PROFESSIONAL INFORMATION

S4

1. NAME OF THE MEDICINE:

DOCETAXEL 20 TEVA (concentrate for solution for infusion)

DOCETAXEL 80 TEVA (concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

DOCETAXEL 20 TEVA: Each single dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel anhydrous.

DOCETAXEL 80 TEVA: Each single dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel anhydrous.

Excipients with known effect:

Ethanol absolute 400 mg/ml.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM:

Concentrate for solution for infusion.

The concentrate is a clear, pale-yellow solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

1. Breast Cancer:

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

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

DOCETAXEL TEVA, 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.

2. Non-small Cell Lung Cancer (NSCLC):

DOCETAXEL TEVA, 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.

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

3. Ovarian Cancer:

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

4. Prostate Cancer:

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

5. Head and neck Cancer:

DOCETAXEL TEVA 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.

4.2 Posology and method of administration:

DOCETAXEL TEVA should be administered by intravenous infusion only.

Dosage:

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 DOCETAXEL TEVA administration, unless contra-indicated, can be used. 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 TEVA infusion.
Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities. DOCETAXEL TEVA is administered as a one-hour infusion every three weeks.

1. Breast Cancer:

In the adjuvant treatment of operable node-positive breast cancer, the recommended DOCETAXEL TEVA dose is 75 mg/m^2 administered one hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (see also **Dosage adjustments during therapy**).

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

For the second line treatment of breast cancer the recommended dosage of DOCETAXEL TEVA therapy is 100 mg/m^2 in monotherapy.
In combination with capecitabine, the recommended dose of DOCETAXEL TEVA is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 orally 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 the professional information for capecitabin.

2. Non-small Cell Lung Cancer:

In combination therapy (chemotherapy naïve patients): The recommended dosage regimen is DOCETAXEL TEVA 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes.
In monotherapy (for previously treated patients): The recommended dosage of DOCETAXEL TEVA therapy is 100 mg/m^2 as a single medicine.

3. Ovarian Cancer

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

4. Prostate Cancer:

The recommended dose of DOCETAXEL TEVA 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 DOCETAXEL TEVA, because of the risk of hypersensitivity reactions.

5. Head and neck Cancer:

For the induction treatment of locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of DOCETAXEL TEVA 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. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered.

For cisplatin and 5-fluorouracil dose modifications, see local professional information.

Dosage adjustments during treatment:

General:

ONLY the healthcare professional can modify the schedule of administration.

DOCETAXEL TEVA should be administered when the neutrophil count is ≥ 1500 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 DOCETAXEL TEVA therapy, should have the dosage of DOCETAXEL TEVA 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, the treatment should be discontinued.

Combination therapy with DOCETAXEL TEVA for NSCLC:

For patients who are dosed initially at DOCETAXEL TEVA 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25000 cells/mm^3, or in patients

who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the DOCETAXEL TEVA dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see the professional information for this medicine.

Combination therapy with DOCETAXEL TEVA for Breast Cancer:

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

For capecitabine dose modifications when combined with DOCETAXEL TEVA, see capecitabine manufacturers' professional information.

For patients developing the first appearance of a Grade 2 toxicity which persists at the time of the next DOCETAXEL TEVA/capecitabine treatment, delay treatment until resolved to Grade 0 to 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 to 1, and then resume treatment with DOCETAXEL TEVA 55 mg/m^2. For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the DOCETAXEL TEVA dose.

For DOCETAXEL TEVA dose modifications due to hepatic impairment, see **section 4.4** section.

Special Populations:

Patients with hepatic impairment:

Patients with bilirubin > ULN should generally not receive DOCETAXEL TEVA. Also, patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase > 2,5 x ULN, should generally not receive DOCETAXEL TEVA.

Elderly population:

Based on a population pharmacokinetic analysis, there are no special instructions for the use in the elderly. For capecitabine, dosage reduction when combined with DOCETAXEL TEVA, see capecitabine manufacturers' prescribing information.

Paediatric population:

The safety and effectiveness of DOCETAXEL TEVA in children have not been established.

Recommendations for safe handling:

Handling precautions for cytostatic medicine should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.
- DOCETAXEL TEVA is an antineoplastic medicine and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing DOCETAXEL TEVA solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If DOCETAXEL TEVA concentrate premix solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If DOCETAXEL TEVA concentrate, premix solution or infusion solution should come into contact with the eyes or mucous membranes, wash immediately and thoroughly with water.
- The cytotoxic preparation must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

Preparation for the intravenous administration:

Preparation of the infusion solution:

DO NOT use other docetaxel medicinal products consisting of more than one vial (concentrate and solvent) with this medicinal product (DOCETAXEL 20 TEVA mg/ml concentrate for solution for infusion, which contains only 1 vial).

