SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cabazitaxel EVER Pharma 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the concentrate for solution for infusion contains cabazitaxel monohydrate or anhydrous equivalent to 10 mg cabazitaxel.

Each vial of 4.5 ml of concentrate for solution for infusion contains cabazitaxel monohydrate or anhydrous equivalent to 45 mg cabazitaxel.

Each vial of 5 ml of concentrate for solution for infusion contains cabazitaxel monohydrate or anhydrous equivalent to 50 mg cabazitaxel.

Each vial of 6 ml of concentrate for solution for infusion contains cabazitaxel monohydrate or anhydrous equivalent to 60 mg cabazitaxel

Cabazitaxel EVER Pharma 10 mg/ml concentrate for solution for infusion contains an overfill. This overfill ensures that there is extractable volume of 4.5 ml, 5 ml or 6 ml containing 10 mg/ml cabazitaxel.

Excipient with known effect

Each ml of concentrate for solution for infusion contains 197.5 mg of ethanol.

Each vial of 4.5 ml concentrate contains 888.8 mg of ethanol (19.75% w/v).

Each vial of 5 ml concentrate contains 987.5 mg of ethanol (19.75% w/v).

Each vial of 6 ml concentrate contains 1,185 mg of ethanol (19.75% w/v).

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 slightly yellow oily solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cabazitaxel EVER Pharma 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 EVER Pharma 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 EVER Pharma 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 EVER Pharma 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 diarrhoea 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 EVER Pharma may be considered. Data in patients below the 20 mg/m2 dose are limited.

Special populations

Patients with 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.

In patients with moderate hepatic impairment (total bilirubin >1.5 to ≤ 3.0 x ULN), the maximum tolerated dose (MTD) was 15 mg/m2. If the treatment is envisaged in patients with moderate hepatic impairment the dose of cabazitaxel should not exceed 15 mg/m2. However, limited efficacy data are available at this dose.

Cabazitaxel should not be given to patients with severe hepatic impairment (total bilirubin >3 x ULN) (see sections 4.3, 4.4 and 5.2).

Patients with 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).

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).

Paediatric population

There is no relevant use of Cabazitaxel EVER Pharma in the paediatric population.

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

Method of administration

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 EVER Pharma 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, polysorbate 80 or any excipients listed in section 6.1.

• Neutrophil counts less than 1,500/mm3.

• Severe hepatic impairment (total bilirubin >3 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 generalised 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 EVER Pharma (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 ≥1,500/mm3 (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 ≥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 people (≥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 EVER Pharma is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 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

This medicinal product contains 197.5 mg ethanol per ml.

Vial 4.5 ml

This medicine contains 888.8 mg of alcohol (ethanol) in each vial. The amount of 4.5 ml in this medicine is equivalent to 22.5 ml beer or 9.4 ml wine.

Vial 5 ml

This medicine contains 987.5 mg of alcohol (ethanol) in each vial. The amount of 5 ml in this medicine is equivalent to 25 ml beer or 10.4 ml wine.

Vial 6 ml

This medicine contains 1185 mg of alcohol (ethanol) in each vial. The amount of 6 ml in this medicine is equivalent to 30 ml beer or 12.5 ml wine.

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.

Breast-feeding

Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk (see section 5.3). A risk to the suckling 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 a 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 3 randomised, open label, controlled studies (TROPIC, PROSELICA and CARD) totalling 1092 patients with metastatic castration resistant prostate cancer who were treated with 25 mg/m2 cabazitaxel once every three weeks. Patients received a median of 6 to 7 cycles of cabazitaxel.

The incidences from the pooled analysis of these 3 trials are presented below and in the tabulated list.

The most common all grades adverse reactions were anaemia (99.0%), leukopenia (93.0%), neutropenia (87.9%), thrombocytopenia (41.1%), diarrhoea (42.1%), fatigue (25.0%) and asthenia (15.4%). The most common grade ≥3 adverse reactions occurring in at least 5% of patients were neutropenia (73.1%), leukopenia (59.5%), anaemia (12.0%), febrile neutropenia (8.0%) and diarrhoea (4.7%).

