PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CABAZITAXEL ADCO, 60 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CABAZITAXEL ADCO: Each single dose vial contains 60 mg cabazitaxel per 1,5 ml.

Diluent: Each vial contains 5,67 ml water for injection and ethanol 96 % (13 % w/w).

After initial dilution with the entire solvent, each ml of solution contains 10 mg cabazitaxel.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

CABAZITAXEL ADCO: Colourless to pale yellow viscous solution.

Diluent: Clear colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CABAZITAXEL ADCO in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

4.2 Posology and method of administration

Posology

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The use of CABAZITAXEL ADCO should be confined to units specialised in the administration of cytotoxics and it should be administered under the supervision of a medical practitioner experienced in the use of anticancer chemotherapy.

Premedication:

Premedicate prior to each administration of CABAZITAXEL ADCO with the following intravenous medicines to reduce the incidence and severity of a hypersensitivity reaction:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent) and with
- H_2 antagonist (ranitidine or equivalent) (see section 4.4)

Antiemetics prophylaxis is recommended and can be given orally or intravenously as needed.

Dosage:

The recommended dose of CABAZITAXEL ADCO is 25 mg/m2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout CABAZITAXEL ADCO treatment.

Dosage adjustments:

Dosage modifications should be made if patients experience the following adverse reactions.

Table 1: Recommended dosage modifications for adverse reaction in patients treated with CABAZITAXEL ADCO.

Adverse reactions	**Dosage modification**
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including granulocytecolony stimulating factor (G-CSF)	Delay treatment until neutrophil count is > 1 500 cells/mm^3, then reduce dosage of

	CABAZITAXEL ADCO from 25 mg/m^2 to 20 mg/m^2.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is > 1 500 cells/mm^3, then reduce dosage of CABAZITAXEL ADCO from 25 mg/m^2 to 20 mg/m^2.
Grade ≥ 3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of CABAZITAXEL ADCO from 25 mg/m^2 to 20 mg/m^2.
Grade > 2 peripheral neuropathy	Delay treatment until improvement, then consider a dose reduction.

Discontinue CABAZITAXEL ADCO treatment if a patient continues to experience any of these reactions at 20 mg/m2.

Paediatric population:

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

No data are available

Elderly ≥ 65 years:

No specific dose adjustment for the use of CABAZITAXEL ADCO in the elderly is recommended (see section 4.4 and 4.8).

Hepatic impairment:

CABAZITAXEL ADCO is extensively metabolised by the liver. No formal studies were conducted in patients with hepatic impairment. As a precautionary measure, CABAZITAXEL ADCO should not be given to patients with hepatic impairment [bilirubin ≥ 1 x Upper Limit of Normal (ULN), or AST/SGOT and/or ALT/SGPT ≥ 1,5 x ULN] (see section 4.3 and 4.4).

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Renal impairment:

CABAZITAXEL ADCO is minimally excreted through the kidney. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance (CrCl): 50 to 80 ml/min). Data in patients with moderate (CrCl: 30 to 50 ml/min) and severe renal impairment (CrCl < 30 ml/min) or end-stage renal disease is limited; therefore, these patients should be treated with caution and monitored carefully during treatment.

Concomitant medicine use:

Concomitant medicines that are CYP3A inducers or potent CYP3A inhibitors should be avoided (see section 4.5).

Method of administration

Precautions to be taken before manipulating or administering the product:

Caution should be exercised when handling and preparing CABAZITAXEL ADCO solutions. The use of gloves is recommended.

If CABAZITAXEL ADCO, at any step of its handling, should come into contact with the skin, wash immediately and thoroughly with soap and water. If it should come into contact with mucous membranes, wash immediately and thoroughly with water.

CABAZITAXEL ADCO should only be prepared and administered by personnel trained in handling cytotoxic medicines. Pregnant staff should not handle it (see section 6.6).

CABAZITAXEL ADCO is administered as a 1 hour intravenous infusion.

Use an in-line filter of 0,22 micrometre nominal pore size (also referred to as 0,2 micrometre) during administration.

Do not use PVC infusion containers and polyurethane infusion sets for the preparation and administration of CABAZITAXEL ADCO.