DOCETAXEL 20 TEVA mg/ml 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.

Allow the required number of boxes of DOCETAXEL TEVA concentrate for solution for infusion to stand below 25 °C for 5 minutes before use.

More than one vial of DOCETAXEL TEVA concentrate for solution for infusion may be necessary to obtain the required dose for the patient. Aseptically withdraw the required amount of DOCETAXEL TEVA

concentrate for solution for infusion using a calibrated syringe.

In DOCETAXEL 20 TEVA mg/ml vial the concentration of DOCETAXEL TEVA is 20 mg/ml.

The required volume of DOCETAXEL TEVA concentrate for solution for infusion must be injected into a 250 ml infusion bag or bottle containing either glucose solution 50 mg/ml (5 %) or sodium chloride 9 mg/ml (0.9 %) solution for infusion.

If a dose greater than 190 mg of DOCETAXEL TEVA is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml DOCETAXEL TEVA is not exceeded.

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

The infusion bag solution should be used within 8 hours below 25 °C including the one hour infusion to the patient.

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

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

4.3 Contraindications:

Hypersensitivity to docetaxel or to any of the excipients listed in **section 6.1.**

DOCETAXEL TEVA must not be used in patients with baseline neutrophil count of < 1500 cells/mm^3.

DOCETAXEL TEVA must not be used in patients with severe liver impairment (see **sections 4.2** and **4.4**).

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

The safe use of docetaxel in children has not been established.

Pregnancy and lactation as docetaxel is teratogenic in animals.

4.4 Special warnings and precautions for use:

DOCETAXEL TEVA should be administered under the supervision of a qualified healthcare professional experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

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

DOCETAXEL TEVA 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 DOCETAXEL TEVA therapy and reviewed by the treating medical practitioner.

DOCETAXEL TEVA therapy should not be given to patients with neutrophil counts of < 1500 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 DOCETAXEL TEVA.

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 TEVA were reported in some patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. DOCETAXEL TEVA must not be given to patients who have a history of severe hypersensitivity reactions to DOCETAXEL TEVA 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).

The use of DOCETAXEL TEVA should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist. Since

significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. During the infusion it is recommended that vital functions should be closely monitored.
Premedication consisting of an oral corticosteroid (see below for prostate), such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to DOCETAXEL TEVA administration, unless contraindicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The pre-treatment regimen for prostate cancer is oral dexamethasone 8 mg administered 12 hours, 3 hours and 1 hour before the DOCETAXEL TEVA regimen.

Haematology:

Neutropenia is the most frequent adverse reaction of DOCETAXEL TEVA. 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 TEVA. Patients should be retreated with DOCETAXEL TEVA 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 DOCETAXEL TEVA 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 TEVA 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 TEVA 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 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 **section 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 DOCETAXEL TEVA, 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 DOCETAXEL TEVA and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCETAXEL TEVA. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to DOCETAXEL TEVA, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of DOCETAXEL TEVA 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 leads to interruption or discontinuation of DOCETAXEL TEVA 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.
If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of DOCETAXEL TEVA therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming DOCETAXEL TEVA treatment must be carefully evaluated.

Patients with liver impairment:

In patients treated with DOCETAXEL TEVA at 100 mg/m^2 as single medicine 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 TEVA 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 DOCETAXEL TEVA should not be used unless strictly indicated.
No data are available in patients with hepatic impairment treated by DOCETAXEL TEVA in combination in the other indications.

Patients with renal impairment:

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

Nervous system:

The development of severe peripheral neurotoxicity, including paraesthesia, dysaesthesia and pain, has been observed in patients and requires a reduction of dose. When symptoms persist, treatment should be stopped.

Cardiac toxicity:

Ventricular dysrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with DOCETAXEL TEVA 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 TEVA. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, DOCETAXEL TEVA treatment should be discontinued, and appropriate treatment initiated (see **section 4.8**).

Second primary malignancies:

Second primary malignancies have been reported when, DOCETAXEL TEVA was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukemia, 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**).

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 DOCETAXEL TEVA 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).**

Leukaemia:

In the DOCETAXEL TEVA, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow up.

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.

Elderly patients:

There are limited data available in patients > 70 years of age on DOCETAXEL TEVA use in combination with doxorubicin and cyclophosphamide.

