

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg cabazitaxel.

Each vial of 3 ml of concentrate contains 60 mg cabazitaxel.

Excipient with known effect

The finished product contains 395 mg/ml of ethanol anhydrous, thus each 3 ml vial contains 1,185 mg ethanol anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear colourless to pale yellow or brownish yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cabazitaxel Accord in combination with prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen (see section 5.1).

4.2 Posology and method of administration

The use of cabazitaxel should be confined to units specialised in the administration of cytotoxics and it should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy. Facilities and equipment for the treatment of serious hypersensitivity reactions like hypotension and bronchospasm must be available (see section 4.4).

Premedication

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent), and
- H2 antagonist (ranitidine or equivalent) (see section 4.4).

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

Throughout the treatment, adequate hydration of the patient needs to be ensured, in order to prevent complications like renal failure.

Posology

The recommended dose of cabazitaxel 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 treatment.

Dose adjustments

Dose modifications should be made if patients experience the following adverse reactions (Grades refer to Common Terminology Criteria for Adverse Events [CTCAE 4.0]):

Table 1 - Recommended dose modifications for adverse reaction in patients treated with cabazitaxel

Adverse reactions	Dose modification
Prolonged grade ≥ 3 neutropenia (longer than 1 week) despite appropriate treatment including G-CSF	Delay treatment until neutrophil count is $>1,500$ cells/mm ³ , then reduce cabazitaxel dose 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 cabazitaxel dose from 25 mg/m ² to 20 mg/m ² .
Grade ≥ 3 diarrhoea or persisting diarrhea despite appropriate treatment, including fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m ² to 20 mg/m ² .
Grade ≥ 2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m ² to 20 mg/m ² .

If patients continue to experience any of these reactions at 20 mg/m², further dose reduction to 15 mg/m² or discontinuation of cabazitaxel may be considered. Data in patients below the 20 mg/m² dose are limited.

Concomitant medicinal products use

Concomitant medicinal products that are strong inducers or strong inhibitors of CYP3A should be avoided. However, if patients require co-administration of a strong CYP3A inhibitor, a 25% cabazitaxel dose reduction should be considered (see sections 4.4 and 4.5).

Special populations

Hepatic impairment

Cabazitaxel is extensively metabolised by the liver. Patients with mild hepatic impairment (total bilirubin >1 to ≤ 1.5 x Upper Limit of Normal (ULN) or Aspartate Aminotransferase (AST) >1.5 x ULN), should have cabazitaxel dose reduced to 20 mg/m². Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety.

Cabazitaxel Accord must not be given to patients with moderate and severe hepatic impairment (total bilirubin > 1.5 x ULN) (see sections 4.3, 4.4 and 5.2).

Renal impairment

Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis. Patients presenting end stage renal disease (creatinine clearance (CLCR) < 15 mL/min/1.73 m²), by their condition and the limited amount of data available should be treated with caution and monitored carefully during treatment (see sections 4.4 and 5.2).

Elderly

No specific dose adjustment for the use of cabazitaxel in elderly patients is recommended (see also sections 4.4, 4.8 and 5.2).

Paediatric population

There is no relevant use of cabazitaxel in the paediatric population.

The safety and the efficacy of cabazitaxel in children and adolescents below 18 years of age have not been established (see section 5.1).

Method of administration

Cabazitaxel Accord is for intravenous use.

For instructions on preparation and administration of the product, see section 6.6.

PVC infusion containers and polyurethane infusion sets should not be used.
Cabazitaxel must not be mixed with any other medicinal products than those mentioned in section 6.6.

4.3 Contraindications

- Hypersensitivity to cabazitaxel, to other taxanes, or polysorbate 80 or any excipients listed in section 6.1.
- Neutrophil counts less than 1,500/mm³.
- Moderate and severe hepatic impairment (total bilirubin > 1.5 x ULN).
- Concomitant vaccination with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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

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 cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy. Patients with a hypersensitivity reaction must stop treatment with cabazitaxel (see section 4.3).

Bone marrow suppression

Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur (see “Risk of neutropenia” and “Anaemia” in section 4.4 below).

Risk of neutropenia

Patients treated with cabazitaxel may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

Neutropenia is the most common adverse reaction of cabazitaxel (see section 4.8). Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed.

The dose should be reduced in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see section 4.2).

Patients should be re-treated only when neutrophils recover to a level $\geq 1,500/\text{mm}^3$ (see section 4.3).

Gastrointestinal disorders

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 treatment delay or discontinuation may be necessary.

Risk of nausea, vomiting, diarrhoea and dehydration

If patients experience diarrhoea following administration of cabazitaxel they may be treated with commonly used anti-diarrhoeal medicinal products. 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 anti-emetics.

Risk of serious gastrointestinal reactions

Gastrointestinal (GI) hemorrhage and perforation, ileus, colitis, including fatal outcome, have been reported in patients treated with cabazitaxel (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.

Peripheral neuropathy

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

Anaemia

Anaemia has been observed in patients receiving cabazitaxel (see section 4.8). Haemoglobin and haematocrit should be checked before treatment with cabazitaxel 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.

Risk of renal failure

Renal disorders, have been reported in association with sepsis, severe dehydration due to diarrhoea, vomiting and obstructive uropathy. Renal failure including cases with fatal outcome has been observed. Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs.

Adequate hydration should be ensured throughout treatment with cabazitaxel. 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 treatment should be discontinued in case of any degradation of renal function to renal failure \geq CTCAE 4.0 Grade 3.

Respiratory disorders

Interstitial pneumonia/pneumonitis and interstitial lung disease have been reported 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 therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming cabazitaxel treatment must be carefully evaluated.

Risk of cardiac arrhythmias

Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation (see section 4.8).

Elderly

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

Patients with liver impairment

Treatment with Cabazitaxel Accord is contraindicated in patients with moderate and severe hepatic impairment (total bilirubin > 1.5 x ULN) (See sections 4.3 and 5.2).

Dose should be reduced for patients with mild (total bilirubin >1 to ≤ 1.5 x ULN or AST >1.5 x ULN), hepatic impairment (see sections 4.2 and 5.2).

Interactions

Co-administration with strong CYP3A inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel (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 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 (see sections 4.2 and 4.5).

Excipients

The finished product contains 395 mg/ml ethanol anhydrous, thus each 3 ml vial contains 1,185 mg ethanol anhydrous, which is equivalent to 16.33 Vol %. The amount in dose of this medicinal product is equivalent to 30 ml beer or 12 ml wine.

A dose of 60 mg of this medicinal product administered to an adult weighing 70 kg would result in an exposure to 17mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2,8 mg/100 ml.

4.5 Interaction with other medicinal products 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 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 may occur (see sections 4.2 and 4.4).

