1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

KEY-DOCETAXEL 20 mg (concentrate for solution for infusion)

KEY-DOCETAXEL 80 mg (concentrate for solution for infusion)

KEY-DOCETAXEL 20 and 80 Diluent solution

2 QUALITIVE AND QUANTITIVE COMPOSITION

KEY-DOCETAXEL 20 mg:

Each single-dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel (anhydrous) in 0,5 ml polysorbate 80.

KEY-DOCETAXEL 80 mg:

Each single-dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel (anhydrous) in 2,0 ml polysorbate 80.

Each ml of KEY-DOCETAXEL concentrate for solution for infusion contains 40 mg docetaxel (anhydrous) as the active ingredient.

KEY-DOCETAXEL Solvent:

13 % *m/v* ethanol 95 % in water for injection.

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Excipients with known effect:

KEY-DOCETAXEL 20 mg:

Each diluent vial contains 156 mg ethanol.

KEY-DOCETAXEL 80 mg:

Each diluent vial contains 624 mg ethanol.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A viscous yellow to brownish-yellow solution with an accompanying solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. **Breast Cancer**
    - KEY-DOCETAXEL, in combination with doxorubicin and cyclophosphamide, is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.
    - KEY-DOCETAXEL, in combination with doxorubicin, is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.
    - KEY-DOCETAXEL monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer, after failure of cytotoxic therapy.

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

2. **Non-Small Cell Lung Cancer (NSCLC)**
   - KEY-DOCETAXEL, in combination with cisplatin, is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.
   - KEY-DOCETAXEL is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, even after failure of platinum-based chemotherapy.
3. **Ovarian Cancer**
   - KEY-DOCETAXEL is indicated, after failure of first-line or subsequent chemotherapy, for treatment of metastatic carcinoma of the ovary.
4. **Prostate Cancer**
   - KEY-DOCETAXEL, 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**
   - KEY-DOCETAXEL, in combination with cisplatin and 5-fluorouracil, is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

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 KEY-DOCETAXEL 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, 12 hours, 3 hours and 1 hour before the KEY-DOCETAXEL infusion.
- Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
- KEY-DOCETAXEL 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 KEY-DOCETAXEL 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, KEY-DOCETAXEL 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 KEY-DOCETAXEL therapy is 100 mg/m^2 in monotherapy.
- In combination with capecitabine, the recommended dose of KEY-DOCETAXEL 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 a 1-week rest period.

For capecitabine dose calculation according to body surface area, see capecitabine package insert.

2. Non-Small Cell Lung Cancer

In combination therapy (chemotherapy-naïve patients):

- The recommended dosage regimen is KEY-DOCETAXEL 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 KEY-DOCETAXEL therapy is 100 mg/m^2 as a single medicine.

3. Ovarian cancer

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

4. Prostate cancer

- The recommended dose of KEY-DOCETAXEL 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 KEY-DOCETAXEL, 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 KEY-DOCETAXEL is 75 mg/m^2 as a 1-hour intravenous infusion, followed by cisplatin 75 mg/m^2 over 1

hour, on day one, followed by 5-fluorouracil at 750 mg/m^2 per day for 5 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 package insert.

Dosage adjustments during treatment

General

- ONLY the medical practitioner can modify the schedule of administration.
- KEY-DOCETAXEL should be administered when the neutrophil count is > 1 500 cells/mm^3.
- Patients who experienced 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 KEY-DOCETAXEL therapy, should have their dosage of KEY-DOCETAXEL reduced, during the subsequent cycle, from 100 to 75 mg/m^2 and/or from 75 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 KEY-DOCETAXEL for NSCLC

- For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <

25 000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the KEY-DOCETAXEL dosage in subsequent cycles should be reduced to 65 mg/m^2.

- For cisplatin dosage adjustments, see cisplatin package insert.

