PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

DOCETAXEL ADCO 20 mg/1 ml (Concentrate for solution for infusion)

DOCETAXEL ADCO 80 mg/4 ml (Concentrate for solution for infusion)

DOCETAXEL ADCO 140 mg/7 ml (Concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOCETAXEL ADCO 20 mg/1 ml

Each 1 ml single dose vial contains 20 mg docetaxel

DOCETAXEL ADCO 80 mg/4 ml

Each 4 ml single dose vial contains 80 mg docetaxel

DOCETAXEL ADCO 140 mg/7 ml

Each 7 ml single dose vial contains 140 mg docetaxel

Excipient(s) with known effect:

- Ethyl Alcohol: 51 % v/v
- Sugar content: sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, oily pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOCETAXEL ADCO is indicated for the following:

1. Breast Cancer:

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

DOCETAXEL ADCO, 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 his condition.

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

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

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

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

3. Ovarian Cancer:

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

4. Prostate Cancer:

DOCETAXEL ADCO 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 ADCO in combination with cisplatin and 5-flurouracil is indicated for treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

4.2 Posology and method of administration

Psology

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 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 DOCETAXEL ADCO infusion.

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

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

1. Breast cancer

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of DOCETAXEL ADCO is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (see also "Dosage adjustments during treatment").

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

For the second line treatment of breast cancer the recommended dosage of DOCETAXEL ADCO therapy is 100 mg/m^2 is given in monotherapy.

In combination with capecitaine, the recommended dose of DOCETAXEL ADCO is 75 mg/m^2 every three weeks, combined with capecitabine at 1 250 mg/m^2 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 capecitabine package insert.

2. Non-small cell lung cancer

In combination therapy (chemotherapy naïve patients):

The recommended dose regimen is DOCETAXEL ADCO 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 DOCETAXEL ADCO therapy is 100 mg/m^2 as a single medicine.

3. Ovarian Cancer

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

4. Prostate cancer

The recommended dose of DOCETAXEL ADCO 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 ADCO, because of 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 ADCO 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 package insert.

Dosage adjustments during treatment

General

ONLY the medical practitioner can modify the schedule of administration.

DOCETAXEL ADCO should be administered when the neutrophil count is > 1 500 cells/mm^3. Patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms, during DOCETAXEL ADCO therapy, should have the dosage of DOCETAXEL ADCO reduced, during the subsequent cycle, from 100 mg/m^2 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, the treatment should be discontinued.

Combination therapy with DOCETAXEL ADCO for non-small cell lung cancer (NSCLC)

For patients who are dosed initially at DOCETAXEL ADCO 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-hematologic toxicities, the docetaxel dosage of DOCETAXEL ADCO in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see relevant prescribing information.

Combination therapy with ADCO DOXETAXEL for Breast cancer

Patients who received 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 dose reduced to 60 mg/m^2. If G-CSF is not used, the DOCETAXEL ADCO dose should be reduced from 75 to 60 mg/m^2.

For capecitabine dose modifications when combined with docetaxel, see capecitabine relevant prescribing information.

For patients developing the first appearance of a Grade 2 toxicity, which persists at the time of the next DOCETAXEL ADCO/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 DOCETAXEL ADCO 55 mg/m^2. For any

subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the DOCETAXEL ADCO treatment.

For DOCETAXEL ADCO dose modifications due to hepatic impairment (see **section.4.4**).

Elderly

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

Hepatic impairment

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

Paediatric population

The safety and efficacy of DOCETAXEL ADCO in children have not been established.

Method of administration

DOCETAXEL ADCO should be administered by intravenous infusion only.

DOCETAXEL ADCO concentrate or infusion solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

Do not admix with other medicines.

DOCETAXEL ADCO infusion is compatible with commonly available administration sets,

including PVC sets.

For single use only, discard any unused portions.

For precaution to be taken before manipulating or administering the product, see section 6.6

For instructions on dilution of the medicine before administration, see section 6.6

4.3 Contraindications

DOCETAXEL ADCO is contra-indicated in patients who have a history of severe hypersensitivity reactions to docetaxel or polysorbate 80 or any of the other inactive ingredients contained in DOCETAXEL ADCO.