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

CYP3A inducers

Repeated administration of rifampin (600 mg once daily), a strong CYP3A inducer, resulted in an increase in cabazitaxel 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, phenobarbital) should be avoided as a decrease of plasma concentrations of cabazitaxel may occur (see sections 4.2 and 4.4). In addition, patients should also refrain from taking St. John's Wort.

OATP1B1

In vitro, cabazitaxel 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 agents may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving cabazitaxel. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of cabazitaxel in pregnant women. Studies in animals have shown reproductive toxicity at maternotoxic doses (see section 5.3) and that cabazitaxel crosses the placenta

barrier (see section 5.3). As with other cytotoxic medicinal products, cabazitaxel may cause foetal harm in exposed pregnant women.

Cabazitaxel is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk (see section 5.3). A risk to the breast-feeding child cannot be excluded.

Cabazitaxel should not be used during breast-feeding.

Fertility

Animal studies showed that cabazitaxel affected reproductive system in male rats and dogs without any functional effect on fertility (see section 5.3). Nevertheless, considering the pharmacological activity of taxanes, their genotoxic potential and effect of several compounds of this class on fertility in animal studies, effect on male fertility could not be excluded in human.

Due to potential effects on male gametes and to potential exposure via seminal liquid, men treated with cabazitaxel should use effective contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of cabazitaxel. Due to potential exposure via seminal liquid, men treated with cabazitaxel should prevent contact with the ejaculate by another person throughout treatment. Men being treated with cabazitaxel are advised to seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of cabazitaxel in combination with prednisone or prednisolone was evaluated in 371 patients with metastatic castration resistant prostate cancer who were treated with 25 mg/m² cabazitaxel once every three weeks in a randomised open label, controlled phase III study. Patients received a median duration of 6 cycles of cabazitaxel.

The most commonly ($\geq 10\%$) occurring adverse reactions in all grades were anaemia (97.3%), leukopenia (95.7%), neutropenia (93.5%), thrombocytopenia (47.4%), and diarrhoea (46.6%). The most commonly ($\geq 5\%$) occurring grade ≥ 3 adverse reactions in the cabazitaxel group were neutropenia (81.7%), leukopenia (68.2%), anaemia (10.5%), febrile neutropenia (7.5%), diarrhoea (6.2%).

Discontinuation of treatment due to adverse reactions occurred in 68 patients (18.3%) receiving cabazitaxel. The most common adverse reactions leading to cabazitaxel discontinuation was neutropenia.

Tabulated list of adverse reactions

Adverse reactions are listed in table 2 according to MedDRA system organ class and frequency categories. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Intensity of the adverse reactions is graded according to CTCAE 4.0 (grade $\geq 3 = G \geq 3$). Frequencies are based on all grades and defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 2: Reported adverse reactions and haematological abnormalities with cabazitaxel in combination with prednisone or prednisolone in the TROPIC study (n=371)

System Organ Class	Adverse reaction	All grades n (%)		Grade>3 n (%)
		Very common	Common	
Infections and infestations	Septic shock		4 (1.1)	4 (1.1)
	Sepsis		4 (1.1)	4 (1.1)
	Cellulitis		6 (1.6)	2 (0.5)
	Urinary tract infection		27 (7.3)	4 (1.1)
	Influenza		11 (3)	0
	Cystitis		10 (2.7)	1 (0.3)
	Upper respiratory tract infection		10 (2.7)	0
	Herpes zoster		5 (1.3)	0
	Candidiasis		4 (1.1)	0
Blood and lymphatic system disorders	Neutropenia ^{a*}	347 (93.5)		303 (81.7)
	Anaemia ^a	361 (97.3)		39 (10.5)
	Leukopenia ^a	355 (95.7)		253 (68.2)
	Thrombocytopenia ^a	176 (47.4)		15 (4)
	Febrile neutropenia		28 (7.5)	28 (7.5)
Immune system disorders	Hypersensitivity		5 (1.3)	0
Metabolism and nutrition disorders	Anorexia	59 (15.9)		3 (0.8)
	Dehydration		18 (4.9)	8 (2.2)
	Hyperglycaemia		4 (1.1)	3 (0.8)
	Hypokalemia		4 (1.1)	2 (0.5)
Psychiatric disorders	Anxiety		11 (3)	0
	Confusional state		5 (1.3)	0
Nervous system disorders	Dysgeusia	41 (11.1)		0
	Neuropathy peripheral		30 (8.1)	2 (0.5)
	Peripheral sensory neuropathy		20 (5.4)	1 (0.3)
	Dizziness		30 (8.1)	0
	Headache		28 (7.5)	0
	Paraesthesia		17 (4.6)	0
	Lethargy		5 (1.3)	1 (0.3)
	Hypoaesthesia		5 (1.3)	0
	Sciatica		4 (1.1)	1 (0.3)
Eye disorders	Conjunctivitis		5 (1.3)	0
	Lacrimation increased		5 (1.3)	0
Ear and labyrinth disorders	Tinnitus		5 (1.3)	0
	Vertigo		5 (1.3)	0
Cardiac disorders*	Atrial fibrillation		4 (1.1)	2 (0.5)
	Tachycardia		6 (1.6)	0
Vascular disorders	Hypotension		20 (5.4)	2 (0.5)
	Deep vein thrombosis		8 (2.2)	7 (1.9)
	Hypertension		6 (1.6)	1 (0.3)
	Orthostatic hypotension		5 (1.3)	1 (0.3)
	Hot flush		5 (1.3)	0
	Flushing		4 (1.1)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	44 (11.9)		5 (1.3)
	Cough	40 (10.8)		0
	Oropharyngeal pain		13 (3.5)	0
	Pneumonia		9 (2.4)	6 (1.6)

