PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOCETURAS 20 mg concentrate for solution for infusion

DOCETURAS 80 mg concentrate for solution for infusion

DOCETURAS 160 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg docetaxel trihydrate.

DOCETURAS 20 mg vial of 1 mL concentrate contains docetaxel trihydrate equivalent to 20 mg docetaxel.

DOCETURAS 80 mg vial of 4 mL concentrate contains docetaxel trihydrate equivalent to 80 mg docetaxel.

DOCETURAS 160 mg vial of 8 mL concentrate contains docetaxel trihydrate equivalent to 160 mg docetaxel.

Excipients with known effect:

DOCETURAS 20 mg contains 0,5 mL (395 mg) ethanol (alcohol) per 1 mL vial.

DOCETURAS 80 mg contains 2 mL (1,58 g) ethanol (alcohol) per 4 mL vial.

DOCETURAS 160 mg contains 4 mL (3,16 g) ethanol (alcohol) per 8 mL vial.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Pale yellow to brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

DOCETURAS, 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.

DOCETURAS monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer, after failure of cytotoxic therapy.

DOCETURAS, 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.

Non-small cell lung cancer

DOCETURAS, 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.

DOCETURAS is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, even after failure of platinum-based chemotherapy.

Ovarian cancer

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

Prostate cancer

DOCETURAS, in combination with prednisone or prednisolone, is indicated for the treatment of patients with androgen-independent (hormone refractory) metastatic prostate cancer.

4.2 Posology and method of administration

Posology

A premedication consisting of a corticosteroid (see below for prostate cancer), such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to DOCETURAS administration, unless contraindicated, can be used.

For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg administered 12 hours, 3 hours and 1 hour before the DOCETURAS infusion.

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

Breast cancer

In first-line treatment, DOCETURAS 75 mg/m^2 is administered in combination therapy with doxorubicin (50 mg/m^2).

For second-line monotherapy for previously treated patients, the recommended dosage of DOCETURAS therapy is 100 mg/m^2 in monotherapy.

In combination with capecitabine, the recommended dose of DOCETURAS is 75 mg/m^2 every three weeks, combined with capecitabine at 1 250 mg/m^2 orally 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 approved professional information (PI).

Non-small cell lung cancer

In combination therapy (chemotherapy-naïve patients):

The recommended dosage regimen is DOCETURAS 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30 – 60 minutes.

In monotherapy (for previously treated patients):

The recommended dosage of DOCETURAS therapy is 100 mg/m^2 as a single medicine.

Ovarian cancer

The recommended dosage of DOCETURAS therapy is 100 mg/m^2.

Prostate cancer

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

Patients should be observed closely, especially during the first and second infusion of DOCETURAS, because of the risk of hypersensitivity reactions.

Dosage adjustments during treatment

General

ONLY the medical practitioner can modify the schedule of administration. DOCETURAS should be administered when the neutrophil count is ≥ 1 500 cells/mm^3. Patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during DOCETURAS therapy, should have the dosage of DOCETURAS reduced during the subsequent cycle, from 100 mg/m^2 to 75 mg/m^2 and/or from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Combination therapy with DOCETURAS for non-small cell lung cancer

For patients who were dosed initially at DOCETURAS 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy was < 25 000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematological toxicities, the DOCETURAS dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see the cisplatin approved PI.

Combination therapy with DOCETURAS for breast cancer

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive granulocyte colony-stimulating factor (G-CSF) in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their DOCETURAS dose reduced to 60 mg/m^2. If G-CSF is not used, the DOCETURAS dose should be reduced from 75 to 60 mg/m^2.

For capecitabine dose modifications when combined with DOCETURAS, see capecitabine approved PI.

For patients developing the first appearance of grade 2 toxicity which persists at the time of the next DOCETURAS/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 grade 2 toxicity, or the first appearance of grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to grade 0 – 1, then resume treatment with DOCETURAS 55 mg/m^2. For any subsequent appearances of toxicities, or any grade 4 toxicities, discontinue the DOCETURAS dose.

For DOCETURAS dose modifications due to hepatic impairment, see section 4.4.

Special populations

Patients with hepatic impairment

Patients with bilirubin > ULN (upper limit of normal) should generally not receive DOCETURAS. Also, patients with AST (aspartate aminotransferase) and/or ALT (alanine transaminase) > 1,5 x ULN concomitant with alkaline phosphatase > 2,5 x ULN should generally not receive DOCETURAS.