Combination therapy with KEY-DOCETAXEL 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 KEY-DOCETAXEL dose reduced to 60 mg/m^2. If G-CSF is not used, the KEY-DOCETAXEL dose should be reduced from 75 to 60 mg/m^2.
- For capecitabine dose modifications when combined with KEY-DOCETAXEL, see capecitabine package insert.
- For patients developing the first appearance of a Grade 2 toxicity which persists at the time of the next KEY-DOCETAXEL/capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100 % of the original dose.
- For patients developing the second appearance of a Grade 2 toxicity, or the first appearance of a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with KEY-DOCETAXEL 55 mg/m^2.
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the KEY-DOCETAXEL dose.
- For KEY-DOCETAXEL dose modifications due to hepatic impairment (see section 4.4).

Special populations

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 KEY-DOCETAXEL, see capecitabine package insert.

Patients with hepatic impairment:

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

Paediatric population

- The safety and efficacy of KEY-DOCETAXEL in children under 18 years of age, have not been established.

Method of administration

KEY-DOCETAXEL should be administered by intravenous infusion only.

Recommendation for safe handling:

Handling precautions for cytostatic medicines should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.

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

Directions for use:

KEY-DOCETAXEL 20 mg vial and KEY-DOCETAXEL Solvent vial:

Each KEY-DOCETAXEL 20 mg vial contains 20 mg docetaxel per 0,5 ml of polysorbate 80.

Each KEY-DOCETAXEL solvent vial for KEY-DOCETAXEL 20 mg contains 1,5 ml solvent.

KEY-DOCETAXEL 80 mg vial and KEY-DOCETAXEL Solvent vial:

Each KEY-DOCETAXEL 80 mg vial contains 80 mg docetaxel per 2 ml polysorbate 80.

Each KEY-DOCETAXEL solvent vial for KEY-DOCETAXEL 80 mg contains 6 ml solvent.

Preparation for intravenous administration:

a) Preparation of the KEY-DOCETAXEL premix solution (10 mg docetaxel /ml):

- If the vials are stored under refrigeration, allow the required number of KEY-DOCETAXEL boxes to stand at room temperature for 5 minutes.
- Using a syringe fitted with a needle, aseptically withdraw the entire contents of the KEY-DOCETAXEL Solvent vial by partially inverting the vial.
- Inject the entire contents of the syringe into the corresponding KEY-DOCETAXEL vial.
- Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds.
- Do not shake.
- Allow the premix vial to stand for 5 minutes at room temperature.
- The solution should be homogenous and clear. There may be foaming, which is normal, even after 5 minutes, due to the presence of polysorbate 80 in the formulation.
- The premix solution contains 10 mg/ml docetaxel and should be used immediately to prepare the infusion solution. It is however stable for a maximum of 8 hours at room temperature or in the refrigerator.

b) Preparation of the Infusion solution:

- More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the required amount of premix solution from the appropriate number of premix vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 14 ml KEY-DOCETAXEL premix solution.
- Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5 % dextrose solution or 0,9 % sodium chloride solution to provide a final concentration

of 0,3 to 0,9 mg docetaxel/ml. If a dose greater than 240 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0,9 mg/ml docetaxel is not exceeded.

- Mix the infusion bag or bottle manually using a rocking motion.
- The KEY-DOCETAXEL infusion solution should be aseptically administered intravenously as soon as possible after preparation as a one-hour infusion, under room temperature and normal lighting conditions. The total duration of manipulation from start of the preparation of the bag to the end of the infusion must not exceed 4 hours.
- KEY-DOCETAXEL premix solution and infusion solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.
- Do not admix with other medicines.
- Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patients' exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, docetaxel diluted solution should be stored in bottles (glass, polypropylene and polyolefin) and administered through polyethylene-lined administration sets.

4.3 Contraindications

- KEY-DOCETAXEL is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel, ethanol (anhydrous), polysorbate 80, or to any of the other excipients.

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- KEY-DOCETAXEL should not be used in patients with baseline neutrophil count of < 1500 cells/mm^3.
- KEY-DOCETAXEL should not be used in pregnancy and lactation as docetaxel is teratogenic in animals.
- The safe use of KEY-DOCETAXEL in children has not been established.
- KEY-DOCETAXEL should not be used in patients with severe liver impairment since there is no data available (see section 4.4 and section 4.2).