The incidence of serious adverse events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, neutropenic infection occurred at rates ≥ 10 % higher in patients who were 65 years of age or older compared to younger patients.

Elderly patients treated with TCF should be closely monitored.

Excipients:

Ethanol: DOCETAXEL TEVA contains 400 mg ethanol per ml concentrate.

This medicinal product contains 51 vol. % ethanol (alcohol), i.e. up to 3200 mg per vial containing 8 ml, equivalent to 82 ml of beer or 34 ml wine.

Harmful for those suffering from alcoholism.

To be taken into account in 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 medicinal products and other forms of interaction:

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 TEVA 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 TEVA 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 TEVA may be suitable during the treatment with the strong CYP3A4 inhibitor (see **section 4.4**). In a pharmacokinetic study, the co-administration of DOCETAXEL TEVA with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in DOCETAXEL TEVA clearance by 49 %.

DOCETAXEL TEVA is metabolised by CYP3A4, and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the pharmacokinetics of **DOCETAXEL TEVA** was observed in studies.

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

The pharmacokinetics of DOCETAXEL TEVA, doxorubicin and cyclophosphamide were not influenced by their co administration. Limited data were suggestive of an interaction between DOCETAXEL TEVA and carboplatin. When combined to DOCETAXEL TEVA, the clearance of carboplatin was about 50 % higher than values previously reported for carboplatin monotherapy.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety on the use of DOCETAXEL TEVA in pregnant women has not been established. As with other cytotoxic medicinal products, DOCETAXEL TEVA may cause foetal harm when administered to pregnant women. Therefore, DOCETAXEL TEVA must not be used during pregnancy unless clearly indicated (see **section 4.3**).

Women of childbearing age receiving DOCETAXEL TEVA should be advised to avoid becoming pregnant, and to inform the treating healthcare professional immediately should this occur.

Breastfeeding:

DOCETAXEL TEVA 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, breastfeeding must be discontinued for the duration of DOCETAXEL TEVA therapy (see **section 4.3**).

Contraception in males and females:

An effective method of contraception should be used during treatment.

Fertility:

Contraception in males and females:

DOCETAXEL TEVA has genotoxic effects and may alter male fertility (see **section 5.3).** Therefore, men being treated with DOCETAXEL TEVA are advised not to father a child during and up to 3 months after treatment and to seek advice on conservation of sperm prior to treatment.

Due to the genotoxic potential of DOCETAXEL TEVA, women of childbearing potential should use effective contraceptive measures while being treated with DOCETAXEL TEVA for 6 months following completion of treatment.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. The amount of alcohol in DOCETAXEL TEVA and the side effects may impair the ability to drive or use machines (see **sections 4.4** and **4.8**). Therefore, patients should be warned of the potential impact of the amount of alcohol and the side effects of DOCETAXEL TEVA on the ability to drive or use machines and be advised not to drive or use machines if they experience these side effects during treatment.

4.8 Undesirable effects:

Summary of the safety profile for all indications:

The most commonly reported adverse reactions of DOCETAXEL TEVA alone are neutropenia anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of DOCETAXEL TEVA may be increased when DOCETAXEL TEVA is given in combination with other chemotherapeutic medicine.

The following adverse reactions are frequently observed with DOCETAXEL TEVA:

Immune system disorders:

Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of DOCETAXEL TEVA 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 (see **section 4.4**).

Nervous system disorders:

The development of severe peripheral neurotoxicity requires a reduction of dose (see **sections 4.2** and **4.4**). Mild to moderate neuro-sensory signs are characterised by paraesthesia, 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 TEVA infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely leads to interruption or discontinuation of DOCETAXEL TEVA treatment were reported (see **sections 4.2** and **4.4**). 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 (see **section 4.4**).