Paediatric population

The safety and effectiveness of DOCETURAS in children have not been established (see section 4.3).

Elderly population

Based on a population pharmacokinetic analysis, there are no special instructions for use in elderly patients.

For capecitabine dosage reduction when combined with DOCETURAS, see capecitabine approved PI.

Method of administration

DOCETURAS should be administered by intravenous infusion only.

4.3 Contraindications

- Hypersensitivity to docetaxel or to any of the ingredients in DOCETURAS (see section 6.1).
- Patients with baseline neutrophil count of < 1 500 cells/mm^3.
- Pregnancy and lactation, as DOCETURAS is teratogenic in animals (see section 4.6).
- The safe use of DOCETURAS in children has not been established.
- Patients with severe liver impairment, since there are no data available (see sections 4.4).
- Contraindications for other medicines also apply when combined with DOCETURAS.

4.4 Special warnings and precautions for use

DOCETURAS should be administered under the supervision of a qualified medical practitioner experienced in the use of antineoplastic medicines. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are

readily available.

The incidence of treatment-related mortality associated with DOCETURAS therapy is increased in patients with abnormal liver function and in patients receiving higher doses.

DOCETURAS should generally not be given to patients with serum bilirubin levels > upper limit of normal (ULN), or to patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase levels > 2,5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminases concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity and toxic death.

Patients with isolated elevations of transaminase > 1,5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT and alkaline phosphatase values should be obtained prior to each cycle of DOCETURAS therapy and reviewed by the treating medical practitioner.

DOCETURAS therapy should not be given to patients with neutrophil counts of < 1 500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving DOCETURAS.

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema occurred in 2,2 % of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of docetaxel were reported in some patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

DOCETURAS must not be given to patients who have a history of severe hypersensitivity reactions to DOCETURAS or to other medicines formulated with polysorbate 80.

Severe fluid retention occurred in 6,5 % of patients despite use of a 3-day dexamethasone premedication regimen. It was characterised by one or more of the following events: poorly tolerated peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade or pronounced abdominal distension (due to ascites).

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 twice per day) for 3 days starting 1 day prior to DOCETURAS 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 DOCETURAS infusion (see section 4.2).

Haematology

Neutropenia is the most frequent adverse reaction of docetaxel, as in DOCETURAS. 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 DOCETURAS. Patients should be retreated with DOCETURAS when neutrophils recover to a level ≥ 1 500 cells/mm^3 (see section 4.2).

In the case of severe neutropenia (< 500 cells/mm^3 for seven days or more) during a course of DOCETURAS therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended (see section 4.2).

In patients treated with docetaxel as in DOCETURAS in combination with cisplatin and 5-

fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G-CSF.

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 (see sections 4.2 and 4.8).

In patients treated with docetaxel as in DOCETURAS in combination with doxorubicin and cyclophosphamide (TAC), febrile neutropenia and/or neutropenic infection occurred at lower rates when patients received primary G-CSF prophylaxis. Primary G-CSF prophylaxis should be considered in patients who receive adjuvant therapy with TAC for breast cancer to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TAC should be closely monitored (see sections 4.2 and 4.8).

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, as in DOCETURAS, 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 (see sections 4.2, 4.4 and 4.8).

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 DOCETURAS, 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. However,

severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCETURAS and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCETURAS. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, as in DOCETURAS, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of therapy with DOCETURAS.

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 (see section 4.2).

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

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.

If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated and appropriately treated. Interruption of DOCETURAS therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming DOCETURAS treatment must be carefully evaluated.

Patients with liver impairment

In patients treated with DOCETURAS at 100 mg/m^2 as single medicine who have serum transaminase levels (ALT and/or AST) > 1,5 times the ULN concurrent with serum alkaline phosphatase levels > 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 DOCETURAS 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 (see section 4.2).

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 DOCETURAS should not be used unless strictly indicated.

In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical study excluded patients with ALT and/or AST > 1,5 x ULN associated with alkaline phosphatase > 2,5 x ULN and bilirubin > 1 x ULN; for these patients, no dose-reductions can be recommended and DOCETURAS should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by DOCETURAS in combination in the other indications.

