# Docetaxel Injection IP 120mg/6ml, 80mg/4ml 20mg/ml

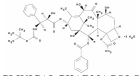
**DOCE-ACE**™ 120mg/80mg/20mg
Injection

Each ml contains :

| | |
|---|---|
| Docetaxel Anhydrous IP | 20 mg |
| Polysorbate 80 IP | 540 mg |
| Dehydrated Alcohol IP | 395 mg |

**DESCRIPTION**

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis 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 5 ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



**CLINICAL PHARMACOLOGY**

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their 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.

**INDICATIONS AND USAGE**

**Breast cancer**

Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

• operable node- positive breast cancer.

• operable node- negative breast cancer.

For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early 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 monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

**Non-small cell lung cancer**

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior 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.

**Prostate cancer**

Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

**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 locally advanced squamous cell carcinoma of the head and neck.

**DOSAGE & ADMINISTRATION**

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.

For metastatic castration-resistant 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.

For metastatic hormone-sensitive prostate cancer, irrespective of the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg 12 hours, 3 hours, and 1 hour before docetaxel infusion.

Prophylactic G CSF may be used to mitigate the risk of haematological toxicities.

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

**Breast cancer**

In the adjuvant treatment of operable node-positive and node-negative 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 (TAC regimen) (see also Dose adjustments during treatment).

For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose 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 trastuzumab the recommended dose of docetaxel is 100 mg/m$^2$ every three weeks, with trastuzumab administered weekly. In the pivotal study the initial docetaxel infusion was started the day following the first dose of trastuzumab. The subsequent docetaxel doses were administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. For trastuzumab dose and administration, see trastuzumab summary of product characteristics.

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

**Prostate cancer**

*Metastatic castration-resistant prostate cancer*

The recommended dose of docetaxel is 75 mg/m$^2$. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

*Metastatic hormone-sensitive prostate cancer*

The recommended dose of docetaxel is 75 mg/m$^2$ every 3 weeks for 6 cycles. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

**Gastric adenocarcinoma**

The recommended dose of docetaxel is 75 mg/m2 as a 1-hour infusion, followed by cisplatin 75 mg/m$^2$, as a 1- to 3-hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg/m$^2$ 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 haematological toxicities.

**Head and neck cancer**

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 haematological toxicities. All patients on the docetaxel-containing arm of the TAX 323 and TAX 324 studies, received prophylactic antibiotics.

• Induction chemotherapy followed by radiotherapy (TAX 323)

For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m$^2$ as a 1 hour infusion followed by cisplatin 75 mg/m$^2$ over 1 hour, on day one, followed by 5-fluorouracil as a continuous 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 (TAX 324)

For the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, and aiming at organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel 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 5-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 chemoradiotherapy.

**CONTRAINDICATIONS**

Hypersensitivity to the active substance.

Patients with baseline neutrophil count of < 1,500 cells/mm$^3$.

Patients with severe liver impairment.

Contraindications for other medicinal products also apply, when combined with docetaxel.

**WARNINGS & PRECAUTIONS**

For breast and non-small cell lung 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 reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. For prostate cancer, the premedication is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion.

**Haematology**

Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level ≥ 1,500 cells/mm$^3$.

In the case of severe neutropenia (< 500 cells/mm$^3$ for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended.

Gastrointestinal reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Although majority of cases occurred during the first or second cycle of docetaxel containing regimen, enterocolitis could develop at any time, and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity.

**Hypersensitivity reactions**

Patients should be observed 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, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy.

**Cutaneous reactions**

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation which lead to interruption or discontinuation of docetaxel treatment were reported.

**Fluid retention**

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

**Respiratory disorders**

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

**Patients with liver impairment**

In patients treated with docetaxel at 100 mg/m$^2$ as single agent who have serum transaminase levels (ALT and/or AST) greater than 1.5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of docetaxel in those patients with elevated liver function test (LFTs) is 75 mg/m$^2$ and LFTs should be measured at baseline and before each cycle.

For patients with serum bilirubin levels > ULN and/or ALT and AST > 3.5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

**Patients with renal impairment**

There are no data available in patients with severely impaired renal function treated with docetaxel.

**Nervous system**

The development of severe peripheral neurotoxicity requires a reduction of dose.

**Cardiac toxicity**

Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death.

**Eye disorders**

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.

**PREGNANCY AND LACTATION**

**Pregnancy**

There is no information on the use of docetaxel in pregnant women. Docetaxel has been shown to be both embryotoxic and foetotoxic in rabbits and rats, and to reduce fertility in rats. As with other cytotoxic medicinal products, docetaxel may cause foetal harm when administered to pregnant women. Therefore, docetaxel must not be used during pregnancy unless clearly indicated.

Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

**Breastfeeding**

Docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of docetaxel therapy.

**DRUG INTERACTIONS**

The amount of alcohol in this medicinal product may alter the effects of other medicinal products.

*In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, ketoconazole and erythromycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor. In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49%.

Docetaxel pharmacokinetics in the presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolised by CYP3A4 and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the pharmacokinetics of docetaxel was observed.

**ADVERSE EFFECTS**

The most commonly reported adverse reactions of docetaxel alone are: neutropenia (which was reversible and not cumulative; the median day to nadir was 7 days and the median duration of severe neutropenia (< 500 cells/mm$^3$) was 7 days), anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

For combination with trastuzumab, adverse events (all grades) reported in ≥ 10% are displayed. There was an increased incidence of SAEs (40% vs. 31%) and Grade 4 AEs (34% vs. 23%) in the trastuzumab combination arm compared to docetaxel monotherapy.

For combination with capecitabine, the most frequent treatment-related undesirable effects (≥ 5%) reported in a phase III study in breast cancer patients failing anthracycline treatment are presented (see capecitabine summary of product characteristics).

For combination with ADT and with prednisone or prednisolone (STAMPEDE study), adverse events occurring over the 6 cycles of treatment with docetaxel and having at least 2% higher incidence in the docetaxel treatment arm by comparison to the control arm, are presented, using the CTCAE grading scale.

The following adverse reactions are frequently observed with docetaxel:

*Immune system disorders*

Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of docetaxel and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills. Severe reactions were characterised by hypotension and/or bronchospasm or generalized rash/erythema.

*Nervous system disorders*

The development of severe peripheral neurotoxicity requires a reduction of dose. Mild to moderate neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

*Skin and subcutaneous tissue disorders*

Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the arms, face or thorax, and frequently associated with pruritus. Eruptions generally occurred within one week after the docetaxel infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely lead to interruption or discontinuation of docetaxel treatment were reported. Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

*General disorders and administration site conditions*

Infusion site reactions were generally mild and consisted of hyper pigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Fluid retention includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity.

**Storage : Store at a temperature not exceeding 25°C.**

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