PROFESSIONAL INFORMATION FOR CIPLA DOCETAXEL 20 / 80 (INJECTION) AND SOLVENT FOR CIPLA DOCETAXEL 20 / 80

SCHEDULING STATUS:

S4: CIPLA DOCETAXEL 20 and **CIPLA DOCETAXEL 80**

S1: SOLVENT FOR CIPLA DOCETAXEL 20 and **SOLVENT FOR CIPLA DOCETAXEL 80**

1. NAME OF THE MEDICINE:

CIPLA DOCETAXEL 20 (Solution for infusion)

CIPLA DOCETAXEL 80 (Solution for infusion)

SOLVENT FOR CIPLA DOCETAXEL 20 (Solvent for infusion)

SOLVENT FOR CIPLA DOCETAXEL 80 (Solvent for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

CIPLA DOCETAXEL 20: Each single-dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel (anhydrous) in 0,5 mL polysorbate 80. Inactive ingredients include anhydrous citric acid and polysorbate 80.

CIPLA DOCETAXEL 80: Each single-dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel (anhydrous) in 2,0 mL polysorbate 80. Inactive ingredients include anhydrous citric acid and polysorbate 80.

SOLVENT FOR CIPLA DOCETAXEL 20:

Each vial contains 13,0 % m/v ethanol 95 % v/v.

SOLVENT FOR CIPLA DOCETAXEL 80:

Each vial contains 13,0 % m/v ethanol 95 % v/v.

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

3. PHARMACEUTICAL FORM

CIPLA DOCETAXEL 20: Solution for infusion.

A light yellow viscous clear solution in 5 mL glass vials.

CIPLA DOCETAXEL 80: Solution for infusion.

A light yellow viscous clear solution in 15 mL glass vials.

SOLVENT FOR CIPLA DOCETAXEL 20:

Solvent for infusion.

A clear colourless solution packed in transparent glass vial with a grey butyl stopper and a red opaque aluminium flip-off seal.

SOLVENT FOR CIPLA DOCETAXEL 80:

Solvent for infusion.

A clear colourless solution packed in transparent glass vial with a grey butyl stopper and a serulin blue aluminium flip-off seal.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1 Breast cancer:

CIPLA 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.

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

CIPLA 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.

4.1.2 Non-small cell lung cancer:

CIPLA 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.

CIPLA 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.

4.1.3 Ovarian cancer:

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

4.1.4 Prostate cancer:

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

4.2 Posology and method of administration

CIPLA DOCETAXEL should be administered by intravenous infusion only.

CIPLA DOCETAXEL solvent vials are for single use only.

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 CIPLA 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 administered 12 hours, 3 hours and 1 hour before the CIPLA DOCETAXEL infusion.

4.2.1 Breast cancer:

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

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

In combination with capecitabine, the recommended dose of CIPLA 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 manufacturer's prescribing information.

4.2.2 Non-small cell lung cancer:

In combination therapy (chemotherapy-naïve patients):

The recommended dosage regimen is CIPLA 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 CIPLA DOCETAXEL therapy is 100 mg/m^2 as a single agent.

4.2.3 Ovarian cancer:

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

4.2.4 Prostate cancer:

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

Dosage adjustments during treatment:

General:

ONLY the medical practitioner can modify the schedule of administration.

CIPLA DOCETAXEL 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 CIPLA DOCETAXEL therapy, should have the dosage of CIPLA DOCETAXEL reduced during the subsequent cycle, from 100 mg/m^2 to 75 mg/m^2 and/or from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Combination therapy with CIPLA DOCETAXEL for non-small cell lung cancer:

For patients who were dosed initially at CIPLA DOCETAXEL 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy was < 25000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with

serious non-haematological toxicities, the CIPLA DOCETAXEL dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see the manufacturer's prescribing information.

Combination therapy with CIPLA 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 CIPLA DOCETAXEL dose reduced to 60 mg/m^2. If G-CSF is not used, the CIPLA DOCETAXEL dose should be reduced from 75 to 60 mg/m^2.

For capecitabine dose modifications when combined with CIPLA DOCETAXEL, see capecitabine manufacturer's prescribing information.

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

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

Special populations

Patients with hepatic impairment:

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

ULN should generally not receive CIPLA DOCETAXEL.

Elderly:

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

For capecitabine dosage reduction when combined with CIPLA DOCETAXEL, see capecitabine manufacturer's prescribing information.

