ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

JEVTANA 60 mg concentrate and solvent for solution for infusion.

2. 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 JEVTANA 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.

Excipient with known effect
Each vial of solvent contains 573.3 mg of ethanol 96%.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The use of JEVTANA 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 JEVTANA 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 JEVTANA is 25 mg/m^2 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.

The treatment should be discontinued if a patient continues to experience any of these reactions at 20 mg/m^2.

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/m^2. 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/m^2. If the treatment is envisaged in patients with moderate hepatic impairment the dose of cabazitaxel should not exceed 15 mg/m^2. 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 (CL_{CR}< 15 mL/min/1.73 m^2), 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
The safety and the efficacy of JEVTANA in children and adolescents below 18 years of age have not been established. No data are available.

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.
JEVTANA must not be mixed with any other medicinal products than those mentioned in section 6.6.

4.3 Contraindications

- Hypersensitivity to cabazitaxel, to other taxanes, or polysorbate 80 or any excipients listed in section 6.1.
- Neutrophil counts less than 1,500/mm^3.
- 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 JEVTANA (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/mm^3 (see section 4.3).

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

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

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

Peripheral neuropathy
Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel. Patients under treatment with cabazitaxel should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Physicians should assess for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. The dose of cabazitaxel should be reduced from 25 mg/m^2 to 20 mg/m^2 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 JEVTANA 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
The solvent contains 573.3 mg ethanol 96% (15% v/v), equivalent to 14 ml of beer or 6 ml of wine. Harmful for those suffering from alcoholism.
To be taken into account in high-risk groups such as patients with liver disease, or epilepsy.

4.5 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 may influence 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 JEVTANA in combination with prednisone or prednisolone was evaluated in 371 patients with hormone refractory metastatic prostate cancer who were treated with 25 mg/m^2 cabazitaxel once every three weeks in a randomised open label, controlled phase III study. Patients received a median duration of 6 cycles of cabazitaxel.

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

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

Tabulated list of adverse reactions

Adverse reactions are listed in table 2 according to MedDRA system organ class and frequency categories. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Intensity of the adverse reactions is graded according to CTCAE 4.0 (grade ≥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 in the TROPIC study (n=371)

System Organ Class	**Adverse reaction**	**All grades n (%)**		**Grade≥3 n (%)**
		Very common	**Common**	
Infections and infestations	Septic shock		4 (1.1)	4 (1.1)
	Sepsis		4 (1.1)	4 (1.1)
	Cellulitis		6 (1.6)	2 (0.5)
	Urinary tract infection		27 (7.3)	4 (1.1)
	Influenza		11 (3)	0
	Cystitis		10 (2.7)	1 (0.3)
	Upper respiratory tract infection		10 (2.7)	0
	Herpes zoster		5 (1.3)	0
	Candidiasis		4 (1.1)	0
Blood and lymphatic system disorders	Neutropenia[a*]	347 (93.5)		303 (81.7)
	Anaemia [a]	361 (97.3)		39 (10.5)
	Leukopenia[a]	355 (95.7)		253 (68.2)
	Thrombocytopenia[a]	176 (47.4)		15 (4)
	Febrile neutropenia		28 (7.5)	28 (7.5)
Immune system disorders	Hypersensitivity		5 (1.3)	0
Metabolism and nutrition disorders	Anorexia	59 (15.9)		3 (0.8)
	Dehydration		18 (4.9)	8 (2.2)
	Hyperglycaemia		4 (1.1)	3 (0.8)
	Hypokalemia		4 (1.1)	2 (0.5)
Psychiatric disorders	Anxiety		11 (3)	0
	Confusional state		5 (1.3)	0
Nervous system disorders	Dysgeusia	41 (11.1)		0
	Neuropathy peripheral		30 (8.1)	2 (0.5)
	Peripheral sensory neuropathy		20 (5.4)	1 (0.3)
	Dizziness		30 (8.1)	0
	Headache		28 (7.5)	0
	Paraesthesia		17 (4.6)	0
	Lethargy		5 (1.3)	1 (0.3)
	Hypoaesthesia		5 (1.3)	0
	Sciatica		4 (1.1)	1 (0.3)

