubin level greater than the ULN or SGOT and/or SGPT levels greater than 1.5 x ULN concomitant with an alkaline phosphatase (AP) level greater than 2.5 x ULN; monitor LFTs prior to each treatment cycle; dosage adjustment recommended for LFT elevations during treatment; discontinue treatment in patients who develop AST/ALT levels greater than 5 x ULN and/or AP level greater than 5 x ULN

- Severe neurosensory symptoms (eg, paresthesia, dysesthesia, pain) have been reported; dose reduction or therapy discontinuation may be warranted

- Contraceptive measures must be taken during and for at least three months after cessation of therapy.

- Acute myeloid leukemia has been reported rarely in patients with breast cancer who received adjuvant therapy with docetaxel, doxorubicin, and cyclophosphamide; hematological follow-up recommended in this patient population

Additional cautions for use in adjuvant treatment of breast cancer

Complicated neutropenia
For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G-CSF and dose reduction should be considered.

Gastrointestinal reactions
Symptoms such as early abdominal pain and tenderness, fever, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.

Congestive heart failure
Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period.

Leukemia
In the Docetaxel, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires haematological follow-up.

Patients with 4+ nodes
The benefit/risk ratio for TAC in patients with 4+ nodes was not defined fully at the interim analysis.

Interactions with Other Medicaments

Docetaxel is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with inducers or inhibitors or other substrates of this enzyme may affect exposure to docetaxel. It should be given with caution to patients taking strong CYP3A4 inhibitors including HIV-protease inhibitors such as ritonavir, and azole antifungals like ketoconazole or itraconazole.

Concurrent use of rotavirus vaccine and chemotherapeutic agents may result in an increased risk of infection by the live vaccine. Hence it is contraindicated.

Concurrent use of docetaxel and thalidomide may result in an increased risk of venous thromboembolism.

Concurrent use of live vaccines and chemotherapeutic agents may result in an increased risk of infection by the live vaccine.

Concurrent use of docetaxel and doxorubicin may result in cholestatic jaundice and pseudomembranous colitis.

Concurrent use of docetaxel and itraconazole may result in an increased risk of docetaxel toxicity.

Concurrent use of docetaxel and the following may result in an increased risk of docetaxel toxicity (anemia, leukopenia, thrombocytopenia, fever, diarrhea)

- erythromycin
- terfenadine
- troleandomycin
- telithromycin
- indinavir
- nefazodone
- atazanavir
- nelfinavir
- clarithromycin
- cyclosporine
- ketoconazole
- voriconazole
- ritonavir

Concurrent use of cisplatin and docetaxel may result in increased risk of neuropathy.

Concurrent use of docetaxel and sorafenib may result in increased docetaxel exposure and plasma concentrations

Concurrent use of docetaxel and quinupristin/dalfopristin may result in an increased risk of docetaxel toxicity (neutropenia, anemia, neuropathy).

Concurrent use of docetaxel and doxorubicin hydrochloride liposome may result in increase in doxorubicin exposure.

Concurrent use of docetaxel and grapefruit juice may result in increased docetaxel exposure

Statement on Usage During Pregnancy and Lactation

Pregnancy
In general, antineoplastic agents when given during the first trimester are believed to cause increases in the risk of congenital malformations, but when given during the second or third trimesters are believed to only increase the risk of growth retardation. Depending upon the nature of the malignancy, the progression of the disease and how advanced the gestation, chemotherapy can, in some cases, be deferred allowing fetal maturation to occur, and in some cases, earlier-than-term delivery may provide an acceptable compromise between maternal and fetal risk.

Due to the potential for fetotoxicity and maternal toxicity demonstrated in animal studies and the lack of adequate, well-controlled human studies, docetaxel must not be used during pregnancy. Women of childbearing potential should be instructed to avoid pregnancy during docetaxel therapy and to inform the treating physician immediately should this occur. If docetaxel therapy is initiated in a pregnant woman or if a woman becomes pregnant while receiving docetaxel treatment, she should be apprised of the potential harm to the fetus and of the possible risk of losing the pregnancy

Lactation
It is not known whether docetaxel is excreted into human breast milk and the potential for adverse effects in the nursing infant from docetaxel exposure is unknown. Due of the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue docetaxel, taking into consideration the importance of the drug to the mother

Adverse Effects / Undesirable Effects

Common

- Cardiovascular: Edema, Vasodilatation
- Dermatologic: Alopecia, Disorder of nail, Disorder of skin AND/OR subcutaneous tissue, Nail changes, Pruritus, Rash
- Gastrointestinal: Diarrhea, Nausea , Stomatitis, Vomiting
- Hematologic: Anemia, Leukopenia, Neutropenia
- Neurologic: Asthenia, Neuropathy
- Reproductive: Amenorrhea
- Other: Fever of unknown origin, weight gain

Serious

- Cardiovascular: Edema (Severe)
- Dermatologic: Stevens-Johnson syndrome, Toxic epidermal necrolysis
- Gastrointestinal: Colitis
- Hematologic: Anemia, less than 8 g/dL , Febrile neutropenia, Leukopenia, less than 1000 cells/mm(3), Neutropenia, less than 500 cells/mm(3), Thrombocytopenia
- Hepatic: Hepatotoxicity
- Immunologic: Anaphylaxis (rare)
- Renal: Renal failure
- Respiratory: Interstitial pneumonia, Pulmonary embolism
- Other: Infectious disease

Martindale, Micromedex

- Rare cases of ototoxicity, hearing impairment or loss have occurred.
- Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported with combination chemotherapy regimens containing docetaxel; haematological follow-up may be required.

Overdose and Treatment

Symptoms
Overdose effects are expected to be an extension of adverse events and include bone marrow suppression, peripheral neurotoxicity, and mucositis.
Mild to moderate toxicity: Early symptoms may include: nausea, vomiting and diarrhea.
Severe toxicity: Myelosuppression (neutropenia and febrile neutropenia) is likely to develop and can be severe. Anemia and thrombocytopenia may develop. Other potentially serious events include: liver function impairment; fluid retention leading to edema, dyspnea, cardiac tamponade, or pleural effusion; and severe stomatitis. Patients with abnormal liver function are at increased risk of toxicity.

Treatment
Treatment is primarily symptomatic and supportive, there is no antidote. Colony stimulating factor (filgrastim or sargramostim) should be initiated as soon as possible. Patients with severe neutropenia should be in protective isolation. Platelet and red cell transfusions may be necessary. In case of emesis, aggressively treat with antiemetics and fluid and electrolyte replacement as indicated. Closely monitor patients for hypotension, bradycardia, and other cardiac dysrhythmias. Monitor liver enzymes and renal function.

Incompatibilities
[This medicinal product must not be mixed with ..]

Instructions for use and handling, and disposal
[Instructions on use, handling and disposal]

Storage Conditions
[eg Store below… °C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]