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The CABAZITAXEL ADCO infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned under section 6.4.

As the infusion solution is supersaturated, it may crystallise over time. In this case, the solution must not be used and should be discarded.

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

CABAZITAXEL ADCO must not be mixed with any other medicines.

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

4.3 Contraindications

CABAZITAXEL ADCO is contraindicated in:

- patients with a known hypersensitivity to cabazitaxel, polysorbate 80 or to any of the excipients listed in section 6.1.
- patients with neutrophil counts of ≤1 500/mm3
- patients with hepatic impairment (bilirubin ≥ 1 x ULN, or AST/SGOT and/or ALT/SGPT ≥ 1,5 x ULN)
- Concomitant vaccination with yellow fever vaccine (see section 4.5)
- pregnancy, lactation and in women of childbearing potential. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for up to 3 months after the last dose (see section 4.6)

4.4 Special warnings and precautions for use

Woman should not become pregnant during treatment. Women of childbearing potential must use effective contraception to avoid pregnancy while they are receiving CABAZITAXEL ADCO. The recommended duration of contraception in female patients of childbearing potential is until the end of the relevant systemic exposure to CABAZITAXEL ADCO including potential metabolites (i.e.: five half-life's after the last dose) plus 6 months. On this basis, female patients of childbearing potential should

be advised to use effective contraception during treatment with CABAZITAXEL ADCO and for at least 7 months after the final dose.

Male patients should be advised not to father a child during treatment and should be advised on the use of effective contraception to avoid conception. The recommended duration of contraception in male patients is until the end of the relevant systemic exposure to CABAZITAXEL ADCO including potential metabolites (i.e.: five half-life's after the last dose) plus 3 months. On this basis male patients should be advised on the use of effective contraception during treatment with CABAZITAXEL ADCO and for at least 4 months after the final dose (see section 4.6). Male patients should also be counselled to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with CABAZITAXEL ADCO

Neutropenia:

Neutropenia is the most common adverse reaction of CABAZITAXEL ADCO (see section 4.4). The use of granulocyte-colony stimulating factor (G-CSF) has been shown to limit the incidence and severity of neutropenia and its complications. Monitoring of complete blood count is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed (see section 4.2).

Reduce dose in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see section 4.2).

Retreat only when neutrophils recover to a level ≥ 1 500/mm3 (see section 4.3).

Hypersensitivity reactions:

All patients should be pre-medicated prior to the initiation of the infusion of CABAZITAXEL ADCO (see section 4.2).

Patients should be observed closely for hypersensitivity reactions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of CABAZITAXEL ADCO, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions

can occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of CABAZITAXEL ADCO and appropriate therapy.

Patients who have a history of severe hypersensitivity reactions should not be re-challenged with CABAZITAXEL ADCO (see section 4.3).

Gastrointestinal symptoms:

Symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhoea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. CABAZITAXEL ADCO treatment delay or discontinuation may be necessary.

Risk of nausea, vomiting, diarrhoea and dehydration

If patients experience diarrhoea following administration of CABAZITAXEL ADCO they may be treated with commonly used antidiarrhoeal

medicines. Appropriate measures should be taken to re-hydrate patients. Diarrhoea can occur more frequently in patients that have received prior abdomino-pelvic radiation. Dehydration is more common in patients aged 65 or older. Appropriate measures should be taken to rehydrate patients and to monitor and correct serum electrolyte levels, particularly potassium. Treatment delay or dose reduction may be necessary for grade ≥ 3 diarrhoea (see section 4.2). If patients experience nausea or vomiting, they may be treated with commonly used antiemetics.

Risk of serious gastrointestinal reactions

Gastrointestinal (GI) haemorrhage and perforation, ileus, colitis, including fatal outcome, have been reported in patients treated with CABAZITAXEL ADCO (see section 4.8). Caution is advised with treatment of patients most at risk of developing gastrointestinal complications: those with neutropenia, the elderly, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and patients with a prior history of pelvic radiotherapy or gastrointestinal disease, such as ulceration and GI bleeding.

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Renal disorders:

Renal disorders may occur in association with sepsis, severe dehydration due to diarrhoea, vomiting and obstructive uropathy. Renal failure including fatal outcome may occur. Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs. Renal function should be monitored.