DOCETAXEL ADCO should not be used in patients with baseline neutrophil count of < 1 500 cells/mm^3.

DOCETAXEL ADCO should not be used in pregnancy and lactation.

The safe use of DOCETAXEL ADCO in children has not been established.

DOCETAXEL ADCO should not be used in patients with severe liver impairment since there are no data available (see **section 4.4 and 4.2**).

4.4 Special warnings and precautions for use

DOCETAXEL ADCO (docetaxel) concentrate for infusion should be administered under the supervision of a qualified physician 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 ADCO therapy is increased in patients with abnormal liver function and in patients receiving higher doses.

DOCETAXEL ADCO should generally not be given to patients with serum bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase > 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 may have a higher rate of febrile neutropenia grade 4, but may 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 ADCO therapy and reviewed by the treating medical doctor.

DOCETAXEL ADCO therapy should not be given to patients with neutrophil counts of < 1 500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving DOCETAXEL ADCO. Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or generalised rash/erythema may occur in 2,2 % (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the DOCETAXEL ADCO infusion may occur in patients who did not receive premedication. These reactions may resolve after discontinuation of the infusion and the administration of appropriate therapy.

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

Severe fluid retention may occur in 6,5 % (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. This is 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 DOCETAXEL ADCO 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 such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to DOCETAXEL ADCO administration, unless contra-indicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Haematology:

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

Neutrophil nadirs may occur at approximately 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 ADCO. Patients should be re-treated with DOCETAXEL ADCO only after 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 ADCO 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 DOCETAXEL ADCO, 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 DOCETAXEL ADCO or any other docetaxel containing medicines.

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 DOCETAXEL ADCO 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.

The pretreatment regimen for prostate cancer is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the DOCETAXEL ADCO regimen.

Patients with Liver Impairment:

In patients treated with DOCETAXEL ADCO at 100 mg/m^2 who have transaminase (ALT and/or AST) greater than 1,5 times the upper limit of the normal range (ULN) concurrent with alkaline phosphatase greater than 2,5 times the upper limit of the normal range (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 ADCO 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 > ULN and/or ALT and AST > 3,5 times the ULN concurrent with alkaline phosphatase > 6 times the ULN, no dose-reduction can be recommended and DOCETAXEL ADCO 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, dysesthesia 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 DOCETAXEL ADCO 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, weight loss may occur at rates > 10 % higher in patients who are 65 years of age or older compared to younger patients.

Cardiac toxicity:

Heart failure has been observed in patients received DOCETAXEL ADCO 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 DOCETAXEL ADCO 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, 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.

4.5 Interactions with other medicines and other forms of interaction

In vitro studies have shown that the metabolism of DOCETAXEL ADCO may be modified by the concomitant administration of medicines 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 a potential for a significant interaction. DOCETAXEL ADCO is highly protein bound (> 95 %). Although the possible in vivo interaction of DOCETAXEL ADCO with concomitantly administered medicines has not been investigated formally, *in vitro* interactions with tightly protein-bound drugs such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel. In addition, dexamethasone does not affect protein binding of docetaxel. DOCETAXEL ADCO does not influence the binding of digoxin.
In the doxorubicin/docetaxel combination, the clearance of docetaxel is increased.

Dexamethasone did not affect protein binding of DOCETAXEL ADCO.

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

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

Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of DOCETAXEL ADCO and *vice versa* showed no effect by capecitabine on the pharmacokinetics of DOCETAXEL ADCO (Cmax and AUC) and no effect by DOCETAXEL ADCO on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.
The effect of prednisone on the pharmacokinetics of DOCETAXEL ADCO administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetic of DOCETAXEL ADCO was observed.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation are contraindicated as DOCETAXEL ADCO is teratogenic in animals. 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

DOCETAXEL ADCO contains ethanol and this may impair the ability to drive or use machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Not Applicable

b. Tabulated summary of adverse reactions

DOCETAXEL 100 mg/m^2 single agent:

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; Diarrhea; 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	

DOCETAXEL 75 mg/m^2 single agent:

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; Diarrhea; 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; Diarrhea; 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; Diarrhea; 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; Diarrhea; 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; Diarrhea; 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/m^2 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; Diarrhea; 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; Diarrhea; 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	

c. Description of selected adverse reactions

Not applicable

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 Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email

Adcock.aereports@adcock.com

4.9 Overdose

In case of overdose, the patient should be kept in a specialised unit and vital functions monitored. The anticipated complications of overdosage would consist of neutropenia, mucositis, cutaneous reactions and paraesthesia.