Paediatric population

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

Method of administration

For instructions on preparation and administration, see **section 6.6**.

4.3 Contraindications

- CIPLA DOCETAXEL is contraindicated in patients who have a history of hypersensitivity reactions to docetaxel or polysorbate 80, or to any of the ingredients.
- CIPLA DOCETAXEL should not be used in patients with baseline neutrophil count of < 1500 cells/mm^3.
- Pregnancy and lactation as CIPLA DOCETAXEL is teratogenic in animals.
- The safe use of CIPLA DOCETAXEL in children has not been established.
- CIPLA DOCETAXEL should not be used in patients with severe liver impairment since there are no data available (see **section 4.4** and **section 4.2**).

Contraindications for other medicines also apply when combined with CIPLA DOCETAXEL.

4.4 Special warnings and precautions for use

CIPLA DOCETAXEL should be administered under the supervision of a qualified medical practitioner 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 CIPLA DOCETAXEL therapy is increased in patients with abnormal liver function and in patients receiving higher doses.

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

CIPLA 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 CIPLA DOCETAXEL.

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 CIPLA DOCETAXEL were reported in some patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

CIPLA DOCETAXEL must not be given to patients who have a history of severe hypersensitivity reactions to CIPLA DOCETAXEL 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).

Please note: Contact of the CIPLA DOCETAXEL concentrate with plasticised PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final CIPLA DOCETAXEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets (see section 6.6).

The use of CIPLA 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 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 CIPLA 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 administered 12 hours, 3 hours and 1 hour before the CIPLA DOCETAXEL regimen.

Haematology:

Neutropenia is the most frequent adverse reaction of CIPLA DOCETAXEL and occurs in almost all patients. Severe neutropenia (grade 3 – 4) occurred in 99 % of patients on combination therapy with doxorubicin.

Neutrophil nadirs occurred at a median of 7 days, but this interval may be shorter in heavily pretreated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving CIPLA DOCETAXEL. Patients should be retreated with CIPLA 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 CIPLA 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 the initiation of the infusion of CIPLA 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 mm Hg, 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 rechallenged with CIPLA 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 CIPLA 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 effusion, pericardial effusion and ascites, should be monitored closely.

Liver impairment:

In patients treated with CIPLA 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 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 CIPLA DOCETAXEL in patients with elevated liver function tests (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 CIPLA DOCETAXEL should not be used unless strictly indicated.

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. 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 CIPLA 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. In patients treated with CIPLA DOCETAXEL every three weeks the incidence of anaemia, infection, nail changes, anorexia, and weight loss occurred at rates > 10 % higher in patients who were 65 years of age.

Others:

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

Excipients

SOLVENT FOR CIPLA DOCETAXEL 20 and **SOLVENT FOR CIPLA DOCETAXEL 80** contain 13 % m/v ethanol per vial.

4.5 Interaction with other medicines and other forms of interaction

There have been no formal clinical studies to evaluate the interactions of CIPLA DOCETAXEL.

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

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

CIPLA DOCETAXEL does not influence the binding of digoxin.

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

Clearance of CIPLA DOCETAXEL in combination therapy with cisplatin is similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after CIPLA DOCETAXEL infusion is similar to that observed with cisplatin alone. There is no effect by capecitabine on the pharmacokinetics of CIPLA DOCETAXEL (C_{max} and AUC) and no effect by CIPLA DOCETAXEL on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.

There is no effect of prednisone on the pharmacokinetics of CIPLA DOCETAXEL.

CIPLA DOCETAXEL should be administered with caution in patients concomitantly receiving potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir and azole antifungals like ketoconazole or itraconazole). A medicine interaction study performed in patients receiving ketoconazole and docetaxel, as in CIPLA DOCETAXEL, showed that the clearance of docetaxel was reduced by half by ketoconazole, probably because the metabolism of docetaxel involves CYP3A4 as a major (single) metabolic pathway. Reduced tolerance of CIPLA DOCETAXEL may occur, even at lower doses.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation are contraindications to the use of CIPLA DOCETAXEL, as CIPLA DOCETAXEL is teratogenic in animals (see **section 4.3** and **section 4.4**).

4.7 Effects on ability to drive and use machines

To avoid accidents, patients should be advised to exercise caution when driving or operating machinery if they develop dizziness, fatigue or weakness.