Discontinuation of treatment due to adverse reactions occurred with similar frequencies across the 3 studies (TROPIC, PROSELICA and CARD) in patients receiving cabazitaxel. The most common adverse reactions (> 1.0%) leading to cabazitaxel discontinuation were hematuria, fatigue and 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 ≥3 = G≥3). Frequencies are based on all grades and defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

Table 2: Reported adverse reactions and haematological abnormalities with cabazitaxel in combination with prednisone or prednisolone from pooled analysis (n=1092)

System Organ Class	**Adverse reaction**	**All grades n (%)**			**Grade≥3 n (%)**
		Very common	**Common**	**Uncommon**	

Infections and infestations	Neutropenic infection/sepsis*		48 (4.4)		42 (3.8)
	Septic shock			10 (0.9)	10 (0.9)
	Sepsis		13 (1.2)		13 (1.2)
	Cellulitis			8 (0.7)	3 (0.3)
	Urinary tract infection		103 (9.4)		19 (1.7)
	Influenza		22 (2.0)		0
	Cystitis		22 (2.0)		2 (0.2)
	Upper respiratory tract infection		23 (2.1)		0
	Herpes zoster		14 (1.3)		0
	Candidiasis		11 (1.0)		1 (<0.1)
Blood and lymphatic system disorders	Neutropenia[a*]	950 (87.9)			790 (73.1)
	Anaemia [a]	1073 (99.0)			130 (12.0)
	Leukopenia[a]	1008 (93.0)			645 (59.5)
	Thrombocytopenia[a]	478 (44.1)			44 (4.1)
	Febrile neutropenia		87 (8.0)		87 (8.0)
Immune system disorders	Hypersensitivity			7 (0.6)	0
Metabolism and nutrition disorders	Decreased appetite	192 (17.6)			11 (1.0)
	Dehydration		27 (2.5)		11 (1.0)
	Hyperglycaemia		11 (1.0)		7 (0.6)
	Hypokalemia			8 (0.7)	2 (0.2)
Psychiatric disorders	Insomnia		45 (4.1)		0
	Anxiety		13 (1.2)		0
	Confusional state		12 (1.1)		2 (0.2)
Nervous system disorders	Dysgeusia		64 (5.9)		0
	Taste disorder		56 (5.1)		0
	Neuropathy peripheral		40 (3.7)		2 (0.2)
	Peripheral sensory neuropathy		89 (8.2)		6 (0.5)
	Polyneuropathy			9 (0.8)	2 (0.2)
	Dizziness		63 (5.8)		0
	Headache		56 (5.1)		1 (<0.1)
	Paraesthesia		46 (4.2)		0
	Lethargy		15 (1.4)		1 (<0.1)
	Hypoaesthesia		18 (1.6)		1 (<0.1)

	Sciatica			9 (0.8)	1 (<0.1)
Eye disorders	Conjunctivitis		11 (1.0)		0
	Lacrimation increased		22 (2.0)		0
Ear and labyrinth disorders	Tinnitus			7 (0.6)	0
	Vertigo		15 (1.4)		1 (<0.1)
Cardiac disorders*	Atrial fibrillation		14 (1.3)		5 (0.5)
	Tachycardia		11 (1.0)		1 (<0.1)
Vascular disorders	Hypotension		38 (3.5)		5 (0.5)
	Deep vein thrombosis		12 (1.1)		9 (0.8)
	Hypertension		29 (2.7)		12 (1.1)
	Orthostatic hypotension			6 (0.5)	1 (<0.1)
	Hot flush		23 (2.1)		1 (<0.1)
	Flushing			9 (0.8)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea		97 (8.9)		9 (0.8)
	Cough		79 (7.2)		0
	Oropharyngeal pain		26 (2.4)		1 (< 0.1)
	Pneumonia		26 (2.4)		16 (1.5)
	Pulmonary embolism		30 (2.7)		23 (2.1)
Gastrointestinal disorders	Diarrhoea	460 (42.1)			51 (4.7)
	Nausea	347 (31.8)			14 (1.3)
	Vomiting	207 (19.0)			14 (1.3)
	Constipation	202 (18.5)			8 (0.7)
	Abdominal pain		105 (9.6)		15 (1.4)
	Dyspepsia		53 (4.9)		0
	Abdominal pain upper		46 (4.2)		1 (< 0.1)
	Haemorrhoids		22 (2.0)		0
	Gastroesophageal reflux disease		26 (2.4)		1 (< 0.1)
	Rectal haemorrhage		14 (1.3)		4 (0.4)
	Dry mouth		19 (1.7)		2 (0.2)
	Abdominal distension		14 (1.3)		1 (< 0.1)
	Stomatitis		46 (4.2)		2 (0.2)