Patients with renal impairment

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

Nervous system

The development of severe peripheral neurotoxicity requires a reduction of dose (see section 4.2).

Cardiac toxicity

Ventricular dysrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide (see section 4.8).

Baseline cardiac assessment is recommended.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel, as in DOCETURAS. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, DOCETURAS treatment should be discontinued and appropriate treatment initiated (see section 4.8).

Second primary malignancies

Second primary malignancies have been reported when docetaxel was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukaemia, myelodysplastic syndrome and non-Hodgkin lymphoma) may occur several months or years after docetaxel-containing therapy. Patients should be monitored for second primary malignancies (see section 4.8).

Tumour lysis syndrome

Tumour lysis syndrome has been reported with docetaxel, as in DOCETURAS, after the first or the second cycle (see section 4.8). Patients at risk of tumour lysis syndrome (e.g. with renal impairment, hyperuricemia, bulky tumour, rapid progression) should be closely monitored. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

Others

Contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy (see section 4.6).

The concomitant use of DOCTUTRAS with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see section 4.5).

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 (see section 4.2).

Gastrointestinal reactions

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

Congestive heart failure (CHF)

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period. In patients treated with the TAC regimen for node positive breast

cancer, the risk of CHF has been shown to be higher during the first year after treatment (see section 4.8 and 5.1).

Patients with 4+ nodes

As the benefit observed in patient with 4+ nodes was not statistically significant on disease-free survival (DFS) and overall survival (OS), the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis (see section 5.1).

Elderly population

Elderly patients treated with TCF should be closely monitored.

Excipients

DOCETURAS contains 50 % *v/v* ethanol (alcohol).

DOCETURAS 20 mg contains 0,5 mL ethanol (alcohol) (395 mg), equivalent to 10 mL of beer or 4 mL wine per 1 mL vial.

DOCETURAS 80 mg contains 2 mL ethanol (alcohol) (1,58 g), equivalent to 40 mL of beer or 17 mL wine per 4 mL vial.

DOCETURAS 160 mg contains 4 mL ethanol (alcohol) (3,16 g), equivalent to 80 mL beer or 33 mL wine per 8 mL vial.

DOCETURAS may be harmful for those suffering from alcoholism.

To be taken into account in pregnant or breastfeeding women (see section 4.6), children and high-risk groups such as patients with liver disease or epilepsy.

Consideration should be given to possible effects on the central nervous system.

4.5 Interaction with other medicines and other forms of interaction

The quantity of alcohol in DOCETURAS may alter the effects of other medicines.

In vitro studies have shown that the metabolism of docetaxel, as in DOCETURAS, 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 ciclosporin, ketoconazole and erythromycin. As a result, caution should be exercised when treating patients with these medicines as concomitant therapy, since there is a potential for a significant interaction.

In case of combination with CYP3A4 inhibitors, the occurrence of DOCETURAS 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 DOCETURAS may be suitable during the treatment with strong CYP3A4 inhibitors (see section 4.4).

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, as in DOCETURAS was observed.

Docetaxel is highly protein bound (> 95 %). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicines has not been investigated formally, *in vitro* interactions with tightly protein-bound medicines such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel, as in DOCETURAS. In addition, dexamethasone did not affect protein binding of docetaxel, as in DOCETURAS.

Docetaxel did not influence the binding of digoxin.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration. Limited data from a single uncontrolled study were suggestive of an interaction between docetaxel and carboplatin. When combined to docetaxel, as in DOCETURAS, the clearance of carboplatin was approximately 50 % higher than values previously reported for carboplatin monotherapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Contraceptive measures must be taken by both men and women during treatment. It should be taken by women for at least three months after cessation of DOCETURAS therapy and by men 6 months after cessation of therapy.

Pregnancy

The use of DOCETURAS is contraindicated in pregnancy as docetaxel is teratogenic in animals.

Breastfeeding

The use of DOCETURAS is contraindicated in lactation.

Fertility

Men being treated with DOCETURAS are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects of DOCETURAS on the ability to drive a vehicle and use machines have been performed. The amount of alcohol in DOCETURAS and the side effects may impair a patient’s ability to perform tasks requiring attention (see sections 4.4 and 4.8). Patients should be advised to exercise caution when driving a vehicle and operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent reported adverse reactions of docetaxel, as in DOCETURAS, alone are neutropenia, anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events may be increased when DOCETURAS is given in combination with other chemotherapeutic medicines.

