CAZEXA (Cabazitaxel 60 mg/1.5mL Concentrate and solvent for solution for infusion)_Leaflet, Camber-Malaysia

Pharma code

®CAZEXA
(Cabazitaxel 60mg/1.5ml concentrate and solvent for solution for Infusion)
20xxxxx

NAME AND STRENGTH OF ACTIVE INGREDIENT
CAZEXA (CABAZITAXEL 60MG/1.5ML CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION)

QUALITATIVE AND QUANTITATIVE COMPOSITION
One ml of concentrate contains 40 mg cabazitaxel.
Each vial of 1.5 ml (nominal volume) of concentrate contains 60 mg cabazitaxel.
After initial dilution with the entire solvent, each ml of solution contains 10 mg cabazitaxel.

Note: Both the CAZEXA 60 mg/1.5 ml concentrate vial (fill volume: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (fill volume: 5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **ENTIRE** contents of the accompanying solvent, there is solution containing 10 mg/ml cabazitaxel.

PRODUCT DESCRIPTION
Concentrate and solvent for solution for infusion (sterile concentrate).
The concentrate is a clear yellow to brownish-yellow viscous solution.
The solvent is a clear colourless solution.
The reconstituted solution is a clear yellow to brownish-yellow viscous solution.

PHARMACODYNAMICS
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.

PHARMACOKINETICS
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. 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 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 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-17ß-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.

Elimination
After a 1-hour intravenous infusion [^{14}C]-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 CAZEXA 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. CAZEXA is contraindicated in patients with severe hepatic impairment.

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.

INDICATION
CAZEXA 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.

RECOMMENDED DOSE
The use of CAZEXA should be confined to units specialized 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.

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

Antihistamine (dexchlorpheniramine5 mg or diphenhydramine 25 mg or equivalent), Corticosteroid (dexamethasone 8 mg or equivalent), and H^2 antagonist (ranitidine or equivalent).

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 CAXEZA is 25 mg/m².administered as a 1 hour intravenous infusion every 3 weeks in combinations with oral prednisone or prednisolone 10 mg administered daily throughout treatment.

Dose adjustment
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/mm³, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m².
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm³, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m².
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/m² to 20 mg/m².
Grade ≥ 2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m².

If patients continue to experience any of these reactions at 20 mg/m²., further dose reduction to 15 mg/m². or discontinuation of CAZEXA 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 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).

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.

Elderly
No specific dose adjustment for the use of cabazitaxel in elderly patients is recommended.

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.

Paediatric Population
There is no relevant use of CAZEXA in the paediatric population.
The safety and the efficacy of CAZEXA in children and adolescents below 18 years of age have not been established.

Method of Administration
CAZEXA is for intravenous use.

For instructions on preparation and administration of the product, see section Instructions for Use. 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 Instructions for Use.

CONTRAINDICATIONS
- Hypersensitivity to cabazitaxel, to other taxanes, or polysorbate 80 or any excipients listed in this package insert.
- Neutrophil counts less than 1,500/mm³.
- Severe hepatic impairment (total bilirubin > 3 x ULN).
- Concomitant vaccination with yellow fever vaccine.

WARNING AND PRECAUTIONS
Hypersensitivity Reactions
All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel.

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 CAZEXA.

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

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. 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. Patients should be re-treated only when neutrophils recover to a level ≥ 1,500/mm³.

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. 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. 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.

Anaemia
Anaemia has been observed in patients receiving cabazitaxel. 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. 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.

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

Patients with Liver Impairment
Treatment with CAXEZA is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN) Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN), hepatic impairment.

Interactions
Co-administration with strong CYP3A inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel. If co-administration with a strong CYP3A inhibitor cannot be avoided, close monitoring for toxicity and a cabazitaxel dose reduction should be considered.

Co-administration with strong CYP3A inducers should be avoided since they may decrease plasma concentrations of cabazitaxel.

Excipients
This medicine contains 130 mg of alcohol (ethanol) in each solvent vial. The small amount of alcohol in this medicine will not have any noticeable effects. However, special precaution needs to be taken in high-risk groups such as patients with liver disease, epilepsy and patients with the history of alcoholism.

Contraception measure
Men should use contraceptive measures during treatment and for 4 months after cessation of treatment with cabazitaxel.