	Ileus*			7 (0.6)	5 (0.5)
	Gastritis			10 (0.9)	0
	Colitis*			10 (0.9)	5 (0.5)
	Gastrointestinal perforation			3 (0.3)	1 (< 0.1)
	Gastrointestinal haemorrhage			2 (0.2)	1 (< 0.1)
Skin and subcutaneous tissue disorders	Alopecia		80 (7.3)		0
	Dry skin		23 (2.1)		0
	Erythema			8 (0.7)	0
	Nail disorder		18 (1.6)		0
Musculoskeletal and connective tissue disorders	Back pain	166 (15.2)			24 (2.2)
	Arthralgia		88 (8.1)		9 (0.8)
	Pain in extremity		76 (7.0)		9 (0.8)
	Muscle spasms		51 (4.7)		0
	Myalgia		40 (3.7)		2 (0.2)
	Musculoskeletal chest pain		34 (3.1)		3 (0.3)
	Muscular weakness		31 (2.8)		1 (0.2)
	Flank pain		17 (1.6)		5 (0.5)
Renal and urinary disorders	Acute renal failure		21 (1.9)		14 (1.3)
	Renal failure			8 (0.7)	6 (0.5)
	Dysuria		52 (4.8)		0
	Renal colic		14 (1.3)		2 (0.2)
	Haematuria	205 (18.8)			33 (3.0)
	Pollakiuria		26 (2.4)		2 (0.2)
	Hydronephrosis		25 (2.3)		13 (1.2)
	Urinary retention		36 (3.3)		4 (0.4)
	Urinary incontinence		22 (2.0)		0
	Ureteric obstruction			8 (0.7)	6 (0.5)
Reproductive system and breast disorders	Pelvic pain		20 (1.8)		5 (0.5)
General disorders and administration site conditions	Fatigue	333 (30.5)			42 (3.8)
	Asthenia	227 (20.8)			32 (2.9)
	Pyrexia		90 (8.2)		5 (0.5)
	Peripheral oedema		96 (8.8)		2 (0.2)

	Mucosal inflammation		23 (2.1)		1 (<0.1)
	Pain		36 (3.3)		7 (0.6)
	Chest pain		11 (1.0)		2 (0.2)
	Oedema			8 (0.7)	1 (<0.1)
	Chills		12 (1.1)		0
	Malaise		21 (1.9)		0
Investigations	Weight decreased		81 (7.4)		0
	Aspartate aminotransferase increased		13 (1.2)		1 (<0.1)
	Transaminases increased			7 (0.6)	1 (<0.1)

a based-on laboratory values

* see detailed section below

Description of selected adverse reactions

Neutropenia, and associated clinical events

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

Incidence of grade ≥3 neutropenia based on laboratory data varied depending on use of G-CSF from 44.7% to 76.7%, with the lowest incidence reported when G-CSF prophylaxis was used. Similarly, the incidence of grade ≥ 3 febrile neutropenia ranged from 3.2% to 8.6%.