System Organ Class	Adverse reaction	All grades n (%)		Grade>3 n (%)
		Very common	Common	
Gastrointestinal disorders	Diarrhoea	173 (46.6)		23 (6.2)
	Nausea	127 (34.2)		7 (1.9)
	Vomiting	84 (22.6)		7 (1.9)
	Constipation	76 (20.5)		4 (1.1)
	Abdominal pain	43 (11.6)		7 (1.9)
	Dyspepsia		25 (6.7)	0
	Abdominal pain upper		20 (5.4)	0
	Haemorrhoids		14 (3.8)	0
	Gastroesophageal reflux disease		12 (3.2)	0
	Rectal haemorrhage		8 (2.2)	2 (0.5)
	Dry mouth		8 (2.2)	1 (0.3)
	Abdominal distension		5 (1.3)	1 (0.3)
Skin and subcutaneous tissue disorders	Alopecia	37 (10)		0
	Dry skin		9 (2.4)	0
	Erythema		5 (1.3)	0
Musculoskeletal and connective tissue disorders	Back pain	60 (16.2)		14 (3.8)
	Arthralgia	39 (10.5)		4 (1.1)
	Pain in extremity		30 (8.1)	6 (1.6)
	Muscle spasms		27 (7.3)	0
	Myalgia		14 (3.8)	1 (0.3)
	Musculoskeletal chest pain		11 (3)	1 (0.3)
	Flank pain		7 (1.9)	3 (0.8)
Renal and urinary disorders	Acute renal failure		8 (2.2)	6 (1.6)
	Renal failure		7 (1.9)	6 (1.6)
	Dysuria		25 (6.7)	0
	Renal colic		5 (1.3)	1 (0.3)
	Haematuria	62 (16.7)		7 (1.9)
	Pollakiuria		13 (3.5)	1 (0.3)
	Hydronephrosis		9 (2.4)	3 (0.8)
	Urinary retention		9 (2.4)	3 (0.8)
	Urinary incontinence		9 (2.4)	0
Ureteric obstruction		7 (1.9)	5 (1.3)	
Reproductive system and breast disorders	Pelvic pain		7 (1.9)	1 (0.3)
General disorders and administration site conditions	Fatigue	136 (36.7)		18 (4.9)
	Asthenia	76 (20.5)		17 (4.6)
	Pyrexia	45 (12.1)		4 (1.1)
	Peripheral oedema		34 (9.2)	2 (0.5)
	Mucosal inflammation		22 (5.9)	1 (0.3)
	Pain		20 (5.4)	4 (1.1)
	Chest pain		9 (2.4)	2 (0.5)
	Oedema		7 (1.9)	1 (0.3)
	Chills		6 (1.6)	0
	Malaise		5 (1.3)	0

System Organ Class	Adverse reaction	All grades n (%)		Grade>3 n (%)
		Very common	Common	
Investigations	Weight decreased		32 (8.6)	0
	Aspartate aminotransferase increased		4 (1.1)	0
	Transaminases increased		4 (1.1)	0

^a based on laboratory values

* see detailed section below

Description of selected adverse reactions

Neutropenia, and associated clinical events

Incidence of grade ≥ 3 neutropenia based on laboratory data was 81.7%. The incidence of grade ≥ 3 clinical neutropenia and febrile neutropenia adverse reactions were 21.3% and 7.5% respectively. Neutropenia was the most common adverse reaction leading to medicinal product discontinuation (2.4%).

Neutropenic complications included neutropenic infections (0.5%), neutropenic sepsis (0.8%), and septic shock (1.1%), 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).

Cardiac disorders and arrhythmias

All Grade events among cardiac disorders were more common on cabazitaxel of which 6 patients (1.6%) had Grade ≥ 3 cardiac arrhythmias. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥ 3 . The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%). One patient in the cabazitaxel group died from cardiac failure. Fatal ventricular fibrillation was reported in 1 patient (0.3%), and cardiac arrest in 2 patients (0.5%). None were considered related by the investigator.

Haematuria

Haematuria all grades frequency was 20.8% at 25 mg/m² in EFC11785 study (see section 5.1).

Confounding causes such as disease progression, instrumentation, infection or anticoagulation/NSAID/aspirin therapy were identified in nearly two thirds of the cases.

Other laboratory abnormalities

The incidence of grade ≥ 3 anaemia, increased AST, ALT, and bilirubin based on laboratory abnormalities were 10.5%, 0.7%, 0.9%, and 0.6%, respectively.

Gastrointestinal disorders

Colitis, enterocolitis, gastritis, neutropenic enterocolitis have been observed. Gastrointestinal hemorrhage and perforation, ileus and intestinal obstruction have also been reported (see section 4.4).

Respiratory disorders

Cases of interstitial pneumonia/pneumonitis and interstitial lung disease, sometimes fatal have been reported with an unknown frequency (cannot be estimated from the available data) (see section 4.4).

Renal and urinary disorders

Cystitis due to radiation recall phenomenon, including haemorrhagic cystitis, were reported uncommonly.

Paediatric population

See section 4.2

Other special populations

Elderly

Among the 371 patients treated with cabazitaxel in the prostate cancer study, 240 patients were 65 years or over including 70 patients older than 75 years.

The following adverse reactions reported at rates $\geq 5\%$ higher in patients 65 years of age or greater compared to younger patients were fatigue (40.4% versus 29.8%), clinical neutropenia (24.2% versus 17.6%), asthenia (23.8% versus 14.5%), pyrexia (14.6% versus 7.6%), dizziness (10.0% versus 4.6%), urinary tract infection (9.6% versus 3.1%) and dehydration (6.7% versus 1.5%), respectively.

The incidence of the following grade ≥ 3 adverse reactions were higher in patients ≥ 65 years of age compared to younger patients; neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinical neutropenia (23.8% versus 16.8%) and febrile neutropenia (8.3% versus 6.1%) (see sections 4.2 and 4.4).

Of the 595 patients treated with cabazitaxel 25 mg/m² in the prostate cancer EFC 11785 study, 420 patients were 65 years or over. The adverse reactions reported at rates of at least 5% higher in patients 65 years of age or greater compared to younger patients were diarrhoea (42.9% vs. 32.6%), fatigue (30.2% vs. 19.4%), asthenia (22.4% vs. 13.1%), constipation (20.2% vs. 12.6%), clinical neutropenia (12.9% vs. 6.3%), febrile neutropenia (11.2% vs. 4.6%) and dyspnoea (9.5% vs. 3.4%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

There is no known antidote to cabazitaxel. The anticipated complications of overdose would consist of exacerbation of adverse reactions as bone marrow suppression and gastrointestinal disorders.

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: Antineoplastic agents, taxanes, ATC code: L01CD04

Mechanism of action

Cabazitaxel is an antineoplastic agent 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.

Pharmacodynamic effects

Cabazitaxel demonstrated a broad spectrum of antitumour activity against advanced human tumours xenografted in mice. Cabazitaxel is active in docetaxel-sensitive tumours. In addition, cabazitaxel demonstrated activity in tumour models insensitive to chemotherapy including docetaxel.

Clinical efficacy and safety

The efficacy and safety of cabazitaxel in combination with prednisone or prednisolone were evaluated in a randomised, open-label, international, multi-center, phase III study (EFC6193 study), in patients with metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen.

Overall survival (OS) was the primary efficacy endpoint of the study.

Secondary endpoints included Progression Free Survival [PFS (defined as time from randomization to tumour progression, Prostatic Specific Antigen (PSA) progression, pain progression, or death due to any cause, whichever occurred first), Tumour Response Rate based on Response Evaluation Criteria in Solid Tumours (RECIST), PSA Progression (defined as a $\geq 25\%$ increase or $>50\%$ in PSA non-responders or responders respectively), PSA response (declines in serum PSA levels of at least 50%), pain progression [assessed using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire and an Analgesic Score (AS)] and pain response (defined as 2-point greater reduction from baseline median PPI with no concomitant increase in AS, or reduction of $\geq 50\%$ in analgesic use from baseline mean AS with no concomitant increase in pain).