Adequate hydration should be ensured throughout treatment with CABAZITAXEL ADCO. The patient should be advised to report any significant change in daily urinary volume immediately. Serum creatinine should be measured at baseline, with each blood count and whenever the patient reports a change in urinary output. CABAZITAXEL ADCO treatment should be discontinued in case of any degradation of renal function to renal failure.

Cardiac dysrhythmias:

Cardiac dysrhythmias, tachycardia and atrial fibrillation may occur (see section 4.8).

Elderly patients ≥ 65 years:

Senior adult patients (≥ 65 years of age) may be more likely to experience certain adverse reactions including neutropenia or febrile neutropenia (see section 4.8).

Patients with hepatic impairment:

Treatment with CABAZITAXEL ADCO is contraindicated in patients with hepatic impairment (see section 4.3). Cabazitaxel as in CABAZITAXEL ADCO is extensively metabolised in the liver, and hepatic impairment is likely to increase Cabazitaxel as in CABAZITAXEL ADCO concentrations.

Bone marrow suppression:

Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur.

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Peripheral neuropathy:

Peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy may occur in patients receiving CABAZITAXEL ADCO. Patients under treatment with CABAZITAXEL ADCO should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Medical practitioners should assess for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. The dose of CABAZITAXEL ADCO should be reduced from 25 mg/m2 to 20 mg/m2 for persistent grade > 2 peripheral neuropathy (see section 4.2).

Anaemia:

Anaemia may occur in patients receiving CABAZITAXEL ADCO (see section 4.8). Haemoglobin and haematocrit should be checked before treatment with CABAZITAXEL ADCO and if patients exhibit signs or symptoms of anaemia or blood loss.

Caution is recommended in patients with haemoglobin < 10 g/dl and appropriate measures should be taken as clinically indicated.

Respiratory disorders:

Interstitial pneumonia/pneumonitis and interstitial lung disease may occur and may be associated with fatal outcome (see section 4.8).

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

carefully evaluated.

Interactions:

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Co-administration with strong CYP3A inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel as in CABAZITAXEL ADCO (see sections 4.2 and 4.5). If co-administration with a strong CYP3A inhibitor cannot be avoided, close monitoring for toxicity and a CABAZITAXEL ADCO dose reduction should be considered (see sections 4.2 and 4.5).

Co-administration with strong CYP3A inducers should be avoided since they may decrease plasma concentrations of cabazitaxel as in CABAZITAXEL ADCO (see sections 4.2 and 4.5).

Excipients:

The solvent contains ethanol 96% (13 % w/w), equivalent to 14 ml of beer or 6 ml of wine.

Harmful for those suffering from alcoholism.

To be taken into account in high-risk groups such as patients with liver disease, or epilepsy.

4.5 Interactions with other medicines and other forms of interaction

In vitro studies have shown that cabazitaxel is mainly metabolised through CYP3A (80 % to 90 %) (see section 5.2).

CYP3A inhibitors:

Repeated administration of ketoconazole (400 mg once daily), a strong CYP3A inhibitor, resulted in a 20 % decrease in CABAZITAXEL ADCO clearance corresponding to a 25 % increase in AUC. Therefore, concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir,

saquinavir, telithromycin, voriconazole) should be avoided as an increase of plasma concentrations of cabazitaxel as in CABAZITAXEL ADCO may occur.

Concomitant administration of aprepitant, a moderate CYP3A inhibitor, had no effect on CABAZITAXEL ADCO clearance.

CYP3A inducers:

Repeated administration of rifampin (600 mg once daily), a strong CYP3A inducer, resulted in an increase in CABAZITAXEL ADCO clearance of 21 % corresponding to a decrease in AUC of 17 %.

Therefore, concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin,phenobarbitone) should be avoided as a decrease of plasma concentrations of CABAZITAXEL ADCO may occur.

In addition, patients should also refrain from taking St. John's Wort.