Blood and lymphatic system disorders

Frequent: Bone marrow suppression and other haematological adverse reactions include neutropenia, febrile neutropenia, thrombocytopenia, anaemia and infections. Neutropenia is reversible and not cumulative. The median time to nadir is 7 days and the median duration of severe neutropenia (< 500 cells/mm^3) is 7 days. Fever in absence of infection, has been reported in patients with non-small cell lung cancer.

Less frequent: Bleeding episodes have occurred and were rarely associated with severe thrombocytopenia (< 50 000 cells/mm^3).

Immune system disorders

Frequent: Hypersensitivity reactions may occur, usually within a few minutes following the start of the infusion of DOCETURAS and are mostly mild to moderate. Symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills.

Severe reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema, requiring therapeutic intervention, may occur. These may resolve after discontinuation of the infusion and institution of appropriate therapy.

Metabolism and nutrition disorders

Less frequent: Fluid accumulation: Peripheral oedema, pleural effusion, pericardial effusion, ascites, increased capillary permeability and increased body mass, have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with an increase in body mass of 3 kg or more after 4 cycles or a cumulative dose ≥ 400 mg/m^2. Fluid retention is cumulative in incidence and severity.

The onset of moderate and severe retention is delayed in patients with premedication compared with patients without premedication. However, it has been reported in some patients during the early courses of therapy. The median time to fluid retention reversibility is 16,4 weeks (range 0 to 42 weeks) in patients receiving the recommended premedication. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

Fluid retention has been less frequently reported in patients receiving the recommended premedication compared with patients without premedication. Dehydration and pulmonary oedema have been reported.

Nervous system disorders

Frequent: Neurosensory signs (characterised by paraesthesia, dysaesthesia or pain, including burning).

Neuromotor events (mainly characterised by weakness).

Cases of convulsion or transient loss of consciousness have been observed with DOCETURAS administration. These reactions may appear during the infusion of DOCETURAS.

Eye disorders

Less frequent: Lacrimation, with or without conjunctivitis, individual cases of lacrimal duct obstruction resulting in excessive tearing, transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during DOCETURAS infusion and in association with hypersensitivity reactions.

Cardiovascular system disorders

Less frequent: Venous thromboembolic events, myocardial infarction, left ventricular dysfunction, unstable angina, dysrhythmia, sinus tachycardia, atrial flutter or paroxysmal atrial tachycardia.

Vascular disorders

Less frequent: Hypertension, hypotension.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea may occur and is associated with acute hypersensitivity reactions, respiratory infections and cancerous lung involvement.

Less frequent: Cough and epistaxis. Acute respiratory distress syndrome, interstitial pneumonia, pulmonary fibrosis and radiation recall phenomena have been reported.

Gastrointestinal system disorders

Frequent: Gastrointestinal effects, such as nausea, vomiting, diarrhoea and abdominal pain, constipation, stomatitis, oesophagitis and taste perversion.

Gastrointestinal bleeding, anorexia.

Occurrences of dehydration due to gastrointestinal events,

gastrointestinal perforation, ischaemic colitis, colitis and neutropenic enterocolitis.

Less frequent: Ileus and intestinal obstruction.

Hepatobiliary system disorders

Less frequent: Increases in serum levels of AST, ALT, bilirubin and alkaline phosphatase > 2,5 times ULN, hepatitis.

Skin and subcutaneous tissue disorders

Frequent: Reversible cutaneous reactions (characterised by a rash, including localised eruptions mainly on the feet and hands, but also on the arms, face or thorax, and frequently associated with pruritus). Eruptions generally occurred within one week after the DOCETURAS infusion.

Nail disorders may occur (characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis).

Less frequent: Severe symptoms, such as eruptions followed by desquamation, may lead to interruption or discontinuation of DOCETURAS treatment. Bullous eruptions, such as erythema multiforme or Stevens-Johnson syndrome.

Musculoskeletal, connective tissue and bone disorders

Frequent: Arthralgia and myalgia.

General disorders and administrative site conditions

Frequent: Infusion site reactions are generally mild and consist of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Generalised or localised pain (including chest pain without any cardiac

or respiratory involvement), alopecia and asthenia.