4.4 Special warnings and precautions for use

KEY-DOCETAXEL (DOCETAXEL) Concentrate for Solution for Infusion 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 KEY-DOCETAXEL therapy is increased in patients with abnormal liver function, and in patients receiving higher doses.

KEY-DOCETAXEL should generally not be given to patients with bilirubin > 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 transaminase 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 KEY-DOCETAXEL therapy and reviewed by the treating medical practitioner.

KEY-DOCETAXEL 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 KEY-DOCETAXEL.

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or by generalised rash/erythema occurred in patients who received the recommended 3-day dexamethasone premedication.

Hypersensitivity reactions requiring discontinuation of the KEY-DOCETAXEL infusion have also been reported in patients who did not receive pre-medication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

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

Severe fluid retention occurred in 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 distention (due to ascites).

- The use of KEY-DOCETAXEL should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified medical practitioner. 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 administration, unless contraindicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The pretreatment regimen for prostate cancer is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the KEY-DOCETAXEL regimen (see sub-header Fluid Retention).

Haematology

- Neutropenia is the most frequent reaction of KEY-DOCETAXEL and occurs in almost all patients. Severe neutropenia (Grade 3-4) occurred in almost all patients on combination therapy with doxorubicin.
- 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 KEY-DOCETAXEL. Patients should be re-treated with KEY-DOCETAXEL only after neutrophils recover to a level > 1500 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 therapy, a reduction in dose for subsequent courses of therapy and the use of appropriate symptomatic measures are recommended.

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 initiation of the infusion of KEY-DOCETAXEL, thus facilities for the treatment of hypotension and bronchospasm should be available.
- If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy.
- However, more severe reactions, such as hypotension with a reduction of more than 20 mmHg, bronchospasm or generalised rash/erythema require immediate discontinuation of the infusion and appropriate symptomatic therapy.

- Patients who have developed severe hypersensitivity reactions should not be re-challenged with KEY-DOCETAXEL.

Fluid Retention

- A premedication consisting of a corticosteroid such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to KEY-DOCETAXEL administration, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.
- Patients with severe fluid retention such as pleural effusions, pericardial effusion and ascites should be closely monitored.
- The pretreatment regimen for prostate cancer is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the KEY-DOCETAXEL regimen.

Patients with Liver impairment

- In patients treated with KEY-DOCETAXEL at 100 mg/m^2 who have serum transaminase levels (ALT and/or AST) greater than 1,5 times the upper limit of the normal range (ULN) concurrent with serum alkaline phosphatase levels greater than 2,5 times the upper limit of the normal range (ULN), there is a greater risk of developing severe adverse reactions such as toxic death, including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of KEY-DOCETAXEL in 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 KEY-DOCETAXEL should not be used unless strictly indicated.

Cutaneous reactions

- Localised skin erythema of the extremities with oedema followed by desquamation (hand-foot syndrome) has been observed.
- This type of toxicity can lead to the interruption or discontinuation of treatment.

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.

Elderly

- An analysis of safety data in patients equal to or greater than 60 years of age treated with KEY-DOCETAXEL and capecitabine combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 adverse events, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age.
- The incidence of anaemia, infection, nail changes, anorexia and weight loss may occur at higher rates in patients who are 65 years of age or older, compared to younger patients.

Cardiac toxicity

Heart failure has been observed in patients who have received KEY-DOCETAXEL in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death. When patients are candidates for treatment with KEY-DOCETAXEL in combination with trastuzumab, they should undergo baseline cardiac assessment. Cardiac function should be further monitored during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction.

Congestive heart failure

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

Respiratory disorders

Acute respiratory distress syndrome, interstitial pneumonia and pulmonary fibrosis may occur. Radiation pneumonitis may occur in patients receiving concomitant radiotherapy.

Eye disorders

Transient visual disturbances (flashes, flashing lights or scotomata) typically occurring during infusion and in association with hypersensitivity reactions may occur. These are reversible upon discontinuation of the infusion.