OATP1B1:

In vitro, cabazitaxel as in CABAZITAXEL ADCO has also been shown to inhibit the transport proteins of the Organic Anion Transport Polypeptides OATP1B1. The risk of interaction with OATP1B1 substrates (e.g. statins, valsartan, repaglinide) is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of the infusion. A time interval of 12 hours is recommended before the infusion and at least 3 hours after the end of infusion before administering the OATP1B1 substrates.

Vaccinations:

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving CABAZITAXEL ADCO. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception to avoid pregnancy while they are receiving CABAZITAXEL ADCO, and for at least 7 months following completion of treatment (i.e.: after the final dose).

Pregnancy

CABAZITAXEL ADCO is contraindicated in pregnancy.

There are no data from the use of CABAZITAXEL ADCO in pregnant women. Studies in animals have shown reproductive toxicity and that CABAZITAXEL ADCO crosses the placental barrier. CABAZITAXEL ADCO is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

Available pharmacokinetic data in animals have shown excretion of CABAZITAXEL ADCO and its metabolites in milk. CABAZITAXEL ADCO should not be used during breastfeeding.

Fertility

Animal studies showed that CABAZITAXEL ADCO affected the reproductive system in male rats and dogs.

Male fertility

CABAZITAXEL ADCO can have genotoxic effects. Therefore, male patients should not father a child during and up to 4 months following completion of treatment (i.e.: after the final dose). Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with CABAZITAXEL ADCO.

4.7 Effects on ability to drive and use machines

CABAZITAXEL ADCO may have a moderate influence on the ability to drive and use machines as it may cause fatigue and dizziness. Patients should be advised to not drive or use machines if they experience these adverse reactions during treatment.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of CABAZITAXEL ADCO in combination with prednisone or prednisolone was evaluated in patients with hormone refractory metastatic prostate cancer. Patients received a median duration of 6 cycles of CABAZITAXEL ADCO.

The most commonly occurring Grade ≥ 3 adverse reactions were neutropenia, leucopenia, anaemia, febrile neutropenia and diarrhoea.

The most common adverse reaction leading to treatment discontinuation was neutropenia and renal failure.

b. Tabulated summary of adverse reactions

Reported adverse reactions and haematological abnormalities with CABAZITAXEL ADCO in combination with prednisone or prednisolone:

Infections and infestations:

Frequent: Urinary tract infection, septic shock, sepsis, cellulitis, influenza, cystitis, upper respiratory tract infection, herpes zoster, candidiasis

Blood and lymphatic system disorders:

Frequent: Neutropenia, febrile neutropenia, anaemia, leucopenia, thrombocytopenia

Immune system disorders:

Frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Anorexia, dehydration, hyperglycaemia, hypokalaemia

Psychiatric disorders:

Frequent: Anxiety, confusional state

Nervous system disorders:

Frequent: Dysgeusia, peripheral neuropathy, dizziness and headache, paraesthesia, lethargy, hypoaesthesia, sciatica

Eye disorders:

Frequent: Conjunctivitis, increased lacrimation

Ear and labyrinth disorders:

Frequent: Tinnitus, vertigo

Cardiac disorders:

Frequent: Atrial fibrillation, tachycardia

Vascular disorders:

Frequent: Hypotension, deep vein thrombosis, hypertension, orthostatic hypotension, hot flush, flushing

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, cough, pneumonia, oropharyngeal pain

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, constipation, abdominal pain, dyspepsia, upper abdominal pain, haemorrhoids, gastro-oesophagael reflux disease, rectal haemorrhage, dry mouth, abdominal distension

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, dry skin, erythema

Musculoskeletal and connective tissue disorders:

Frequent: Back pain, arthralgia, muscle spasms, pain in extremities, myalgia

Renal and urinary disorders:

Frequent: Hematuria, dysuria, urinary incontinence, acute renal failure, renal colic, pollakiuria, hydronephrosis, urinary retention, ureteric obstruction

Reproductive system and breast disorders:

Frequent: Pelvic pain

General disorders and administration site conditions:

Frequent: Fatigue, asthenia, peripheral oedema, pyrexia, pain, mucosal inflammation, chest pain, oedema, chills, malaise

Investigations:

Frequent: Decreased weight, increased aspartate aminotransferase, increase transaminases

c. Description of selected adverse reactions

Neutropenic complications included neutropenic infections, neutropenic sepsis, and septic shock which in some cases resulted in a fatal outcome.