Combination therapy with DOCETURAS in the adjuvant treatment of breast cancer:

Clinically important treatment related adverse events in patients receiving docetaxel, as in DOCETURAS, in combination with doxorubicin and cyclophosphamide:

Infections and infestations

Frequent: Infection.

Blood and lymphatic system disorders

Frequent: Anaemia, neutropenia, fever in absence of infection, thrombocytopenia, febrile neutropenia and neutropenic infection.

Immune system disorders

Frequent: Hypersensitivity reactions.

Metabolism and nutrition disorders

Frequent: Peripheral oedema, increased or decreased body mass.

Less frequent: Lymph oedema.

Nervous system disorders

Frequent: Sensory neuropathy, syncope.

Less frequent: Neuro-cortical adverse events, motor neuropathy and neuro-cerebellar adverse events.

Eye disorders

Less frequent: Lacrimation disorder, conjunctivitis.

Cardiac disorders

Less frequent: Cardiac dysrhythmias.

Vascular disorders

Frequent: Vasodilation.

Less frequent: Hypotension, phlebitis.

Respiratory, thoracic and mediastinal disorders

Less frequent: Cough.

Gastrointestinal disorders

Frequent: Anorexia, nausea, stomatitis, vomiting, diarrhoea, taste perversion, constipation.

Less frequent: Abdominal pain.

Skin and subcutaneous tissue disorders

Frequent: Alopecia, skin toxicity and nail disorders.

Musculoskeletal, connective tissue and bone disorders

Frequent: Myalgia, arthralgia.

Reproductive system and breast disorders

Frequent: Amenorrhoea.

General disorders and administrative site conditions

Frequent: Asthenia.

Combination therapy with DOCETURAS and capecitabine for breast cancer:

Summary of at least remotely related adverse events reported in ≥ 5 % of patients treated with docetaxel, as in DOCETURAS, and capecitabine in combination:

Infections and infestations

Less frequent: Oral candidiasis.

Metabolism and nutrition disorders

Less frequent: Dehydration, decrease in body mass.

Nervous system disorders

Frequent: Paraesthesia.

Less frequent: Dizziness, headache, peripheral neuropathy.

Eye disorders

Frequent: Increased lacrimation.

Vascular disorders

Frequent: Lower limb oedema.

Respiratory, thoracic and mediastinal disorders

Frequent: Sore throat.

Less frequent: Dyspnoea, cough and epistaxis.

Gastrointestinal disorders

Frequent: Taste disturbance, anorexia, decreased appetite, stomatitis, diarrhoea, nausea, vomiting, constipation, abdominal pain and dyspepsia.

Less frequent: Upper abdominal pain, dry mouth.

Skin and subcutaneous tissue disorders

Frequent: Hand-foot syndrome, alopecia and nail disorder.

Less frequent: Dermatitis, rash erythema, nail discolouration and onycholysis.

Musculoskeletal, connective tissue and bone disorders

Frequent: Myalgia, arthralgia.

Less frequent: Back pain.

General disorders and administrative site conditions

Frequent: Asthenia, pyrexia, fatigue and weakness.

Less frequent: Pain in limb, lethargy and pain.

Investigations

Frequent: Neutropenia, anaemia.

Less frequent: Thrombocytopenia, hyperbilirubinaemia.

Combination therapy with DOCETURAS in prostate cancer patients:

Clinically important treatment related adverse events in patients with prostate cancer who received docetaxel, as in DOCETURAS, in combination with prednisone or prednisolone:

Infection and infestations

Frequent: Infection.

Blood and lymphatic system disorders

Frequent: Anaemia, neutropenia.

Less frequent: Thrombocytopenia, febrile neutropenia.

Immune system disorders

Less frequent: Allergic reactions.

Metabolism and nutrition disorders

Frequent: Fluid retention.

Nervous system disorders

Frequent: Sensory neuropathy, motor neuropathy.

Eye disorders

Less frequent: Tearing.

Cardiac disorders

Less frequent: Left ventricular dysfunction.

Respiratory, thoracic and mediastinal disorders

Less frequent: Epistaxis, cough and dyspnoea.

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, stomatitis/pharyngitis, taste disturbance, vomiting, anorexia.

Skin and subcutaneous tissue disorders

Frequent: Alopecia, nail changes.