A total of 755 patients were randomised to receive either cabazitaxel 25 mg/m² intravenously every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m² intravenously every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily (n=377).

This study included patients over 18 years of age with metastatic castration resistant prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Patients had to have neutrophils $>1,500/\text{mm}^3$, platelets $>100,000/\text{mm}^3$, haemoglobin >10 g/dl, creatinine $<1.5 \times \text{ULN}$, total bilirubin $<1 \times \text{ULN}$, AST and ALT $<1.5 \times \text{ULN}$.

Patients with a history of congestive heart failure, or myocardial infarction within last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

Demographics, including age, race, and ECOG performance status (0 to 2), were balanced between the treatment arms. In the cabazitaxel group, the mean age was 68 years, range (46-92) and the racial distribution was 83.9% Caucasian, 6.9% Asian/Oriental, 5.3% Black and 4% Others.

The median number of cycles was 6 in the cabazitaxel group and 4 in the mitoxantrone group. The number of patients who completed the study treatment (10 cycles) was respectively 29.4% and 13.5% in the cabazitaxel group and in the comparator group.

Overall survival was significant longer with cabazitaxel compared to mitoxantrone (15.1 months versus 12.7 respectively), with a 30% reduction in the risk of death compared to mitoxantrone (see table 3 and figure 1).

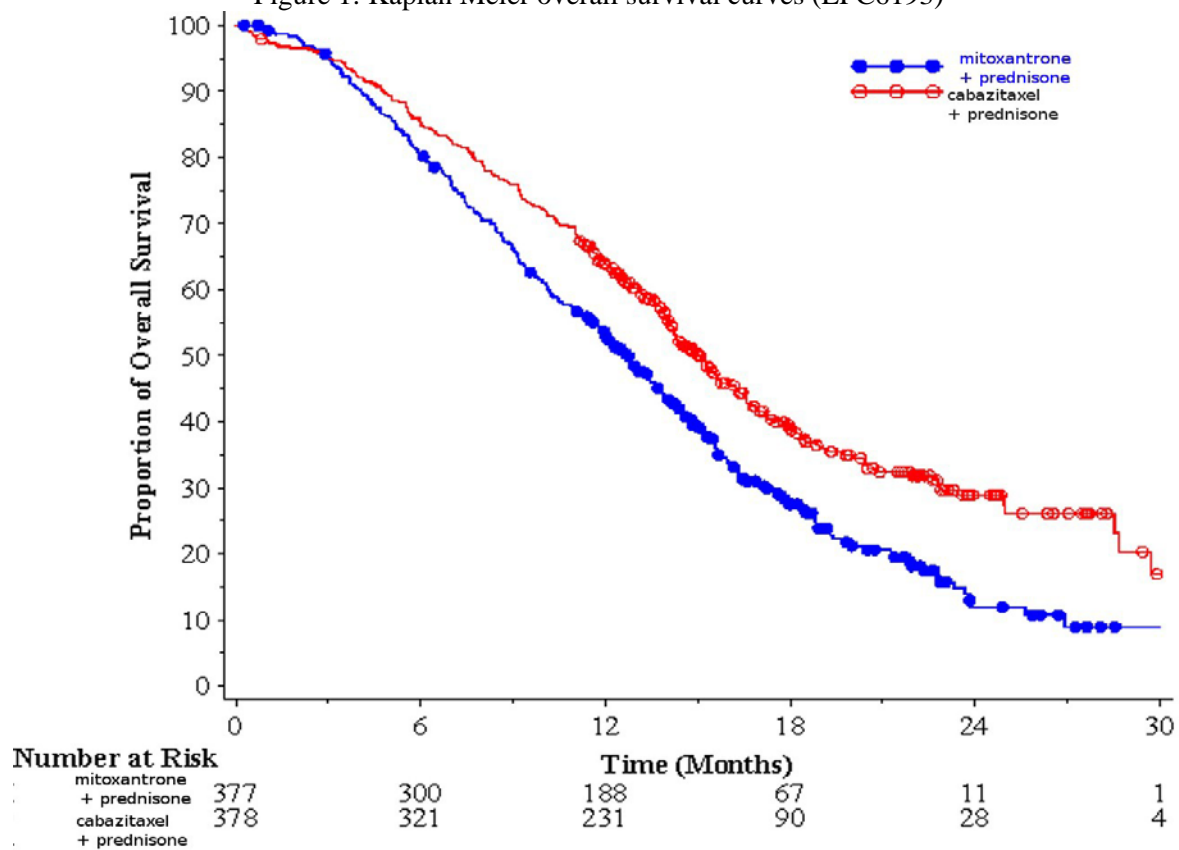
A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in cabazitaxel arm, 30 patients in mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR (95% CI) 0.96 (0.49-1.86)).

Table 3 - Efficacy of cabazitaxel in EFC6193 study in the treatment of patients with metastatic castration resistant prostate cancer

	Cabazitaxel+ prednisone n=378	mitoxantrone+ prednisone n=377
Overall survival		
Number of patients with deaths (%)	234 (61.9%)	279 (74%)
Median survival (months) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio (HR) ¹ (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

¹HR estimated using Cox model; a hazard ratio of less than 1 favours cabazitaxel

Figure 1: Kaplan Meier overall survival curves (EFC6193)



There was an improvement in PFS in the cabazitaxel arm compared to mitoxantrone arm, 2.8 (2.4-3.0) months versus 1.4 (1.4-1.7) respectively, HR (95%CI) 0.74 (0.64-0.86), $p < 0.0001$.

There was a significant higher rate of tumour response of 14.4% (95%CI: 9.6-19.3) in patients in the cabazitaxel arm compared to 4.4% (95%CI: 1.6-7.2) for patients in the mitoxantrone arm, $p = 0.0005$.

PSA secondary endpoints were positive in the cabazitaxel arm. There was a median PSA progression of 6.4 months (95%CI: 5.1-7.3) for patients in cabazitaxel arm, compared to 3.1 months (95%CI: 2.2-4.4) in the mitoxantrone arm, HR 0.75 months (95%CI: 0.63-0.90), $p = 0.0010$. The PSA response was 39.2% in patients on cabazitaxel arm (95%CI: 33.9-44.5) versus 17.8% of patients on mitoxantrone (95%CI: 13.7-22.0), $p = 0.0002$.

There was no statistical difference between both treatment arms in pain progression and pain response.

In a non-inferiority, multicenter, multinational, randomized, open label phase III study (EFC11785 study), 1200 patients with metastatic castration resistant prostate cancer, previously treated with a docetaxel-containing regimen, were randomized to receive either cabazitaxel 25 mg/m² (n=602) or 20 mg/m² (n=598) dose. Overall survival (OS) was the primary efficacy end-point.