The use of G-CSF has been shown to limit the incidence and severity of neutropenia (see sections 4.2 and 4.4).

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

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For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

The anticipated complications of overdose would be exacerbation of adverse reactions as bone marrow suppression and gastrointestinal disorders.

There is no known antidote to CABAZITAXEL ADCO. In case of overdose, the patient should be kept in a specialised unit and closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Antineoplastic agents, taxanes, ATC code: L01CD04

Cabazitaxel is an antineoplastic medicine that acts by disrupting the microtubular network in cells. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

5.2 Pharmacokinetic properties

Absorption

After a 1-hour IV administration dose of cabazitaxel at 25 mg/m2, in patients with metastatic prostate cancer (n = 67), the mean Cmax was 226 ng/ml (coefficient of variation, CV 107 %) and was reached at the end of the 1-hour infusion (Tmax). The mean AUC was 991 ng.h/ml (CV: 34 %).

No major deviation to the dose proportionality was observed from 10 to 30 mg/m² in patients with advanced solid tumors (n = 126).

Distribution

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The volume of distribution (Vss) was 4 870 l (2 640 l/m² for a patient with a median BSA of 1,84 m²) at steady state.

In vitro, the binding of cabazitaxel to human serum proteins was 89 to 92 % and was not saturable up to 50 000 ng/ml, which covers the maximum concentration observed in clinical studies. Cabazitaxel is mainly bound to human serum albumin (82,1 %) and lipoproteins (87,9 % for HDL, 69,8 % for LDL, and 55,8 % for VLDL). The in vitro blood-to-plasma concentration ratios in human blood ranged from 0,90 to 0,99 indicating that cabazitaxel was equally distributed between blood and plasma.

Biotransformation

Cabazitaxel is extensively metabolised in the liver (≥ 95 %), mainly by the CYP3A4 isoenzyme (80 to 90 %). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued from O-demethylation), with the main one accounting for 5 % of parent exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and faeces.

Based on in vitro data, the potential risk of inhibition by cabazitaxel at clinically relevant concentrations is possible for medicines that are mainly substrate of CYP3A. However, there is no potential risk of inhibition of medicines that are substrates of other CYP enzymes (1A2, 2B6, 2C9, 2C8, 2C19, 2E1, and 2D6) as well as no potential risk of induction by cabazitaxel on medicines that are substrates of CYP1A, CYP2C9, and CYP3A.

Interaction studies in humans have shown that cabazitaxel (25 mg/m2 administered as a single 1-hour infusion) did not modify the plasma levels of midazolam, a probe substrate of CYP3A.

Elimination

After a 1-hour IV infusion [14C]-cabazitaxel at 25 mg/m2 in patients, approximately 80 % of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the faeces as numerous metabolites (76 % of the dose); while renal excretion of cabazitaxel and metabolites account for less than 4 % of the dose (2,3 % as unchanged medicine in urine).

Cabazitaxel had a high plasma clearance of 48,5 l/h (26,4 l/h/m² for a patient with a median BSA of 1,84 m²) and a long terminal half-life of 95 hours.

Special Populations

The Elderly ≥ 65 years:

In the population pharmacokinetic analysis in 70 patients of 65 years and older (57 from 65 to 75 and 13 patients above 75), no age effect on the pharmacokinetics of cabazitaxel was observed.

Paediatric patients:

Safety and effectiveness of cabazitaxel have not been established in children.

Hepatic impairment:

No formal studies in patients with hepatic impairment have been conducted.

Renal impairment:

Cabazitaxel is minimally excreted via the kidney (2,3 % of the dose). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate: Polysorbate 80

Diluent: Ethanol 96 %, water for injections

6.2 Incompatibilities

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

PVC infusion containers or polyurethane infusion sets should not be used for the preparation and administration of the infusion solution.