Neutropenic complications (including febrile neutropenia, neutropenic infection/sepsis and neutropenic colitis) which in some cases resulted in a fatal outcome, were reported in 4.0% of the patients when primary G-CSF prophylaxis was used, and in 12.8% of the patients otherwise.

Cardiac disorders and arrhythmias

In the pooled analysis, cardiac events were reported in 5.5% of the patients of which 1.1% had grade ≥3 cardiac arrhythmias. The incidence of tachycardia on cabazitaxel was 1.0%, of which less than 0.1% were grade ≥3. The incidence of atrial fibrillation was 1.3%.. Cardiac failure events were reported for 2 patients (0.2%), one of which resulted in a fatal outcome. Fatal ventricular fibrillation was reported in 1 patient (0.3%), and cardiac arrest in 3 patients (0.5%). None were considered related by the investigator.

Haematuria

In the pooled analysis, haematuria all grades frequency was 18.8% at 25 mg/m^2 (see section 5.1). Confounding causes when documented, such as disease progression, instrumentation, infection or anticoagulation/NSAID/acetylsalicylic acid therapy were identified in nearly half of the cases.

Other laboratory abnormalities

In pooled analysis, the incidence of grade ≥3 anaemia, increased AST, ALT, and bilirubin based on laboratory abnormalities were 12.0%, 1.3%, 1.0%, and 0.5%, respectively.

Gastrointestinal disorders

Colitis (including enterocolitis and neutropenic enterocolitis) and gastritis have been observed. Gastrointestinal hemorrhage, gastrointestinal perforation and ileus (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 population

Of the 1092 patients treated with cabazitaxel 25 mg/m^2 in the prostate cancer studies, 755 patients were 65 years or over including 238 patients older than 75 years. The following non hematologic adverse reactions were reported at rates ≥5% higher in patients 65 years of age or greater compared to younger patients: fatigue (33.5% vs. 23.7%), asthenia (23.7 vs. 14.2%), constipation (20.4% vs. 14.2%) and dyspnoea (10.3% vs. 5.6%) respectively. Neutropenia (90.9% vs. 81.2%) and thrombocytopenia (48.8% vs. 36.1%) were also 5% higher in patients 65 years of age or greater compared to younger patients. Grade ≥3 neutropenia and febrile neutropenia were reported with the highest difference rates between both groups of age (respectively 14% and 4% higher in patients ≥ 65 years old compared to patients < 65 years old) (see sections 4.2 and 4.4).

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 yellow Card Scheme at www.mha.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 ≥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 ≥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/mm3, platelets >100,000/mm3, haemoglobin >10 g/dl, creatinine <1.5 x ULN, total bilirubin <1 x ULN, AST and ALT <1.5 x 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).