The study met its primary objective of demonstrating the non-inferiority of cabazitaxel 20 mg/m² in comparison with 25 mg/m² (see table 4). A statistically significantly higher percentage ($p < 0.001$) of patients showed a PSA response in the 25 mg/m² group (42.9%) compared to the 20 mg/m² group (29.5%). A statistically significantly higher risk of PSA progression in patients with the 20 mg/m² dose with respect to the 25 mg/m² dose was observed (HR 1.195 ; 95%CI: 1.025 to 1.393). There was no statistically difference with regards to the other secondary endpoints (PFS, tumour and pain response, tumour and pain progression, and four subcategories of FACT-P).

Table 4 - Overall survival in EFC11785 study in cabazitaxel 25 mg/m² arm versus cabazitaxel 20 mg/m² arm (Intent-to-treat analysis) – Efficacy primary endpoint

	CBZ20+PRED n=598	CBZ25+PRED n=602
Overall survival		
Number of deaths, n (%)	497 (83.1 %)	501 (83.2%)
Median survival (95% CI) (months)	13.4 (12.19 to 14.88)	14.5 (13.47 to 15.28)
Hazard Ratio ^a		
versus CBZ25+PRED	1.024	-
1-sided 98.89% UCI	1.184	-
1-sided 95% LCI	0.922	-

CBZ20=Cabazitaxel 20 mg/m², CBZ25=Cabazitaxel 25 mg/m², PRED=Prednisone/Prednisolone
CI=confidence interval, LCI=lower bound of the confidence interval, UCI=upper bound of the confidence interval

^a Hazard ratio is estimated using a Cox Proportional Hazards regression model. A hazard ratio < 1 indicates a lower risk of cabazitaxel 20 mg/m² with respect to 25 mg/m².

The safety profile of cabazitaxel 25 mg/m² observed in study EFC11785 was qualitatively and quantitatively similar to that observed in the study EFC6193. Study EFC11785 demonstrated a better safety profile for the cabazitaxel 20 mg/m² dose.

Table 5 - Summary of safety data for cabazitaxel 25 mg/m² arm versus cabazitaxel 20 mg/m² arm in EFC11785 study

	CBZ20+PRED n=580	CBZ25+PRED n=595
Median number of cycles/ median duration of treatment	6/ 18 weeks	7/ 21 weeks
Number of patients with dose reduction n (%)	From 20 to 15 mg/m ² : 58 (10.0%) From 15 to 12 mg/m ² : 9 (1.6%)	From 25 to 20 mg/m ² : 128 (21.5%) From 20 to 15 mg/m ² : 19 (3.2%) From 15 to 12 mg/m ² : 1 (0.2%)
All grade adverse reactions^a (%)		
Diarrhoea	30.7	39.8
Nausea	24.5	32.1
Fatigue	24.7	27.1
Haematuria	14.1	20.8
Asthenia	15.3	19.7
Decreased appetite	13.1	18.5
Vomiting	14.5	18.2
Constipation	17.6	18.0
Back pain	11.0	13.9
Clinical neutropenia	3.1	10.9
Urinary tract infection	6.9	10.8
Peripheral sensory neuropathy	6.6	10.6
Dysgeusia	7.1	10.6
Grade ≥ 3 adverse reactions^b (%)		
Clinical neutropenia	2.4	9.6
Febrile neutropenia	2.1	9.2

	CBZ20+PRED n=580	CBZ25+PRED n=595
Haematological abnormalities^c		
(%)		
Grade ≥ 3 neutropenia	41.8	73.3
Grade ≥ 3 anaemia	9.9	13.7
Grade ≥ 3 thrombocytopenia	2.6	4.2

CBZ20=Cabazitaxel 20 mg/m², CBZ25=Cabazitaxel 25 mg/m², PRED=Prednisone/Prednisolone

^a All grade adverse reactions with an incidence higher than 10%

^b Grade ≥ 3 adverse reactions with an incidence higher than 5%

^c Based on laboratory values

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with cabazitaxel in all subsets of the paediatric population in the indication of prostate cancer (see section 4.2 for information on paediatric use).

Cabazitaxel was evaluated in an open label, multi-center Phase 1/2 study conducted in a total of 39 paediatric patients (aged between 4 to 18 years for the phase 1 part of the study and between 3 to 16 years for the phase 2 part of the study). The phase 2 part did not demonstrate efficacy of cabazitaxel as single agent in paediatric population with recurrent or refractory diffuse intrinsic pontine glioma (DIPG) and high grade glioma (HGG) treated at 30 mg/m².

5.2 Pharmacokinetic properties

A population pharmacokinetic analysis was carried out in 170 patients including patients with advanced solid tumours (n=69), metastatic breast cancer (n=34) and metastatic prostate cancer (n=67). These patients received cabazitaxel at doses of 10 to 30 mg/m² weekly or every 3 weeks.

Absorption

After 1-hour intravenous administration at 25 mg/m² cabazitaxel in patients with metastatic prostate cancer (n=67), the C_{max} was 226 ng/ml (Coefficient of Variation (CV): 107%) and was reached at the end of the 1-hour infusion (T_{max}). 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 tumours (n=126).

Distribution

The volume of distribution (V_{ss}) was 4870 l (2640 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 89-92% 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 (82.0%) 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 CYP3A 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-demethylations), 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* studies, the potential risk of inhibition by cabazitaxel at clinically relevant concentrations is possible towards medicinal products that are mainly substrate of CYP3A. However a clinical study has 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. Therefore, at therapeutic doses,

co-administration of CYP3A substrates with cabazitaxel to patients is not expected to have any clinical impact.

There is no potential risk of inhibition of medicinal products 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 medicinal products that are substrates of CYP1A, CYP2C9, and CYP3A. Cabazitaxel did not inhibit *in vitro* the major biotransformation pathway of warfarin into 7-hydroxywarfarin, which is mediated by CYP2C9. Therefore, no pharmacokinetic interaction of cabazitaxel on warfarin is expected *in vivo*.

In vitro cabazitaxel did not inhibit Multidrug-Resistant Proteins (MRP): MRP1 and MRP2 or Organic Cation Transporter (OCT1). Cabazitaxel inhibited the transport of P-glycoprotein (PgP) (digoxin, vinblastin), Breast-Cancer-Resistant-Proteins (BCRP) (methotrexate) and Organic Anion Transporting Polypeptide OATP1B3 (CCK8) at concentrations at least 15 fold what is observed in clinical setting while it inhibited the transport of OATP1B1 (estradiol-17 β -glucuronide) at concentrations only 5 fold what is observed in clinical setting. Therefore the risk of interaction with substrates of MRP, OCT1, PgP, BCRP and OATP1B3 is unlikely *in vivo* at the dose of 25 mg/m². The risk of interaction with OATP1B1 transporter is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of the infusion (see section 4.5).