6.3 Shelf life

Unopened vials

36 months

After opening

The concentrate and solvent vials must be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution: Fully prepared CABAZITAXEL ADCO infusion solution (in either 0,9 % sodium chloride solution or 5 % glucose solution) should be used within 8 hours when stored between 15 °C and 25 °C (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions at 2 to 8 ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Store at or below 25 ºC. Keep in original container until required for use.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

CABAZITAXEL ADCO: Colourless to pale yellow viscous solution in a 15 ml clear USP Type-I tubular glass vial with a 20 mm grey chlorobutyl fluorotech coated rubber stopper and sealed with an aluminium seal having a polypropylene disc.

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Diluent: Clear colourless solution in a 15 ml clear USP Type-I tubular glass vial with a 20 mm grey chlorobutyl fluorotech coated rubber stopper and sealed with an aluminium seal having a polypropylene disc.

The CABAZITAXEL ADCO and the diluents are packed in a carton. 1 vial and 1 diluent per carton.

6.6 Special precautions for disposal and other handling

Caution should be exercised when handling and preparing CABAZITAXEL ADCO solutions. The use of gloves is recommended.

If CABAZITAXEL ADCO at any step of its handling, should come into contact with the skin, wash immediately and thoroughly with soap and water. If it should come into contact with mucous membranes, wash immediately and thoroughly with water.

CABAZITAXEL ADCO should only be prepared and administered by personnel trained in handling cytotoxic agents. Pregnant staff should not handle it.

Preparation

Read this entire section carefully before mixing and diluting. CABAZITAXEL ADCO requires two dilutions prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to overdose. Reconstitute the CABAZITAXEL ADCO vial using the entire contents of the diluent vial. Following this first dilution, the resultant solution contains a concentration of 10 mg/ml. Withdraw the exact volume required from the 10 mg/ml solution and dilute into 0,9 % sodium chloride or 5 % glucose solution to prepare the final infusion solution.

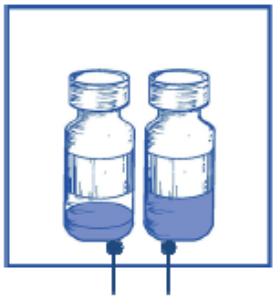
Note: Both the CABAZITAXEL ADCO injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/ml CABAZITAXEL ADCO.

The following two-step dilution process must be carried out in an aseptic manner for preparing the solution for infusion.

Step 1: Initial dilution of the concentrate for solution for infusion with the supplied solvent.

Step 1.1

Inspect the concentrate vial and the supplied solvent. The concentrate solution and the solvent should be clear.

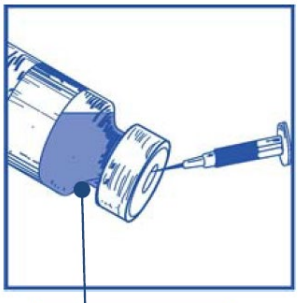


Concentrate vial (60 mg - 1.5 ml)

Solvent vial

Step 1.2

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



Solvent vial

Step 1.3

Inject the **entire** contents into the corresponding concentrate vial.

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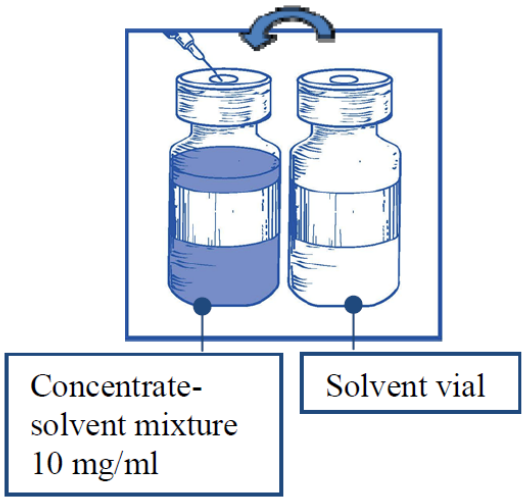
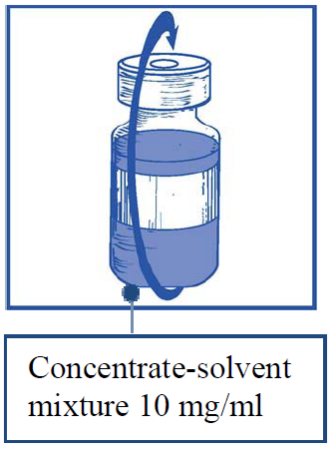
To limit foaming as much as possible when injecting the solvent, direct the needle onto the inside wall of the vial of concentrate solution and inject slowly. Once reconstituted, the resultant solution contains 10 mg/ml of cabazitaxel.