Lacrimation with or without conjunctivitis, as lacrimal duct obstruction resulting in excessive tearing may occur.

Excipients

KEY-DOCETAXEL 20 mg contains 156 mg ethanol per diluent vial, equivalent to 4 ml of beer or 2 ml wine per vial.

KEY-DOCETAXEL 80 mg contains 624 mg ethanol per diluent vial, equivalent to 16 ml of beer or 6 ml wine per vial.

Harmful for those suffering from alcoholism.

4.5 Interaction with other medicines and other forms of Interaction

- There have been no formal clinical studies to evaluate the interactions of KEY-DOCETAXEL. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450 3A, such as ciclosporin, ketoconazole, erythromycin, and troleandomycin. 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.
- Docetaxel is highly protein bound (> 95 %). Although the possible *in vivo* interaction of KEY-DOCETAXEL with concomitantly administered medicines have not been investigated formally, *in vitro* interactions with tightly protein-bound medicines such as erythromycin, diphenhydramine, propranalol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel.
- In addition, dexamethasone did not affect protein binding of docetaxel.
- Docetaxel did not influence the binding of digoxin.
- In the doxorubicin/docetaxel combination, the clearance of docetaxel was increased.

- When used in combination, KEY-DOCETAXEL does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). However, the clearance of KEY-DOCETAXEL was increased.
- Clearance of KEY-DOCETAXEL in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after KEY-DOCETAXEL infusion is similar to that observed with cisplatin alone.
- Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of KEY-DOCETAXEL and vice versa showed no effect by capecitabine on the pharmacokinetics of KEY-DOCETAXEL (Cmax and AUC) and no effect by KEY-DOCETAXEL on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.
- The effect of prednisone on the pharmacokinetics of KEY-DOCETAXEL administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetic of KEY-DOCETAXEL was observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy

Use during pregnancy and lactation is contraindicated as KEY-DOCETAXEL is teratogenic. Contraceptive measures must be taken during and for at least three months after cessation of therapy.

4.7 Effects on ability to drive and use machines

The amount of alcohol in this medicine may impair the patient's ability to perform or execute tasks or activities requiring mental alertness, judgment, sound coordination or vision to drive or use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

Not Applicable

b. Tabulated summary of adverse reactions

DOCETAXEL 100 mg/m^2 single medicine:

Medra System Organ class	**Frequent**	**Less Frequent**
Investigations	Increased blood bilirubin (< 5 %); Increased blood alkaline phosphatase (< 4 %); Increased AST (< 3 %); Increased ALT (< 2 %)	
Cardiac disorders	Dysrhythmia	Cardiac failure
Blood and lymphatic system disorders	Neutropenia; Anaemia; Febrile neutropenia; Thrombocytopenia	

Nervous system disorders	Peripheral sensory neuropathy; Peripheral motor neuropathy; Dysgeusia	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation; Abdominal pain; Gastrointestinal haemorrhage	Oesophagitis
Skin and subcutaneous tissue disorders	Alopecia; Skin reactions; Nail disorders	
Musculoskeletal, connective tissue and bone disorders	Myalgia; Arthralgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infections including sepsis and pneumonia; Infections associated with neutropenia	
Vascular disorders	Hypotension; Hypertension; Haemorrhage	
General disorders and administration site conditions	Fluid retention; Asthenia; Pain; Infusion site reaction; Non-cardiac chest pain	
Immune system disorders	Hypersensitivity	

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DOCETAXEL 75 mg/m^2 single medicine:

Medra System Organ class	Frequent	Less Frequent
Investigations	Increased blood bilirubin (< 2 %)	
Cardiac disorders	Dysrhythmia	
Blood and lymphatic system disorders	Neutropenia; Anaemia; Febrile neutropenia; Thrombocytopenia	
Nervous system disorders	Peripheral sensory neuropathy; Peripheral motor neuropathy	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Skin reactions; Nail disorders	
Musculoskeletal, connective tissue and bone disorders	Myalgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection	
Vascular disorders	Hypotension	
General disorders and administration site conditions	Fluid retention; Asthenia; Pain	
Immune system disorders	Hypersensitivity	