4.8 Undesirable effects

Tabulated list of adverse reactions

Blood and lymphatic system disorders:

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

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

Immune system disorders:

Frequent: Hypersensitivity reactions may occur, usually within a few minutes following the start of the infusion of CIPLA DOCETAXEL 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. The onset of moderate and severe retention is delayed in patients with premedication compared with patients without premedication. However, it has been reported in some patients during the early courses of therapy. The median time to fluid retention reversibility is 16,4 weeks (range 0 to 42 weeks) in patients receiving the recommended

premedication. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

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

Nervous system disorders:

Frequent: Neurosensory signs characterised by paraesthesia, dysaesthesia or pain, including burning, may occur.

Neuromotor events, mainly characterised by weakness, may occur.

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

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.

Cardiac 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 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 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 CIPLA DOCETAXEL 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 CIPLA DOCETAXEL treatment. Bullous eruptions, such as erythema multiforme or Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Frequent:	Arthralgia and myalgia.

General disorders and administration 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 CIPLA DOCETAXEL in the adjuvant treatment of breast cancer:

Clinically important treatment related adverse events in patients receiving docetaxel,

as in CIPLA DOCETAXEL, in combination with doxorubicin and cyclophosphamide:

Infections and infestations:

Frequent: Infection.

Blood and lymphatic system disorders:

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

Immune system disorders:

Frequent: Hypersensitivity reactions.

Metabolism and nutrition disorders:

Frequent: Peripheral oedema, 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.

Cardiac disorders:

Less frequent: Cardiac dysrhythmias.

Vascular disorders:

Frequent: Vasodilation.

Less frequent: Hypotension, phlebitis.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Cough.

Gastrointestinal disorders:

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

Less frequent: Abdominal pain.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, skin toxicity, and nail disorders.

Musculoskeletal and connective tissue disorders:

Frequent: Myalgia, arthralgia.

Reproductive system and breast disorders:

Frequent: Amenorrhoea.

General disorders and administration site conditions:

Frequent: Asthenia.

Combination therapy with CIPLA DOCETAXEL and capecitabine for breast cancer:

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

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:[1] Dermatitis, rash erythema, nail discolouration, and onycholysis.

Musculoskeletal and connective tissue disorders:

Frequent: Myalgia, arthralgia.

Less frequent: Back pain.

General disorders and administration site conditions:

Frequent: Asthenia, pyrexia, fatigue, and weakness.

Less frequent: Pain in limb, lethargy, and pain.

Investigations:

Frequent: Neutropenia, anaemia.

Less frequent: Thrombocytopenia, hyperbilirubinaemia.

Combination therapy with CIPLA DOCETAXEL in prostate cancer patients:

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

Infections and infestations:

Frequent: Infection.

Blood and lymphatic system disorders:

Frequent: Anaemia, neutropenia.

Less frequent: Thrombocytopenia, febrile neutropenia.

Immune system disorders:

Less frequent: Allergic reactions.

Metabolism and nutrition disorders:

Frequent: Fluid retention.

Nervous system disorders:

Frequent: Sensory neuropathy, motor neuropathy.

Eye disorders:

Less frequent: Tearing.

Cardiac disorders:

Less frequent: Left ventricular dysfunction.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Epistaxis, cough, and dyspnoea.

Gastrointestinal disorders:

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

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, nail changes.

Less frequent: Rash/desquamation.

Musculoskeletal and connective tissue disorders:

Less frequent: Myalgia, arthralgia.

General disorders and administration site conditions:

Frequent: Fatigue.

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

4.9 Overdose

In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. There is no known antidote for CIPLA 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic medicines, plant alkaloids and other natural products, Taxanes, ATC Code: L01CD02.

Mechanism of action:

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and by inhibiting their disassembly, which leads to a marked decrease in 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 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 paraglycoprotein which is encoded by the multidrug resistance gene. *In vivo,* docetaxel is schedule-independent.

5.2 Pharmacokinetic properties:

Absorption:

The kinetic profile of docetaxel is dose-independent and consistent with a three-compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11,1 hours, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Distribution:

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

Elimination:

Faecal excretion is the main route of elimination of docetaxel and its metabolites. 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 compound. Based on *in vitro* studies, isoenzymes of the cytochrome P450-3A subfamily appear to be involved in docetaxel metabolism.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CIPLA DOCETAXEL 20 and **CIPLA DOCETAXEL 80**:

Anhydrous citric acid

Polysorbate 80

SOLVENT FOR CIPLA DOCETAXEL 20 and **SOLVENT FOR CIPLA DOCETAXEL 80:**

Ethanol

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in **section** 6.6.