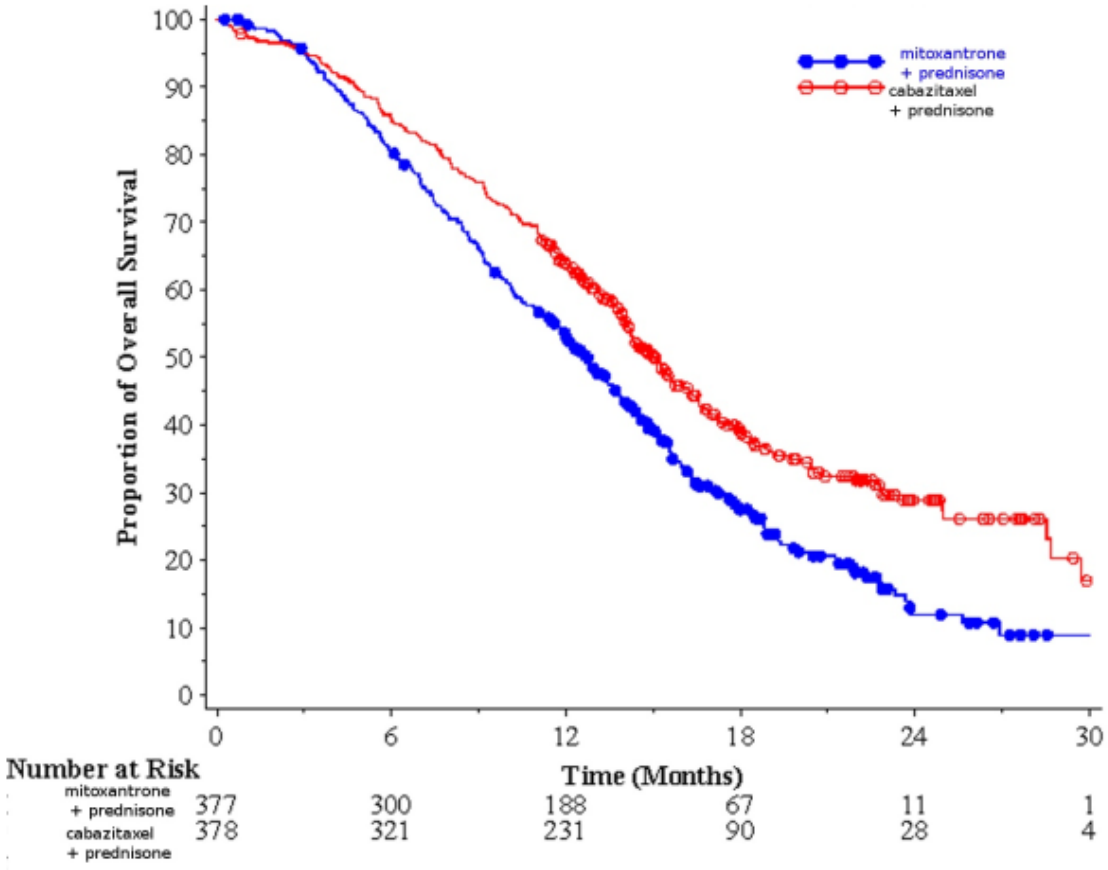
A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in cabazitaxel arm, 30 patients in mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR (95%CI) 0.96 (0.49-1.86)).

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	From 25 to 20 mg/m^2: 128 (21.5%) From 20 to 15 mg/m^2: 19

	(1.6%)	(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
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

In a prospective, multinational, randomized, active-controlled and open-label phase IV study
(LPS14201/CARD study) 255 patients with metastatic castration resistant prostate cancer (mCRPC), previously treated in any order with a docetaxel containing regimen and with an AR-targeted agent (abiraterone or enzalutamide, with disease progression within 12 months of treatment initiation), were randomized to receive either cabazitaxel 25 mg/m^2 every 3 week plus prednisone/prednisolone 10 mg daily (n=129) or AR-targeted agents (abiraterone 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily) (n=126). Radiographic progression free-survival (rPFS) as defined by Prostate Cancer Working Group-2 (PCWG2) was the primary endpoint. Secondary endpoints included overall survival, progression-free survival, PSA response and tumour response. Demographics and disease characteristics were balanced between treatment arms. At baseline, the overall median age was 70 years, 95% of patients had an ECOG PS of 0 to 1 and median Gleason score was 8. Sixty one percent (61%) of the patients had their prior treatment with an AR-targeted agent after prior docetaxel.