INTERACTION WITH OTHER MEDICAMENTS
In vitro studies have shown that cabazitaxel is mainly metabolised through CYP3A (80% to 90%).

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.

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. 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.

PREGNANCY AND LACTATION
Contraception measure
Due to the genotoxic risk of cabazitaxel, men should use effective method of contraception during treatment and for 4 months after cessation of treatment with cabazitaxel.

Pregnancy
There are no data from the use of cabazitaxel in pregnant women. Studies in animals have shown reproductive toxicity at maternotoxic doses and that cabazitaxel crosses the placenta barrier. As with other cytotoxic medicinal products, cabazitaxel may cause foetal harm in exposed pregnant women.

Cabazitaxel is not indicated for use in women.

Breast-feeding
Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk.

Fertility
Animal studies showed that cabazitaxel affected reproductive system in male rats and dogs without any functional effect on fertility. Nevertheless, considering the pharmacological activity of taxanes, their genotoxic potential by an aneugenic mechanism and effect of several compounds of this class on fertility in animal studies, effect on male fertility could not be excluded in human.
Men being treated with cabazitaxel are advised to seek advice on conservation of sperm prior to treatment.

SIDE EFFECTS
The safety of cabazitaxel in combination with prednisone or prednisolone was evaluated in 3 randomized, open label, controlled studies (TROPIC, PROSELICA and CARD), totaling 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 (18.3% in TROPIC, 19.5% in PROSELICA and 19.8% in CARD) in patients receiving cabazitaxel. The most common adverse reactions (> 1.0%) leading to cabazitaxel discontinuation were haematuria, fatigue and neutropenia.

Tabulated List of Adverse Reactions
Adverse reactions are listed in the table 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 (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)

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System Organ Class	Adverse Reaction	All Grades n (%)			Grade ≥ 3 n (%)
		Very Common	Common	Uncommon	
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)
	Hyperglycemia		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 disorder	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
	Lacrimination increased		22 (2.0)		0
Ear and labyrinth disorders	Tinnitus			7 (0.6)	0
	Vertigo		15 (1.4)		1 (<0.1)
Cardiac disorders*	Artrial 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	Diarrhea	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)
	Illeus*			7 (0.6)	5 (0.5)
	Gastritis			10 (0.9)	
	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)
	Muscoskeletal 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)
	Hematuria	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)	
	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 incident and severity of neutropenia. 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/m². 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 the 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.

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).

Renal and urinary disorders
Cystitis due to radiation recall phenomenon, including haemorrhagic cystitis, were reported uncommonly.

Paediatric Population
There is no relevant use of CAZEXA in the paediatric population.
The safety and the efficacy of CAZEXA in children and adolescents below 18 years of age have not been established.

Other Special Populations
Elderly Population
Of the 1092 patients treated with cabazitaxel 25 mg/m² in the prostate cancer studies, 755 patients were 65 years or over including 238 patients older than 75 years.

The following non haematologic 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).

SYMPTOMS AND TREATMENT OF 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.

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.

PRECLINICAL SAFETY DATA
Not Applicable

INSTRUCTIONS FOR USE
Intravenous

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

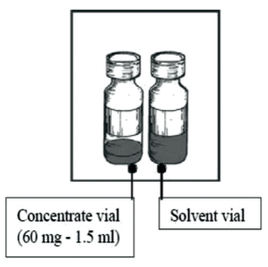
Always dilute the concentrate for solution for infusion with the entire supplied solvent before adding to infusion solution.
Read this ENTIRE section carefully before mixing and diluting. CAZEXA requires TWO dilutions prior to administration. Follow the preparation instructions provided below.

Note: Both the CAZEXA 60 mg/1.5 ml concentrate vial (fill volume: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (fill volume: 5.7 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the ENTIRE contents of the accompanying solvent, there is solution containing 10 mg/ml cabazitaxel.

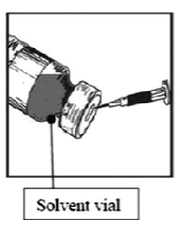
The following two-step dilution process must be carried out in an aseptic manner for preparing the solution for infusion.