DOCETAXEL 75 mg/m^2 in combination with doxorubicin:

Medra System Organ class	Frequent	Less Frequent
Investigations	Increased blood bilirubin (< 2,5 %); Increased blood alkaline phosphatase (< 2,5 %)	Increased AST (< 1 %); Increased ALT (< 1 %)
Cardiac disorders	Cardiac failure; Dysrhythmia	
Blood and lymphatic system disorders	Neutropenia; Anaemia; Febrile neutropenia; Thrombocytopenia	
Nervous system disorders	Peripheral sensory neuropathy; Peripheral motor neuropathy	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Skin reactions; Nail disorders	
Musculoskeletal, connective tissue and bone disorders	Myalgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection	
Vascular disorders		Hypotension
General disorders and administration site conditions	Fluid retention; Asthenia; Pain; infusion site reaction	

Immune system disorders	Hypersensitivity	

DOCETAXEL 75 mg/m^2 in combination with cisplatin:

Medra System Organ class	**Frequent**	**Less Frequent**
Investigations	Increased blood bilirubin (2,1 %); Increased ALT (1,3 %)	Increased AST (0,5 %); Increased blood alkaline phosphatase (0,3 %)
Cardiac disorders	Dysrhythmia	Cardiac failure
Blood and lymphatic system disorders	Neutropenia; Anaemia; Febrile neutropenia; Thrombocytopenia	
Nervous system disorders	Peripheral sensory neuropathy; Peripheral motor neuropathy	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Skin reactions; Nail disorders	
Musculoskeletal, connective tissue and bone disorders	Myalgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection	

Vascular disorders	Hypotension	
General disorders and administration site conditions	Fluid retention; Asthenia; Pain; infusion site reaction	
Immune system disorders	Hypersensitivity	

DOCETAXEL 75 mg/m^2 in combination with capecitabine:

Medra System Organ class	**Frequent**	**Less Frequent**
Blood and lymphatic system disorders	Neutropenia; Anaemia; Thrombocytopenia	
Nervous system disorders	Dysgeusia; Paraesthesia; Dizziness; Headache; Peripheral neuropathy	
Eye disorders	Increased lacrimation	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain; Dyspnoea; Cough; Epistaxis	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation; Abdominal pain; Dyspepsia; Dry mouth	
Skin and subcutaneous tissue disorders	Hand-foot syndrome; Alopecia; Nail disorders; Dermatitis; Erythematous rash; Onycholysis	
Musculoskeletal, connective tissue and bone disorders	Myalgia; Arthralgia; Pain in extremity; Back pain	

Metabolism and nutrition disorders	Anorexia; Decreased appetite; Dehydration	
Infections and infestations	Oral candidiasis	
General disorders and administration site conditions	Asthenia; Pyrexia; Fatigue or weakness; Peripheral oedema; Lethargy; Pain	

DOCETAXEL 75 mg/m^2 in combination with prednisone or prednisolone:

Medra System Organ class	**Frequent**	**Less Frequent**
Cardiac disorders	Decreased cardiac left ventricular function	
Blood and lymphatic system disorders	Neutropenia; Anaemia; Thrombocytopenia; Febrile neutropenia	
Nervous system disorders	Dysgeusia; Peripheral sensory neuropathy; Peripheral motor neuropathy	
Eye disorders	Increased lacrimation	
Respiratory, thoracic and mediastinal disorders	Dyspnoea; Cough; Epistaxis	
Gastrointestinal disorders	Stomatitis/Pharyngitis; Diarrhoea; Nausea; Vomiting	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders; Exfoliative rash	

Musculoskeletal, connective tissue and bone disorders	Myalgia; Arthralgia;	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection	
General disorders and administration site conditions	Fluid retention; Fatigue	
Immune system disorders	Hypersensitivity	

DOCETAXEL 75 mg/m² in combination doxorubicin and with cyclophosphamide:

Medra System Organ class	**Frequent**	**Less Frequent**
Investigations	Increased or decreased weight	
Cardiac disorders	Dysrhythmia; Congestive heart failure	
Blood and lymphatic system disorders	Neutropenia; Anaemia; Thrombocytopenia; Febrile neutropenia	
Nervous system disorders	Dysgeusia; Peripheral sensory neuropathy; Peripheral motor neuropathy; Neurocortical; Neurocerebellar	Syncope
Eye disorders	Lacrimation disorder; Conjunctivitis	
Respiratory, thoracic and mediastinal disorders	Cough	

Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation; Abdominal pain	Colitis/enteritis/large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders; Skin toxicity	
Musculoskeletal, connective tissue and bone disorders	Myalgia; Arthralgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection; Neutropenic infection	
Vascular disorders	Vasodilation; Hypotension	Phlebitis; Lymphoedema
General disorders and administration site conditions	Asthenia; Fever; Peripheral oedema	
Immune system disorders	Hypersensitivity	
Reproductive system and breast disorders	Amenorrhoea	

DOCETAXEL 75 mg/m^2 in combination with cisplatin and 5-fluorouracil for head and neck cancer:

Medra System Organ class	**Frequent**	**Less Frequent**
Investigations	Increased weight	
Cardiac disorders	Myocardial ischaemia	Dysrhythmia

Blood and lymphatic system disorders	Neutropenia; Anaemia; Thrombocytopenia; Febrile neutropenia	
Nervous system disorders	Dysgeusia/Parosmia; Peripheral sensory neuropathy; Dizziness	
Eye disorders	Increase lacrimation; Conjunctivitis	
Ear and labyrinth disorders	Hearing impaired	
Gastrointestinal disorders	Stomatitis; Diarrhoea; Nausea; Vomiting; Constipation; Abdominal pain; Dyspepsia; Gastrointestinal haemorrhage Esophagitis/dysphagia/odynophagia	
Skin and subcutaneous tissue disorders	Alopecia; Pruritic rash; Dry skin; Exfoliative skin	
Musculoskeletal, connective tissue and bone disorders	Myalgia	
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infection; Neutropenic infection	
Neoplasms benign and malignant (including cysts and polyps)	Cancer pain	
Vascular disorders	Venous disorder	

General disorders and administration site conditions	Lethargy; Pyrexia; Fluid retention; Oedema	
Immune system disorders	Hypersensitivity	

Description of selected adverse reactions

Not applicable

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 with docetaxel when used in combination with other anticancer medicines known to be associated with second primary malignancies. Acute myeloid leukemia and myelodysplastic syndrome (rare) have been reported in breast cancer with the TAC regimen.

Blood and lymphatic system disorders

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

Immune system disorders

Anaphylactic shock, sometimes fatal, have been reported. Hypersensitivity reactions (frequency unknown) have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Nervous system disorders

Convulsion or transient loss of consciousness have been reported with docetaxel administration. These reactions sometimes appear during the infusion of the medicine.

Eye disorders

Transient visual disturbances (flashes, flashing lights or scotomata) typically occurring during infusion of the medicine and in association with hypersensitivity reactions, have been reported. These were reversible upon discontinuation of the infusion. Lacrimation with or without conjunctivitis, lacrimal duct obstruction resulting in excessive tearing have been reported. Cystoid macular edema (CME) has been reported in patients treated with docetaxel.

Ear and labyrinth disorders

Ototoxicity, hearing impaired and/or hearing loss have been reported.

Cardiac disorders

Myocardial infarction has been reported.

Ventricular arrhythmia including ventricular tachycardia (frequency not known), sometimes fatal, has been reported in patients treated with docetaxel in combination regimens including doxorubin, 5-fluorouracil and/or cyclophosphamide.

Vascular disorders

Venous thromboembolic events have rarely been reported.

Respiratory, thoracic and mediastinal disorders

Acute respiratory distress syndrome and cases of interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and sometimes fatal respiratory failure have rarely been reported. Radiation pneumonitis has been reported in patients who had received concomitant radiotherapy.