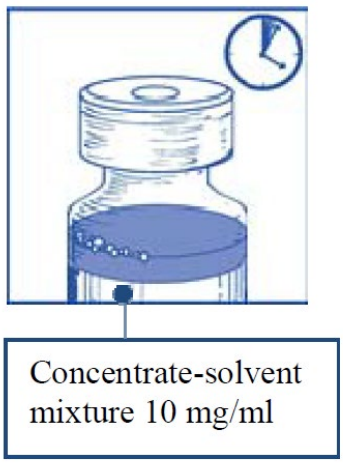
Step 1.4

Remove the syringe and needle and mix manually and gently by repeated inversions until obtaining a clear and homogeneous solution. It could take approximately 45 seconds.



Step 1.5

Let this solution stand for approximately 5 minutes and check then that the solution is homogeneous and clear. It is normal for foam to persist after this time period.



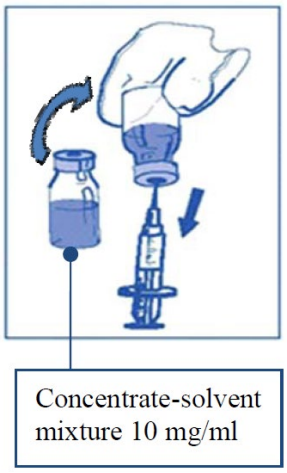
This resulting concentrate-solvent mixture contains 10 mg/ml of cabazitaxel (at least 6 ml deliverable volume). The second dilution should be done immediately (within 1 hour) as detailed in Step 2. More than one vial of the concentrate-solvent mixture may be necessary to administer the prescribed dose.

Step 2: Second (final) dilution for infusion

Step 2.1

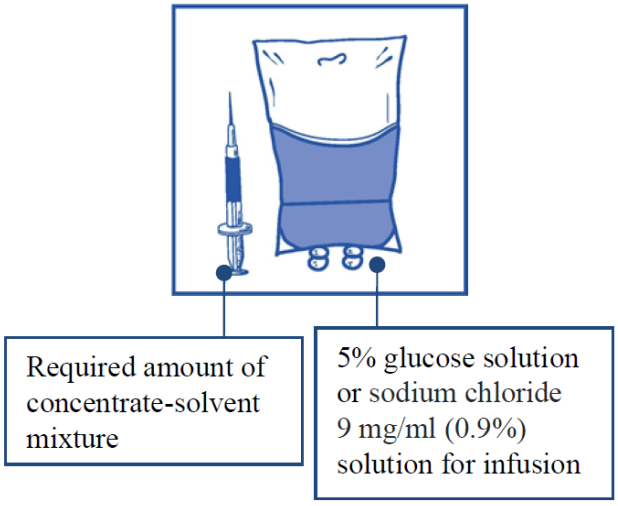
Aseptically withdraw the required amount of concentrate-solvent mixture (10 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg CABAZITAXEL ADCO would require 4,5 ml of the concentrate-solvent mixture prepared following Step 1.

Since foam may persist on the wall of the vial of this solution, following its preparation described in Step 1, it is preferable to place the needle of the syringe in the middle when extracting.



Step 2.2

Inject in a sterile PVC-free container of either 5 % glucose solution or sodium chloride 9 mg/ml (0,9 %) solution for infusion. The concentration of the infusion solution should be between 0,10 mg/ml and 0,26 mg/ml.



Step 2.3

Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion.

Step 2.4

The resulting infusion solution should be visually inspected prior to use. Solution containing a precipitate should be discarded.

Discard any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.

1 Sabax Road,

Aeroton,

Johannesburg,

2013

Tel: +27 11 494 8000

Nobulali Mlindi

8. REGISTRATION NUMBER(S)

53/26/0360

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 December 2020

10. DATE OF REVISION OF THE TEXT

15 June 2026