Treatment of overdose:

There is no known antidote for DOCETAXEL ADCO overdosage.

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 and ATC code: Taxanes, ATC Code: L01CD02

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 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 overexpressing the para-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

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 - 115 mg/m^2 in Phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three compartment pharmacokinetic model with half-lives for the 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. Following the administration of a 100 mg/m^2 dose given as a one-hour infusion, a mean peak plasma level of 3,7 µg/ml was obtained with a corresponding AUC of 4,6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Docetaxel 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 drug. 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

Citric acid anhydrous, povidone, polysorbate 80, nitrogen.

Ethyl alcohol: 51 % v/v

6.2 Incompatibilities

Do not admix with other medicines.

DOCETAXEL ADCO infusion is compatible with commonly available administration sets, including PVC sets.

6.3 Shelf life

Before mixing: 24 months

After mixing: The diluted solution should be used immediately after preparation. If not used immediately the in-use storage times and conditions are the responsibility of the user and would not normally be longer than 8 hours at room temperature (about 25 °C) including the one-hour infusion.

6.4 Special precautions for storage

Store at or below 25 °C. Do not refrigerate or freeze.

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

DOCETAXEL ADCO should not be used after the expiry date shown on the carton and vial.

6.5 Nature and contents of container

DOCETAXEL ADCO 20 mg/1 ml: The solution is contained in a 5 ml, sterile type I

colourless glass vial, and closed with a bromobutyl rubber stopper (type I) sealed with aluminium cap with polypropylene disc. The vial will be packed with or without a clear protective polystyrene plastic overwrap with or without a polystyrene thermoformed tray in a cardboard carton.

DOCETAXEL ADCO 80 mg/4 ml: The solution is contained in a 8 ml, sterile type I colourless glass vial, and closed with a bromobutyl rubber stopper (type I) sealed with aluminium cap with polypropylene disc. The vial will be packed with or without a clear protective polystyrene plastic overwrap with or without a polystyrene thermoformed tray in a cardboard carton.

DOCETAXEL ADCO 140 mg/7 ml: The solution is contained in a 11 ml, sterile type I colourless glass vial, and closed with a bromobutyl rubber stopper (type I) sealed with aluminium cap with polypropylene disc. The vial will be packed with or without a clear protective polystyrene plastic overwrap with or without a polystyrene thermoformed tray in a cardboard carton.

6.6 Special precautions for disposal and other handling

A) Preparation of the solution for infusion:

More than one vial of DOCETAXEL ADCO 20 mg/1 ml or DOCETAXEL ADCO 80 mg/4 ml or DOCETAXEL ADCO 140 mg/7 ml concentrate for solution for infusion 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 corresponding volume of 20 mg/1 ml DOCETAXEL ADCO from the appropriate number of vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 7 ml of DOCETAXEL ADCO 20 mg/ml concentrate for solution for infusion.

For doses below 192 mg of docetaxel, inject the required volume of DOCETAXEL ADCO 20 mg/ 1ml 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 ADCO more than 250 ml of the infusion solution is required, as a maximum concentration of DOCETAXEL ADCO is 0,74 mg per ml of infusion solution.

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

Recommendations for safe handling

Handling precautions for cytostatic medicines should be followed:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.

1 Sabax Road,

Aeroton,

Johannesburg,

2013

8. REGISTRATION NUMBER(S)

DOCETAXEL ADCO 20 mg/1 ml: 46/26/0375

DOCETAXEL ADCO 80 mg/4 ml: 46/26/0376

DOCETAXEL ADCO 140 mg/7 ml: 46/26/0377

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2018

10. DATE OF REVISION OF THE TEXT

16 August 2023