Less frequent: Rash/desquamation.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia, arthralgia.

General disorders and administrative site conditions

Frequent: Fatigue.

Post-marketing experience

Blood and lymphatic system disorders

Bone marrow suppression and other haematologic adverse reactions have been reported. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported.

Immune system disorders

Some cases of anaphylactic shock, sometimes fatal, have been reported. Hypersensitivity reactions have been reported with docetaxel, as in DOCETURAS, in patients who previously experienced hypersensitivity reactions to paclitaxel.

Nervous system disorders

Cases of convulsion or transient loss of consciousness have been observed with docetaxel, as in DOCETURAS, administration. These reactions sometimes appear during the infusion of docetaxel, as in DOCETURAS.

Eye disorders

Cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during infusion of DOCETURAS and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion. Cases of lacrimation with or without conjunctivitis, as cases of lacrimal duct obstruction resulting in excessive tearing have been rarely reported. Cases of cystoid macular oedema (CMO) have been reported in patients treated with DOCETURAS.

Ear and labyrinth disorders

Cases of ototoxicity, hearing impairment and/or hearing loss have been reported.

Cardiac disorders

Cases of myocardial infarction have been reported.

Ventricular dysrhythmia including ventricular tachycardia, sometimes fatal, has been reported in patients treated with DOCETURAS in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide.

Vascular disorders

Venous thromboembolic events have been reported.

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

Cases of enterocolitis, including colitis, ischemic colitis and neutropenic enterocolitis, have been reported with a potentially fatal outcome.

Occurrences of dehydration have been reported due to gastrointestinal events including enterocolitis and gastrointestinal perforation.

Cases of ileus and intestinal obstruction have been reported.

Hepatobiliary disorders

Cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Skin and subcutaneous tissue disorders

Cases of cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme and severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) have been reported with docetaxel, as in DOCETURAS. Sclerodermal-like changes usually preceded by peripheral lymphoedema have been reported with docetaxel, as in DOCETURAS. Cases of permanent alopecia have been reported.

Renal and urinary disorders

Renal insufficiency and renal failure have been reported. In approximately 20 % of these cases there were no risk factors for acute renal failure such as concomitant nephrotoxic medicines and gastrointestinal disorders.

General disorders and administration site conditions

Radiation recall phenomena have been reported.

Injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel, as DOCETURAS, at a different site) has been observed at the site of previous extravasation.

Fluid retention has not been accompanied by acute episodes of oliguria or hypotension. Dehydration and pulmonary oedema have been reported.

Metabolism and nutrition disorders

Cases of electrolyte imbalance have been reported. Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia. Hypokalaemia, hypomagnesaemia and hypocalcaemia were observed, usually in association with gastrointestinal disorders and in particular with diarrhoea. Tumour lysis syndrome, potentially fatal, has been reported.

Musculoskeletal disorder

Myositis has been reported with docetaxel, as in DOCETURAS.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DOCETURAS is important. It allows continued monitoring of the benefit/risk balance of DOCETURAS. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There were a few reports of overdose. There is no known antidote for docetaxel, as in DOCETURAS overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. In cases of overdose, exacerbation of adverse events may be expected. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD02

5.1 Pharmacodynamic properties

Mechanism of action

Docetaxel is an antineoplastic medicine which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells which is

essential for vital mitotic and interphase cellular functions.

Pharmacodynamic effects

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some but not all cell lines over expressing the p-glycoprotein which is encoded by the multidrug resistance gene. *In vivo*, docetaxel is schedule independent and has a broad spectrum of experimental anti-tumour activity against advanced murine and human grafted tumours.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 – 115 mg/m^2 in phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three- compartment pharmacokinetic model with half-lives for the α, β and γ phases of 4 minutes, 36 minutes and 11,1 hours, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Distribution

Following the administration of a 100 mg/m^2 dose given as a one-hour infusion a mean peak plasma level of 3,7 µg/mL was obtained with a corresponding AUC of 4,6 h.µg/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m^2 and 113 litres, respectively. Inter individual variation in total body clearance was approximately 50 %. Docetaxel is more than 95 % bound to plasma proteins.