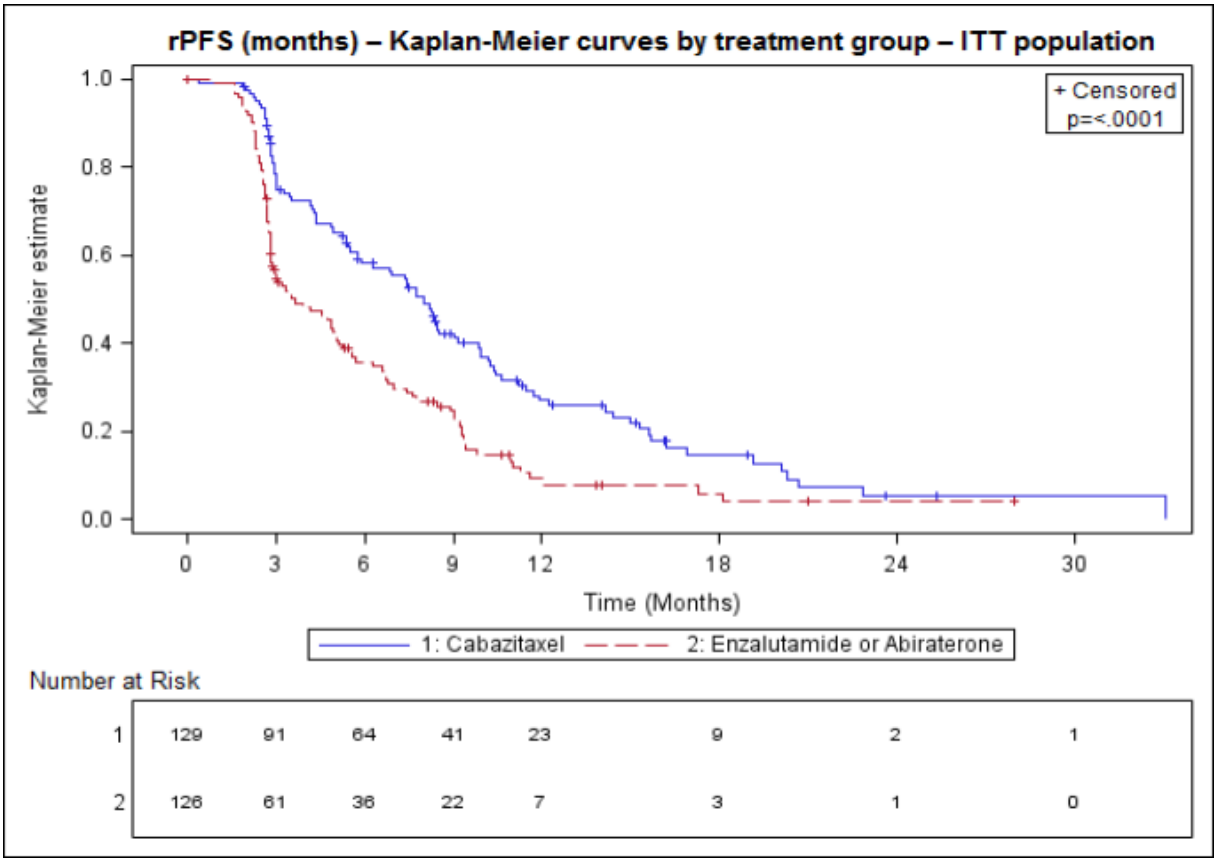
The study met its primary endpoint: rPFS was significantly longer with cabazitaxel compared to AR-targeted agent (8.0 months versus 3.7 respectively), with a 46% reduction in the risk of radiographic progression compared to AR-targeted agent (see table 6 and figure 2).

Table 6 - Efficacy of cabazitaxel in CARD study in the treatment of patients with metastatic castration resistant prostate cancer (Intent-to–treat analysis) – Radiographic progression free-survival (rPFS)

	Cabazitaxel + prednisone/prednisolone + G-CSF n=129	AR-targeted agent Abiraterone + prednisone/prednisolone or Enzalutamide n=126
Number of events at the cut-off date (%)	95 (73.6%)	101 (80.2%)
Median rPFS (months) (95% CI)	8.0 (5.7 to 9.2)	3.7 (2.8 to 5.1)
Hazard Ratio (HR) (95% CI)	0.54 (0.40 to 0.73)	
p-value[1]	<0.0001	

[1]stratified log-rank test, significance threshold = 0.05

Figure 2 - Primary endpoint: Kaplan-Meier plot of radiographic PFS (ITT Population)



Tick marks indicate censored data.