Elimination

After a 1-hour intravenous 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 medicinal product 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

Elderly patients

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 and adolescents below 18 years of age.

Hepatic impairment

Cabazitaxel is eliminated primarily via liver metabolism.

A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to \leq 1.5 x ULN or AST >1.5 x ULN) or moderate (total bilirubin >1.5 to \leq 3.0 x ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated dose (MTD) of cabazitaxel was 20 and 15 mg/m², respectively.

In 3 patients with severe hepatic impairment (total bilirubin >3 ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment, indicating some effect of severe hepatic impairment on cabazitaxel pharmacokinetics. The MTD of cabazitaxel in patients with severe hepatic impairment was not established.

Based on safety and tolerability data, cabazitaxel dose should be reduced in patients with mild hepatic impairment (see sections 4.2, 4.4). Cabazitaxel Accord is contraindicated in patients with moderate and severe hepatic impairment (see section 4.3).

Renal impairment

Cabazitaxel is minimally excreted via the kidney (2.3% of the dose). A 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. This was confirmed by a dedicated comparative pharmacokinetic study in solid cancer patients with normal renal function (8 patients),

moderate (8 patients) and severe (9 patients) renal impairment, who received several cycles of cabazitaxel in single intravenous infusion up to 25 mg/m².

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in dogs after single dose, 5-day and weekly administration at exposure levels lower than clinical exposure levels and with possible relevance to clinical use were arteriolar/periarterolar necrosis in the liver, bile ductule hyperplasia and/or hepatocellular necrosis (see section 4.2).

Adverse reactions not observed in clinical studies, but seen in rats during repeat-dose toxicity studies at exposure levels higher than clinical exposure levels and with possible relevance to clinical use were eye disorders characterized by subcapsular lens fiber swelling/degeneration. These effects were partially reversible after 8 weeks.

Carcinogenicity studies have not been conducted with cabazitaxel.

Cabazitaxel did not induce mutations in the bacterial reverse mutation (Ames) test. It was not clastogenic in an *in vitro* test in human lymphocytes (no induction of structural chromosomal aberration but it increased number of polyploid cells) and induced an increase of micronuclei in the *in vivo* test in rats. However these genotoxicity findings are inherent to the pharmacological activity of the compound (inhibition of tubulin depolymerization) and have been observed with medicinal products exhibiting the same pharmacological activity.

Cabazitaxel did not affect mating performances or fertility of treated male rats. However, in repeated-dose toxicity studies, degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats, and testicular degeneration (minimal epithelial single cell necrosis in epididymis), was observed in dogs. Exposures in animals were similar or lower than those seen in humans receiving clinically relevant doses of cabazitaxel.

Cabazitaxel induced embryofetal toxicity in female rats treated intravenously once daily from gestational days 6 through 17 linked with maternal toxicity and consisted of foetal deaths and decreased mean foetal weight associated with delay in skeletal ossification. Exposures in animals were lower than those seen in humans receiving clinically relevant doses of cabazitaxel. Cabazitaxel crossed the placenta barrier in rats.

In rats, cabazitaxel and its metabolites are excreted in maternal milk at a quantity up to 1.5% of administered dose over 24 hours.

Environmental risk assessment

Results of environmental risk assessment studies indicated that use of cabazitaxel will not cause significant risk to the aquatic environment (see section 6.6 for disposal of unused product).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Citric acid
Ethanol anhydrous

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products 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 vial

3 years.

After opening

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After final dilution in the infusion bag/bottle

Chemical and physical stability of the infusion solution has been demonstrated for 8 hours at ambient temperature (15°C - 30°C) including the 1-hour infusion time and for 48 hours at refrigerated conditions including the 1-hour infusion time.

From a microbiological point of view, the infusion solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hour at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

3 ml of concentrate in a 6 ml clear tubular glass vial (type I) closed with a 20 mm grey siliconized rubber closure (type I) with teflon film on plug surface and sealed by an aluminium cap covered with a violet plastic flip-off cap.

Each carton contains one single use vial.

6.6 Special precautions for disposal and other handling

Cabazitaxel should only be prepared and administered by personnel trained in handling cytotoxic agents. Pregnant staff should not handle the product. As for any other antineoplastic agent, caution should be exercised when handling and preparing cabazitaxel solutions, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures. If cabazitaxel, 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.

Preparation for the intravenous administration

DO NOT use together with other cabazitaxel medicinal products with a different concentration cabazitaxel. Cabazitaxel Accord contains 20 mg/ml of cabazitaxel (at least 3 ml deliverable volume).

Each vial is of single use and should be used immediately. Discard any unused solution.

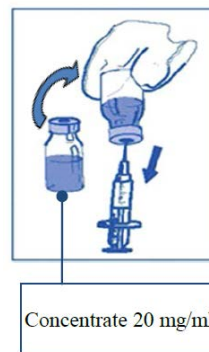
More than one vial of Cabazitaxel Accord may be necessary to administer the prescribed dose.

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

Preparation of the infusion solution

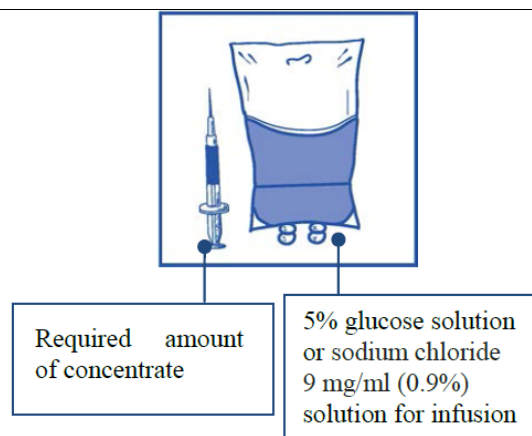
Step 1

Aseptically withdraw the required volume of Cabazitaxel Accord (which contains 20 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg cabazitaxel would require 2.25 ml of the Cabazitaxel Accord.



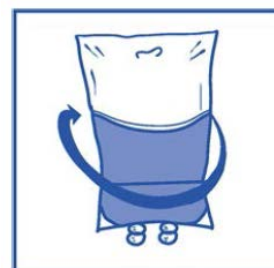
Step 2

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 3

Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion. The infusion solution is clear colourless solution.



Step 4

As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. As the infusion solution is supersaturated, it may crystallize over time. In this case, the solution must not be used and should be discarded.



The infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned in section 6.3.

An in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) is recommended during administration.

Do not use PVC infusion containers or polyurethane infusion sets for the preparation and administration of cabazitaxel.

Cabazitaxel must not be mixed with any other medicinal products than those mentioned.