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

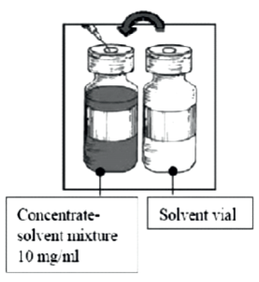
Step 1.1
Inspect the concentrate vial and the supplied diluent. The concentrate solution and the diluent should be clear.



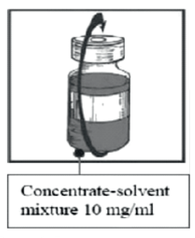
Step 1.2
Using a syringe fitted with a needle, aseptically withdraw the entire contents of the supplied diluent by partially inverting the vial.



Step 1.3
Inject the entire contents into the corresponding concentrate vial.
To limit foaming as much as possible when injecting the solvent, direct the needle onto the inside wall of the vial of concentrate solution and inject slowly.
Once reconstituted, the resultant solution contains 10 mg/ml of cabazitaxel.



Step 1.4
Remove the syringe and needle and mix manually and gently by repeated inversions until obtaining a clear and homogeneous solution. It could take approximately 45 seconds.



Step 1.5
Let the solution stand for approximately 5 minutes to allow any foam to dissipate and check the solution is homogenous and contains no visible particulate matter.
It is normal for foam to persist after this time period.

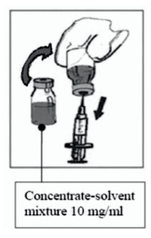
This resulting concentrate-solvent mixture contains 10 mg/ml of cabazitaxel (at least 6 ml deliverable volume). The second dilution should be done immediately (within 1 hour) as detailed in Step 2.

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

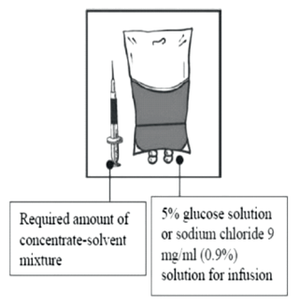
Step 2: Second (final) dilution for infusion

Step 2.1
Aseptically withdraw the required amount of concentrate-solvent mixture (10 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg CAZEXA would require 4.5 ml of the concentrate-solvent mixture prepared following Step 1.

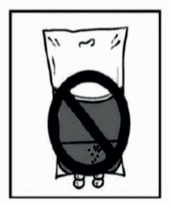
Since foam may persist on the wall of the vial of this solution, following its preparation described in Step 1, it is preferable to place the needle of the syringe in the middle when extracting.



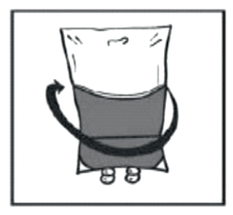
Step 2.2
Inject in a sterile PVC-free container of either 5% Dextrose solution or 0.9% Sodium Chloride solution. The concentration of the infusion solution should be between 0.10 mg/ml and 0.26 mg/ml.



Step 2.3
Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion.



Step 2.4
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 Shelf Life. 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 CAZEXA. CAZEXA 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.

PHARMACEUTICAL PARTICULARS
List of Excipients (Concentrate): Polysorbate 80 (Montanox80LPI), Nitrogen. *Composition of diluent:* Etahanol 96%, Water for injection & Nitrogen.

PACKAGING AVAILABLE:
Nature and Contents of Container

One pack contains one vial of concentrate and one vial of solvent:

Concentrate: Cabazitaxel Injection, 60mg/1.5ml in 15 mL clear tubular glass Type 1 with 20 mm grey rubber stopper and sealed with 20 mm purple colour flip off seals.

Solvent: Solvent for Cabazitaxel Injection in 15 mL clear tubular glass vial Type 1 with 20 mm rubber stopper and sealed with 20 mm purple colour flip off seals.

Secondary Packaging: One vial of cabazitaxel injection and one vial of solvent for cabazitaxel are placed in carton with package insert

STORAGE CONDITIONS
Unopened vials:
Store below 30°C. Do not refrigerate.

Re-constituted shelf-life
After opening:
The concentrate and solvent vials must be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After initial dilution of the concentrate with the solvent:
From a microbiological point of view, the concentrate-solvent mixture should be used immediately. 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 6 hours at 25°C (including the 1-hour infusion time) and for 24 hours at 2 – 8°C (including the 1-hour infusion time). From a microbiological point of view, the concentrate-solvent mixture 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 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions

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