Elimination

A study of ^{14}C-docetaxel has been conducted in three cancer patients. Docetaxel was

eliminated in both the urine and faeces following cytochrome P450-mediated oxidative metabolism of the tert-butyl ester group, within seven days, the urinary and faecal excretion accounted for about 6 % and 75 % of the administered radioactivity, respectively. Approximately 80 % of the radioactivity recovered in faeces is excreted during the first 48 hours as one major inactive metabolite and 3 minor inactive metabolites and very low amounts of unchanged medicine.

Special patient populations

Age and gender

A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not altered by the age or sex of the patient.

Hepatic impairment

In a small number of patients (n = 23) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST ≥ 1,5 times the ULN associated with alkaline phosphatase ≥ 2,5 times the ULN), total clearance was lowered by 27 % on average (see section 4.2).

Fluid retention

Docetaxel clearance was not modified in patients with mild to moderate fluid retention and there are no data available in patients with severe fluid retention.

Combination therapy

Doxorubicin

When used in combination, docetaxel does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). The pharmacokinetics of docetaxel,

doxorubicin and cyclophosphamide were not influenced by their co-administration.

Capecitabine

Phase I study evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of docetaxel (C_{max} and AUC) and no effect by docetaxel on the pharmacokinetics of a relevant capecitabine metabolite 5'-DFUR.

Cisplatin

Clearance of docetaxel in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after docetaxel infusion is similar to that observed with cisplatin alone.

Prednisone and dexamethasone

The effect of prednisone on the pharmacokinetics of docetaxel

administered with standard dexamethasone premedication has been studied in 42 patients.

Prednisone

No effect of prednisone on the pharmacokinetics of docetaxel was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80

Citric acid

Ethanol (alcohol).

6.2 Incompatibilities

DOCETURAS must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

24 months.

After opening of the vial

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added to the infusion bag

From microbiological point of view, reconstitution/dilution must take place in controlled and aseptic conditions and should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added as recommended into the infusion bag, DOCETURAS infusion solution, if stored below 25 °C, is stable for 6 hours (including the one hour infusion IV administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 to 8 °C.

DOCETURAS concentrate for solution for infusion is supersaturated, therefore may crystallise over time.

If crystals appear, the solution must no longer be used and shall be discarded.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

DOCETURAS 20 mg: 5 mL clear, colourless, type-I glass vial, closed with a 20 mm, round, grey chlorobutyl rubber stopper and a light blue aluminium flip off seal, packed in an outer carton.

DOCETURAS 80 mg: 5 mL clear, colourless, type-I glass vial, closed with a 20 mm, round, grey chlorobutyl rubber stopper and a light blue aluminium flip off seal, packed in an outer carton.

DOCETURAS 160 mg: 10 mL clear, colourless, type-I glass vial, closed with a 20 mm, round, grey chlorobutyl rubber stopper and a light blue aluminium flip off seal, packed in an outer carton.

6.6 Special precautions for disposal and other handling

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

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

Preparation for the intravenous administration

Preparation of the infusion solution

DO NOT use other docetaxel medicines consisting of more than one vial (concentrate and solvent) with DOCETURAS 20 mg concentrate for solution for infusion, which contains only 1 vial).

DOCETURAS 20 mg concentrate for solution for infusion requires No prior dilution with

a solvent and is ready to add to the infusion solution.

Each vial is of single use and should be used immediately.

More than one vial of DOCETURAS concentrate for solution for infusion may be necessary to obtain the required dose for the patient. Aseptically withdraw the required amount of DOCETURAS concentrate for solution for infusion using a calibrated syringe.

In DOCETURAS concentrate for solution for infusion, the required volume must be injected via a single injection (one shot) into a 250 mL infusion bag or bottle, containing either 5 % glucose solution or 0,9 % sodium chloride (9 mg/mL) solution for infusion.

If a dose greater than 190 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/mL docetaxel is not exceeded.

Mix the infusion bag or bottle manually using a rocking motion.

The infusion bag solution should be used within 6 hours below 25 °C including the one hour infusion to the patient.

DOCETURAS concentrate for solution for infusion 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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Johannesburg

South Africa

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Tel: 011 247 1600

8. REGISTRATION NUMBERS

DOCETURAS 20 mg: 57/26/0025

DOCETURAS 80 mg: 57/26/0026

DOCETURAS 160 mg: 57/26/0027

9. DATE OF FIRST AUTHORISATION

27 August 2025

10. DATE OF REVISION OF THE TEXT

To follow