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n, Edifici Est 6^a planta,
Barcelona, 08039, Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1448/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Accord Healthcare Limited
Sage House, 319 Pinner Road
Harrow, HA1 4HF
United Kingdom

LABORATORI FUNDACIÓ DAU
C/ C, 12-14 Pol. Ind. Zona Franca,
Barcelona, 08040, Spain

Pharmadox Healthcare Ltd.
KW20A Kordin Industrial Park
Paola, PLA 3000
Malta

Accord Healthcare Polska Sp. z o.o.,
ul. Lutomska 50, Pabianice,
95-200, Poland

Accord Healthcare B.V
Winthontlaan 200, UTRECHT, 3526KV Paola
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion
cabazitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 20 mg cabazitaxel
Each 3 ml vial contains 60 mg cabazitaxel

3. LIST OF EXCIPIENTS

Contains
Polysorbate 80
Citric acid
Ethanol

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
60 mg/3 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
For intravenous use after dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC

8. EXPIRY DATE

EXP

Read the leaflet for the shelf life of the diluted solution

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n, Edifici Est 6ª planta,
Barcelona, 08039, Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1448/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC

SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cabazitaxel Accord 20 mg/ml sterile concentrate
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 mg/3 ml

6. OTHER

CYTOTOXIC

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion cabazitaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

- 1 What Cabazitaxel Accord is and what it is used for
- 2 What you need to know before you are given Cabazitaxel Accord
- 3 How to use Cabazitaxel Accord
- 4 Possible side effects
- 5 How to store Cabazitaxel Accord
- 6 Contents of the pack and other information

1. What Cabazitaxel Accord is and what it is used for

The name of your medicine is Cabazitaxel Accord. Its common name is cabazitaxel. It belongs to a group of medicines called “taxanes” used to treat cancers.

Cabazitaxel Accord is used to treat adults with prostate cancer that has progressed after having had other chemotherapy. It works by stopping cells from growing and multiplying.

As part of your treatment, you will also take a corticosteroid medicine (prednisone or prednisolone) by mouth every day. Ask your doctor to give you information about this other medicine.

2. What you need to know before you are given Cabazitaxel Accord

Do not use Cabazitaxel Accord if

- you are allergic (hypersensitive) to cabazitaxel, to other taxanes, or polysorbate 80 or any of the other excipients of this medicine (listed in section 6),
- the number of your white blood cells is too low (neutrophil counts less than or equal to $1,500/\text{mm}^3$),
- you have severe abnormal liver function,
- you have recently received or are about to receive a vaccine against yellow fever.

You should not be given Cabazitaxel Accord if any of the above apply to you. If you are not sure, talk to your doctor before having Cabazitaxel Accord.

Warnings and precautions

Before each treatment with Cabazitaxel Accord, you will have blood tests to check that you have enough blood cells and sufficient liver and kidney functions to receive Cabazitaxel Accord.

Tell your doctor immediately if:

- you have fever. During treatment with Cabazitaxel Accord, it is more likely that your white blood cell count may be reduced. Your doctor will monitor your blood and general condition for signs of infections. He/she may give you other medicines to maintain the number of your blood cells. People with low blood counts can develop life-threatening infections. The earliest sign of infection may be fever, so if you experience fever, tell your doctor right away.

- you have ever had any allergies. Serious allergic reactions can occur during treatment with Cabazitaxel Accord.
- you have severe or long-lasting diarrhoea, you feel sick (nausea) or you are being sick (vomiting). Any of these events could cause severe dehydration. Your doctor may need to treat you.
- you have feeling of numbness, tingling, burning or decreased sensation in your hands or feet.
- you have any bleeding problems from the gut or have changes in the colour of your stool or stomach pain. If the bleeding or pain is severe, your doctor will stop your treatment with Cabazitaxel Accord. This is because Cabazitaxel Accord may increase the risk of bleeding or developing holes in the gut wall.
- you have kidney problems.
- liver problems occur during the treatment.
- you experience any significant increase or decrease in daily urinary volume.
- you have blood in your urine.

If any of the above applies to you, tell your doctor immediately. Your doctor may reduce the dose of Cabazitaxel Accord or stop the treatment.

Other medicines and Cabazitaxel Accord

Please tell your doctor, pharmacist or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription. This is because some medicines can affect the way Cabazitaxel Accord works or Cabazitaxel Accord can affect how other medicines work. These medicines include the following:

- ketoconazole, rifampicin (for infections);
- carbamazepine, phenobarbital or phenytoin (for seizures);
- St John's Wort (*Hypericum perforatum*) (herbal remedy for depression and other conditions);
- statins (such as simvastatin, lovastatin, atorvastatin, rosuvastatin, or pravastatin) (for reducing the cholesterol in your blood);
- valsartan (for hypertension);
- repaglinide (for diabetes).

Talk to your doctor before getting vaccinations while you are receiving Cabazitaxel Accord.

Pregnancy, breast-feeding and fertility

Cabazitaxel Accord should not be used in pregnant women or women of childbearing age not using contraception.

Cabazitaxel Accord should not be used during breast-feeding.

Use a condom during sex if your partner is or could become pregnant. Cabazitaxel Accord could be present in your semen and may affect the foetus. You are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because Cabazitaxel Accord may alter male fertility.

Driving and using machines

You may feel tired or dizzy when having this medicine. If this happens, do not drive or use any tools or machines until you feel better.

Cabazitaxel Accord contains ethanol (alcohol)

This medicine contains 1,185 mg of alcohol (ethanol) in each vial, which is equivalent to 16.33 Vol %. The amount in dose of this medicine is equivalent to 30 ml beer or 12 ml wine.

The amount of alcohol in this medicine is not likely to have an effect in adults.

The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

3. How to use Cabazitaxel Accord

Instructions for use

Anti-allergic medicines will be given to you before you have Cabazitaxel Accord to reduce the risk of allergic reactions.

- Cabazitaxel Accord will be given to you by a doctor or a nurse.
- Cabazitaxel Accord must be prepared (diluted) before it is given. Practical information for handling and administration of Cabazitaxel Accord for doctors, nurses and pharmacists is provided with this leaflet.
- Cabazitaxel Accord will be given by a drip (infusion) into one of your veins (intravenous use) in hospital for about an hour.
- As part of your treatment, you will also take a corticosteroid medicine (prednisone or prednisolone) by mouth every day.

How much and how often to have

- The usual dose depends on your body surface area. Your doctor will calculate your body surface area in square meters (m²) and will decide the dose you should have.
- You will usually have an infusion once every 3 weeks.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

See a doctor immediately if you notice any of the following side effects:

- fever (high temperature). This is very common (may affect more than 1 in 10 people).
- severe loss of body fluids (dehydration). This is common (may affect up to 1 in 10 people).
- This can occur if you have severe or long-lasting diarrhoea, or fever, or if you are being sick (vomiting).
- severe stomach pain or stomach pain that doesn't go away. This can occur if you have a hole in the stomach, food pipe, gut or bowel (gastrointestinal perforation). This can lead to death.