6.3 Shelf life:

Unopen vials:

CIPLA DOCETAXEL 20 and **CIPLA DOCETAXEL 80**:

24 months.

SOLVENT FOR CIPLA DOCETAXEL 20 and **SOLVENT FOR CIPLA DOCETAXEL 80:**

24 months.

Diluted medicine:

The CIPLA DOCETAXEL premix solution (10 mg docetaxel/mL) may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

The CIPLA DOCETAXEL infusion solution should preferably be used immediately. It may however be stored at room temperature (at or below 25 ºC) for a maximum of 4 hours (this includes the 1-hour infusion time for administration of the infusion, under room temperature

and normal lighting conditions).

Discard any unused solution.

6.4 Special precautions for storage

Unopened vials (including solvent vials) should be stored between 2 ºC and 8 ºC, protected from bright light. Freezing does not adversely affect the product.

For storage conditions of the diluted medicine, see **section 6.3**

6.5 Nature and contents of container

CIPLA DOCETAXEL 20:	Carton containing a 5 mL transparent glass vial of CIPLA DOCETAXEL 20.
CIPLA DOCETAXEL 80:	Carton containing a 15 mL transparent glass vial of CIPLA DOCETAXEL 80.
SOLVENT FOR CIPLA DOCETAXEL 20:	1,5 mL solvent in a 5 mL transparent glass vial with a grey butyl stopper and a red opaque aluminium flip-off seal packed in a carton.
SOLVENT FOR CIPLA DOCETAXEL 80:	6,0 mL solvent in a 15 mL transparent glass vial with a grey butyl stopper and a serulin blue aluminium flip-off seal packed in a carton.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling:

Handling precautions for cytostatic agents should be followed:

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

- CIPLA DOCETAXEL is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing CIPLA DOCETAXEL solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If CIPLA DOCETAXEL concentrate, premix solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If CIPLA DOCETAXEL 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.

Directions for use:

CIPLA DOCETAXEL 20 vial and SOLVENT FOR CIPLA DOCETAXEL 20 vial:

Each CIPLA DOCETAXEL 20 vial contains 20 mg of CIPLA DOCETAXEL per 0,5 mL of polysorbate 80 (fill volume: 24,4 mg / 0,61 mL).

Each **SOLVENT FOR CIPLA DOCETAXEL 20** vial for **CIPLA DOCETAXEL** 20 mg contains 1,5 mL solvent (fill volume: 1,98 mL).

CIPLA DOCETAXEL 80 vial and SOLVENT FOR CIPLA DOCETAXEL 80 vial:

Each CIPLA DOCETAXEL 80 vial contains 80 mg CIPLA DOCETAXEL per 2 mL of polysorbate 80 (fill volume: 94,4 mg / 2,36 mL).

Each **SOLVENT FOR CIPLA DOCETAXEL 80** vial for **CIPLA DOCETAXEL** 80 mg contains 6 mL solvent (fill volume: 7,33 mL).

Preparation for intravenous administration:

a) **Preparation of the CIPLA DOCETAXEL premix solution (10 mg CIPLA DOCETAXEL/mL):**

If the vials are stored under refrigeration, allow the required number of CIPLA DOCETAXEL boxes to stand at room temperature for 5 minutes.

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the CIPLA DOCETAXEL solvent vial by partially inverting the vial.

Inject the entire contents of the syringe into the corresponding CIPLA 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 CIPLA 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 CIPLA DOCETAXEL would require 14 mL CIPLA 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 0,74 mg CIPLA DOCETAXEL/mL. If a dose greater than 200 mg of CIPLA DOCETAXEL is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/mL CIPLA DOCETAXEL is not exceeded.

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

The CIPLA 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.

CIPLA 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 medications.

Contact of the CIPLA DOCETAXEL concentrate with plasticised PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final CIPLA DOCETAXEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets (see section 4.4).

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

CIPLA DOCETAXEL 20: 41/26/0162

CIPLA DOCETAXEL 80: 41/26/0163

SOLVENT FOR CIPLA DOCETAXEL 20: 44/32.2/0393

SOLVENT FOR CIPLA DOCETAXEL 80: 44/32.2/0394

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