Planned subgroup analyses for rPFS based on stratification factors at randomization yielded a hazard ratio of 0.61 (95% CI: 0.39 to 0.96) in patients who received a prior AR-targeted agent before docetaxel and a hazard ratio of 0.48 (95% CI: 0.32 to 0.70) in patients who received a prior AR-targeted agent after docetaxel.
Cabazitaxel was statistically superior to the AR-targeted comparators for each of the alpha-protected key secondary endpoints including overall survival (13.6 months for cabazitaxel arm versus 11.0 months for AR-targeted agent arm, HR 0.64, 95%CI: 0.46 to 0.89; p=0.008), progression-free survival (4.4 months for cabazitaxel arm versus 2.7 months for AR-targeted agent arm, HR 0.52; 95%CI: 0.40 to 0.68), confirmed PSA response (36.3% for cabazitaxel arm versus 14.3% for AR-targeted agent arm, p=0.0003) and best tumour response (36.5% for cabazitaxel arm versus 11.5% for AR-targeted agent arm, p=0.004).
The safety profile of cabazitaxel 25 mg/m^2 observed in CARD study was overall consistent with that observed in TROPIC and PROSELICA studies (see section 4.8). The incidence of grade ≥ 3 adverse events was 53.2% in cabazitaxel arm versus 46.0% in the AR-targeted agent arm. The incidence of grade ≥ 3 serious adverse events were 31.7% in cabazitaxel arm versus 37.1% in the AR-targeted agent arm. The incidence of patients who permanently discontinued study treatment due to adverse events was 19.8% in cabazitaxel arm versus 8.1% in the AR-targeted agent arm. The incidence of patients having an adverse event leading to death was 5.6% in cabazitaxel arm versus 10.5% in the AR-targeted agent arm.

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 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 tumours (n=126).

Distribution

The volume of distribution (Vss) 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 form 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-17β-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 EVER Pharma 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 ≤1.5 x ULN or AST >1.5 x ULN) or moderate (total bilirubin >1.5 to ≤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 EVER Pharma is contraindicated in patients with 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 IV 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 embryofoetal 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 (ERA)

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

Ethanol, anhydrous

Macrogol

Citric acid

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 first opening

Multi-dose vials: Chemical, physical and microbiological stability of the solution after first opening has been demonstrated for 28 days below 25°C. Cabazitaxel EVER Pharma is suitable for multi-dose use.

After dilution in the infusion bag/bottle

Chemical and physical stability of the infusion solution has been demonstrated for 48 hours at below 25°C and for 14 days at refrigerated conditions.

From a microbiological point of view, the infusion solution 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 below 25°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 storage conditions.

Do not freeze.

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

6.5 Nature and contents of container

One pack contains one vial of concentrate for solution for infusion:

Clear, glass vial closed with a grey bromobutyl rubber stopper sealed with an aluminium cap covered with a plastic flip-off cap.

Pack sizes: 1 x 4,5 ml (45 mg)

1 x 5 ml (50 mg)

1 x 6 ml (60 mg)

Vials may or may not be sheathed in a protective sleeve.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Cabazitaxel EVER Pharma 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 EVER Pharma solutions, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures. If Cabazitaxel EVER Pharma, 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.

Read this **ENTIRE** section carefully. Cabazitaxel EVER Pharma requires **ONE** dilution prior to administration. Follow the preparation instructions provided below.

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

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

Dilution for infusion

Step 1: Aseptically withdraw the required amount of concentrate (10 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg [Cabazitaxel EVER Pharma would require 4.5 ml of the concentrate.

Cabazitaxel EVER Pharma 10 mg/ml concentrate for solution for infusion contains an overfill. This overfill ensures that there is extractable volume of 4.5 ml, 5 ml or 6 ml containing 10 mg/ml cabazitaxel.

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.

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.

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

Cabazitaxel EVER Pharma 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

EVER Valinject GmbH

Oberburgau 3

4866 Unterach am Attersee

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 46654/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/08/2020

10 DATE OF REVISION OF THE TEXT

19/07/2023