If any of the above applies to you, tell your doctor immediately.

Other side effects include:

Very common (may affect more than 1 in 10 people):

- decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection)
- decrease in the number of platelets (which results in increased risk of bleeding)
- loss of appetite (anorexia)
- alteration in sense of taste
- shortness of breath
- cough
- stomach upsets including feeling sick (nausea), being sick (vomiting), diarrhoea or constipation

- abdominal pain
- short term hair loss (in most cases normal hair growth should return)
- back pain
- joint pain
- blood in the urine
- feeling tired, weak or lack of energy.

Common (may affect up to 1 in 10 people):

- urinary tract infection
- lack of white blood cells associated with fever and infection
- feeling of numbness, tingling, burning or decreased sensations in hands and feet
- dizziness
- headache
- decrease or increase in blood pressure
- uncomfortable feeling in the stomach, heart burn or belching
- stomach pain
- haemorrhoids
- muscle spasm
- painful or frequent urination
- urinary incontinence
- kidney disease or problems
- sore in the mouth or on lips
- infections or risk of infections
- high blood sugar
- low blood potassium
- mental confusion
- feeling anxious
- abnormal feeling or loss of sensation or pain in hands and feet
- ringing in the ear
- trouble with balance
- rapid or irregular heartbeat
- blood clot in the leg
- skin feeling hot or flushed
- pain in mouth or throat
- rectal bleeding
- redness of the skin
- muscle discomfort, aches or pain
- swelling of the feet or legs
- chills

Uncommon (may affect up to 1 in 100 people):

- inflammation of the bladder, which can occur when your bladder has been previously exposed to radiation therapy (cystitis due to radiation recall phenomenon).

Frequency not known (cannot be estimated from the available data):

- interstitial lung disease (inflammation of the lungs causing coughing and difficulty breathing).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cabazitaxel Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

After opening

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After final dilution in the infusion bag/bottle

Chemical and physical stability of the infusion solution has been demonstrated for 8 hours at ambient temperature (15°C - 30°C) including the 1-hour infusion time and for 48 hours at refrigerated conditions including the 1-hour infusion time.

From a microbiological point of view, the infusion solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hour at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cabazitaxel Accord contain

The active substance is cabazitaxel. One ml of concentrate contains 20 mg cabazitaxel. Each 3 ml vial of concentrate contains 60 mg cabazitaxel.

The other ingredients are polysorbate 80, citric acid and ethanol anhydrous (see section 2 “Cabazitaxel Accord contains alcohol”).

What Cabazitaxel Accord looks like and contents of the pack

Cabazitaxel Accord is a concentrate for solution for infusion (sterile concentrate). The concentrate is a clear colourless to pale yellow or brownish yellow solution.

It is supplied as a single-use vial with a deliverable volume of 3 ml concentrate in 6 ml clear glass vial.

Pack size:

Each carton contains one single use vial.

Marketing Authorisation Holder

Accord Healthcare S.L.U
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6^a planta, Barcelona,
08039 Barcelona, Spain

Manufacturer

Accord Healthcare Limited
Sage House, 319 Pinner Road
Harrow, Middlesex, HA1 4HF
United Kingdom

LABORATORI FUNDACIÓ DAU
C/ C, 12-14 Pol. Ind. Zona Franca,
Barcelona, 08040, Spain

Pharmadox Healthcare Ltd.
KW20A Kordin Industrial Park
Paola, PLA 3000
Malta

Accord Healthcare Polska Sp. z o.o.,
ul. Lutomierska 50, Pabianice, 95-200
Poland

Accord Healthcare B.V
Winthontlaan 200, UTRECHT, 3526KV Paola
Netherlands

This leaflet was last revised in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only.

PRACTICAL INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS ON PREPARATION, ADMINISTRATION AND HANDLING OF CABAZITAXEL ACCORD 20 mg/ ml CONCENTRATE FOR SOLUTION FOR INFUSION

This information supplements sections 3 and 5 for the user.

It is important that you read the entire content of this procedure prior to the preparation of the infusion solution.

Incompatibilities

This medicine must not be mixed with other medicines except those used for the dilutions.

Shelf life and special precautions for storage

For the pack of Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion

This medicinal product does not require any special storage conditions.

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

After opening

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After final dilution in the infusion bag/bottle

Chemical and physical stability of the infusion solution has been demonstrated for 8 hours at ambient temperature (15°C - 30°C) including the 1-hour infusion time and for 48 hours at refrigerated conditions including the 1-hour infusion time.

From a microbiological point of view, the infusion solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hour at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Preparation and administration precautions

As for any other antineoplastic agent, caution should be exercised when handling and preparing Cabazitaxel Accord solutions, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures.

If Cabazitaxel Accord, 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 Accord should only be prepared and administered by personnel trained in handling cytotoxic agents. Pregnant staff should not handle it.

Preparation steps

DO NOT use together with other cabazitaxel medicinal products with a different concentration cabazitaxel. Cabazitaxel Accord contains 20 mg/ml of cabazitaxel (at least 3 ml deliverable volume).

Each vial is of single use and should be used immediately. Discard any unused solution.

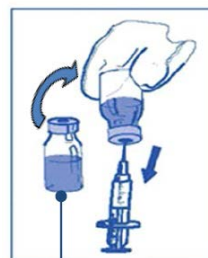
More than one vial of Cabazitaxel Accord may be necessary to administer the prescribed dose.

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

Preparation of the infusion solution

Step 1

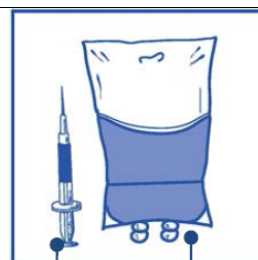
Aseptically withdraw the required volume of Cabazitaxel Accord (which contains 20 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg cabazitaxel would require 2.25 ml of the Cabazitaxel Accord.



Concentrate 20 mg/ml

Step 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.

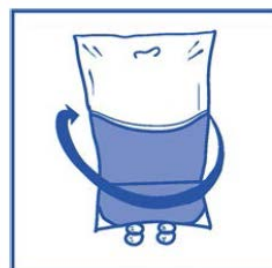


Required amount
of concentrate

5% glucose solution
or sodium chloride
9 mg/ml (0.9%)
solution for infusion

Step 3

Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion. The infusion solution is clear colourless solution.



Step 4

As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. As the infusion solution is supersaturated, it may crystallize over time. In this case, the solution must not be used and should be discarded.



The infusion solution should be used immediately. Information on **shelf life** and **special precautions for storage** are above.

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

Method of administration

Cabazitaxel Accord is administered as a 1 hour infusion.

An in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) is recommended during administration.

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