Gastrointestinal disorders

Enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, have been reported with a potentially fatal outcome (frequency unknown). Dehydration as a consequence of gastrointestinal events including enterocolitis and gastrointestinal perforation have been reported. Ileus obstruction 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, bullous eruptions such as erythema multiforme, and serious cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP) have been reported with docetaxel. Scleroderma-like changes, generally preceded by peripheral

lymphedema, have been reported with docetaxel. Permanent alopecia has been reported (frequency unknown).

Renal and urinary disorders

Renal insufficiency and renal failure have been reported.

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 at a different site) has been reported 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 edema have been reported.

Metabolism and nutrition disorders

Electrolyte imbalances have been reported. Cases of hyponatremia have been reported, in most cases associated with dehydration, vomiting and pneumonia. Hypokalemia, hypomagnesemia and hypocalcemia have been observed, generally associated with gastrointestinal disorders and particularly diarrhoea. Tumour lysis syndrome, potentially fatal, has been reported (frequency not known).

Musculoskeletal disorders

Myositis has been reported with docetaxel (frequency unknown).

1.3.1.1 Professional Information for medicines for human use

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. Healthcare 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://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

In case of overdosage, the patient should be kept in a specialised unit where vital functions can be closely monitored. There is no known antidote for KEY-DOCETAXEL overdosage.

The primary anticipated complications of overdosage would consist of neutropenia, mucositis, cutaneous reactions and paraesthesia.

Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose.

Other appropriate symptomatic measures should be taken, as needed.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic Agents

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic group and ATC code: Taxanes, ATC Code: L01CD02

1.3.1.1 Professional Information for medicines for human use

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. Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excited 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 overexpressing the paraglycoprotein 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

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, ß, and γphases of 4 minutes, 36 minutes, and 11,1 hours, respectively. The late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 ℓ/h/m^2 and 113 ℓ, respectively. Docetexal is more than 95 % bound to plasma proteins. Faecal excretion is the main route of elimination of docetaxel and its metabolites. The faecal and urinary excretions

account for about 75 % and 6 % of the dose, respectively. Only a minor fraction of the dose is excreted as the parent substance.

Based on *in vitro* studies, isoenzymes of the cytochrome P450-3A subfamily appear to be involved in docetaxel metabolism.

Dexamethasone did not affect protein binding of docetaxel.

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

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.

Phase I studies 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 the main capecitabine metabolite 5'-DFUR.

The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of docetaxel was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid

1.3.1.1 Professional Information for medicines for human use

Polisorbate 80 (Nofable 9920 HX)

6.2 Incompatibilities

- Do not admix with other medicines.

6.3 Shelf life

Before mixing:

24 months

Diluent:

60 months

- The KEY-DOCETAXEL premix (10 mg docetaxel/ml) should preferably be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.
- The KEY-DOCETAXEL infusion solution should preferably be used immediately.
- It may however be stored at room temperature (not exceeding 25 °C) for a maximum of 4 hours (this includes one-hour infusion time for administration of the solution, under room temperature and normal lighting conditions).

6.4 Special precautions for storage

- Unopened vials should be stored between 2 – 8 °C, protected from light.
- Discard any unused solution.
- For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

KEY-DOCETAXEL 20 mg: Carton containing a vial of KEY-DOCETAXEL 20 mg/0,5 ml (dark blue flip-off cap) and a vial of KEY-DOCETAXEL 20 diluent solution 1,5 ml (white flip-off cap).

KEY-DOCETAXEL 80 mg: Carton containing a vial of KEY-DOCETAXEL 80 mg/2 ml (violet flip-off cap) and a vial of KEY-DOCETAXEL 80 diluent solution 6,0 ml (white flip-off cap).

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate

2198, Johannesburg

RSA

8 REGISTRATION NUMBER(S)

KEY-DOCETAXEL 20 mg: 45/26/0328

KEY-DOCETAXEL 80 mg: 45/26/0329

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10 DATE OF REVISION OF TEXT

14 November 2024