***List of adverse reactions*:**

System Organ Class	**Frequency**	**Undesirable effects**

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 (< 50000 cells/mm^3).
Immune system disorders	*Frequent:*	Hypersensitivity reactions may occur, usually within a few minutes following the start of the infusion of DOCETAXEL TEVA 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 weight gain, have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more after 4 cycles or a cumulative dose ≥ 400 mg/m^2. Fluid retention is cumulative in incidence and severity. 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, dysesthesia or pain, including burning, may occur. Neuromotor events, mainly characterised by weakness, may occur. Cases of convulsion or transient loss of consciousness have been observed with DOCETAXEL TEVA administration. These reactions may appear during the infusion of DOCETAXEL TEVA.
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 medicine infusion and in association with hypersensitivity reactions.
Cardiovascular system disorders	*Less frequent:*	Venous thromboembolic events, myocardial infarction, and hypertension have been reported. Other adverse events include left ventricular dysfunction, unstable angina, dysrhythmia, sinus tachycardia, atrial flutter or paroxysmal atrial tachycardia and 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 as a consequence of 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 greater than 2,5 times ULN, hepatitis.
Skin and subcutaneous tissue disorders	*Frequent:*	Reversible cutaneous reactions. The cutaneous reactions are 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 DOCETAXEL TEVA infusion. Nail disorders may occur. These are 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 DOCETAXEL TEVA 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 may occur, including chest pain without any cardiac or respiratory involvement. Other side-effects include alopecia and asthenia.

Combination therapy with DOCETAXEL TEVA in the adjuvant treatment of breast cancer:

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

System Organ Class	Frequency	Undesirable effects
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, and weight gain or loss.
	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.
Cardiovascular system disorders	*Less frequent:*	Cardiac dysrhythmias.
Vascular disorders	*Frequent:*	Vasodilation.
	Less frequent:	Hypotension, phlebitis.
Respiratory, thoracic and mediastinal disorders	*Less frequent:*	Cough.
Gastrointestinal system 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:*	Arthralgia and myalgia.
Reproductive system and breast disorders	*Frequent:*	Amenorrhoea.
General disorders and administrative site conditions	*Frequent*	Asthenia.

Combination therapy with DOCETAXEL TEVA and capecitabine for breast cancer:

System Organ Class	Frequency	Undesirable effects
Infections and infestations	*Less frequent:*	Oral candidiasis.
Metabolism and nutrition disorders	*Less frequent:*	Dehydration, decreased weight.
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.

Clinically important treatment related adverse events in patients with prostate cancer who received DOCETAXEL TEVA, in combination with prednisone or prednisolone.

System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	*Less 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	*Frequent:*	Tearing.
Cardiac disorders	*Less frequent:*	Left ventricular dysfunction.
Respiratory, thoracic and mediastinal disorders	*Less frequent:*	Dyspnoea, cough, and epistaxis.
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:

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):

Second primary malignancies (frequency not known), including non-Hodgkin lymphoma have been reported in association with docetaxel when used in combination with other anticancer treatments known to be associated with second primary malignancies. Acute myeloid leukemia and myelodysplastic syndrome have been reported (frequency uncommon) in pivotal clinical studies in breast cancer with TAC regimen.

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 multi organ failure, has been reported.

Immune system disorders:

Some cases of anaphylactic shock, sometimes fatal, have been reported.

Hypersensitivity reactions (frequency not known) have been reported with DOCETAXEL TEVA in patients who previously experienced hypersensitivity reactions to paclitaxel.

Nervous system disorders:

Rare cases of convulsion or transient loss of consciousness have been observed with DOCETAXEL TEVA administration. These reactions sometimes appear during the infusion of the medicinal product.

Eye disorders:

Very rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during infusion of the medicinal product 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 DOCETAXEL TEVA.

Ear and labyrinth disorders:

Rare cases of ototoxicity, hearing impaired and/or hearing loss have been reported.

Cardiac disorders:

Rare cases of myocardial infarction have been reported.

Ventricular dysrhythmia including ventricular tachycardia (frequency not known), sometimes fatal, has been reported in patients treated with DOCETAXEL TEVA 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 rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Gastrointestinal disorders:

Rare occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, colitis ischaemic, colitis and neutropenic enterocolitis have been reported. Rare cases of ileus and intestinal obstruction have been reported.

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, have been reported with DOCETAXEL TEVA. In some cases, concomitant factors may have contributed to the development of these effects. Sclerodermal-like changes usually preceded by peripheral lymphoedema have been reported with DOCETAXEL TEVA. Cases of permanent alopecia have (frequency not known) been reported.

Renal and urinary disorders:

Renal insufficiency and renal failure have been reported. In about 20 % of these cases there were no risk factors for acute renal failure such as concomitant nephrotoxic medicinal products 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 TEVA at a different site) has been observed at the site of previous

extravasation (frequency not known).

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

4.9 Overdose:

There were a few reports of overdose. There is no known antidote for DOCETAXEL TEVA 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. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD02

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 antitumour 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 to 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 min, 36 min and 11,1 h, 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/m2 and 113 l, 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. About 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 medicinal product.

Special populations:

Age and gender:

The pharmacokinetics of DOCETAXEL TEVA 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 TEVA 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 TEVA does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). The pharmacokinetics of DOCETAXEL TEVA, doxorubicin and cyclophosphamide were not influenced by their coadministration.

Capecitabine:

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

Cisplatin:

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

Cisplatin and 5-fluorouracil:

The combined administration of DOCETAXEL TEVA, cisplatin and 5-fluorouracil in 12 patients with solid tumours had no influence on the pharmacokinetics of each individual medicinal product.

Prednisone and dexamethasone:

The effect of prednisone on the pharmacokinetics of DOCETAXEL TEVA administered with standard dexamethasone premedication has been studied in 42 patients.

Prednisone:

No effect of prednisone on the pharmacokinetics of DOCETAXEL TEVA was observed.

5.3 Preclinical safety data:

The carcinogenic potential of DOCETAXEL TEVA has not been studied.

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

Undesirable effects on the testis observed in studies suggest that DOCETAXEL TEVA may impair male fertility.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Citric acid

Povidone

Polysorbate 80

Ethanol absolute

6.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned in **section 6.6**.

6.3 Shelf life:

Unopened Vial:

2 years

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 a microbiological point of view, reconstitution/dilution must take place in controlled and aseptic conditions and the medicinal product 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, the DOCETAXEL TEVA infusion solution, if stored below 25 °C, in non-PVC bags, is stable for 8 hours. It should be used within 8 hours (including the one hour infusion intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated for 3 days when stored between 2 to 8 °C protected from light.

DOCETAXEL TEVA infusion solution is supersaturated, therefore may crystallize 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.

Do not refrigerate or freeze.

For storage conditions after opening of the vials and of the diluted medicinal product, see **section 6.3**.

6.5 Nature and contents of container:

Clear colourless glass vial (Type I) closed with a grey bromobutyl rubber stopper (Type I) sealed with aluminium cap with polypropylene disc. Vial will be packed with or without a protective plastic overwrap.

Pack sizes:

DOCETAXEL 20 TEVA: single dose 5 ml clear colourless glass vial.

DOCETAXEL 80 TEVA: single dose 8 ml or 10 ml clear colourless glass vial.

6.6 Special precautions for disposal and other handling:

DOCETAXEL TEVA is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing DOCETAXEL TEVA solutions. Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of such preparations. Pregnant personnel should not handle cytotoxic agents. Refer to local cytotoxic guidelines before commencing. The use of gloves is recommended. If DOCETAXEL TEVA concentrate or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If DOCETAXEL TEVA concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water. In the event of spillage, trained personnel wearing appropriate personal protective equipment should remove the maximum amount of material by use of a cytotoxic drug spill kit or designated absorbent materials. The area should be rinsed with copious amounts of water. All contaminated cleaning materials should be disposed of in accordance with local requirements.

Preparation of the solution for infusion:

More than one vial of DOCETAXEL 20 TEVA mg/ml concentrate for solution for infusion may be necessary to obtain the required dose for individual patients. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding volume of 20 mg/ml DOCETAXEL TEVA from the appropriate number of vials using graduated syringes fitted with a needle. For example, a dose of 140

mg DOCETAXEL TEVA would require 7 ml of DOCETAXEL 20 TEVA mg/ml concentrate for solution for infusion.

For doses below 192 mg of DOCETAXEL TEVA, inject the required volume of DOCETAXEL 20 TEVA mg/ml concentrate for solution for infusion into a 250 ml infusion bag or bottle containing either 250 ml of 50 mg/ml (5 %) glucose solution for infusion or 9 mg/ml (0,9 %) sodium chloride solution for infusion. For doses exceeding 192 mg of DOCETAXEL TEVA more than 250 ml of the infusion solution is required, as the maximum concentration of DOCETAXEL TEVA is 0,74 mg per ml of infusion solution.

Mix the infusion bag or bottle manually using a rocking motion. The diluted solution should be used within 8 hours and should be aseptically administered as a 1 hour infusion at room temperature and normal lighting conditions.

Administration:

For instructions on administration see **Section 4.2.**

As with all parenteral products, this medicinal product should be visually inspected prior to use and 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:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

South Africa

8. REGISTRATION NUMBER(S):

DOCETAXEL 20 TEVA: 47/26/0940

DOCETAXEL 80 TEVA: 47/26/0941

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

16 March 2021

10. DATE OF REVISION OF THE TEXT:

18 June 2024

11. DOSIMETRY IF APPLICABLE:

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS IF APPLICABLE:

Refer to **section 4.2.**