System Organ Class	Adverse reaction	All grades n (%)		Grade≥3 n (%)
		Very common	Common	
Eye disorders	Conjunctivitis		5 (1.3)	0
	Lacrimation increased		5 (1.3)	0
Ear and labyrinth disorders	Tinnitus		5 (1.3)	0
	Vertigo		5 (1.3)	0
Cardiac disorders*	Atrial fibrillation		4 (1.1)	2 (0.5)
	Tachycardia		6 (1.6)	0
Vascular disorders	Hypotension		20 (5.4)	2 (0.5)
	Deep vein thrombosis		8 (2.2)	7 (1.9)
	Hypertension		6 (1.6)	1 (0.3)
	Orthostatic hypotension		5 (1.3)	1 (0.3)
	Hot flush		5 (1.3)	0
	Flushing		4 (1.1)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	44 (11.9)		5 (1.3)
	Cough	40 (10.8)		0
	Oropharyngeal pain		13 (3.5)	0
	Pneumonia		9 (2.4)	6 (1.6)
Gastrointestinal disorders	Diarrhoea	173 (46.6)		23 (6.2)
	Nausea	127 (34.2)		7 (1.9)
	Vomiting	84 (22.6)		7 (1.9)
	Constipation	76 (20.5)		4 (1.1)
	Abdominal pain	43 (11.6)		7 (1.9)
	Dyspepsia		25 (6.7)	0
	Abdominal pain upper		20 (5.4)	0
	Haemorrhoids		14 (3.8)	0
	Gastroesophageal reflux disease		12 (3.2)	0
	Rectal haemorrhage		8 (2.2)	2 (0.5)
	Dry mouth		8 (2.2)	1 (0.3)
	Abdominal distension		5 (1.3)	1 (0.3)
Skin and subcutaneous tissue disorders	Alopecia	37 (10)		0
	Dry skin		9 (2.4)	0
	Erythema		5 (1.3)	0
Musculoskeletal and connective tissue disorders	Back pain	60 (16.2)		14 (3.8)
	Arthralgia	39 (10.5)		4 (1.1)
	Pain in extremity		30 (8.1)	6 (1.6)
	Muscle spasms		27 (7.3)	0
	Myalgia		14 (3.8)	1 (0.3)
	Musculoskeletal chest pain		11 (3)	1 (0.3)
	Flank pain		7 (1.9)	3 (0.8)
Renal and urinary disorders	Acute renal failure		8 (2.2)	6 (1.6)
	Renal failure		7 (1.9)	6 (1.6)
	Dysuria		25 (6.7)	0
	Renal colic		5 (1.3)	1 (0.3)
	Haematuria	62 (16.7)		7 (1.9)
	Pollakiuria		13 (3.5)	1 (0.3)

System Organ Class	Adverse reaction	All grades n (%)		Grade≥3 n (%)
		Very common	Common	
	Hydronephrosis		9 (2.4)	3 (0.8)
	Urinary retention		9 (2.4)	3 (0.8)
	Urinary incontinence		9 (2.4)	0
	Ureteric obstruction		7 (1.9)	5 (1.3)
Reproductive system and breast disorders	Pelvic pain		7 (1.9)	1 (0.3)
General disorders and administration site conditions	Fatigue	136 (36.7)		18 (4.9)
	Asthenia	76 (20.5)		17 (4.6)
	Pyrexia	45 (12.1)		4 (1.1)
	Peripheral oedema		34 (9.2)	2 (0.5)
	Mucosal inflammation		22 (5.9)	1 (0.3)
	Pain		20 (5.4)	4 (1.1)
	Chest pain		9 (2.4)	2 (0.5)
	Oedema		7 (1.9)	1 (0.3)
	Chills		6 (1.6)	0
	Malaise		5 (1.3)	0
Investigations	Weight decreased		32 (8.6)	0
	Aspartate aminotransferase increased		4 (1.1)	0
	Transaminases increased		4 (1.1)	0

[a] based on laboratory values
* see detailed section below

Description of selected adverse reactions

Neutropenia, and associated clinical events
Incidence of grade ≥3 neutropenia based on laboratory data was 81.7%. The incidence of grade ≥3 clinical neutropenia and febrile neutropenia adverse reactions were 21.3% and 7.5% respectively. Neutropenia was the most common adverse reaction leading to medicinal product discontinuation (2.4%).
Neutropenic complications included neutropenic infections (0.5%), neutropenic sepsis (0.8%), and septic shock (1.1%), which in some cases resulted in a fatal outcome.
The use of G-CSF has been shown to limit the incidence and severity of neutropenia (see sections 4.2 and 4.4).

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

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

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

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

Paediatric population
See section 4.2

Other special populations

Elderly population
Among the 371 patients treated with cabazitaxel in the prostate cancer study, 240 patients were 65 years or over including 70 patients older than 75 years.
The following adverse reactions reported at rates ≥5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40.4% versus 29.8%), clinical neutropenia (24.2% versus 17.6%), asthenia (23.8% versus 14.5%), pyrexia (14.6% versus 7.6%), dizziness (10.0% versus 4.6%), urinary tract infection (9.6% versus 3.1%) and dehydration (6.7% versus 1.5%), respectively.
The incidence of the following grade ≥3 adverse reactions were higher in patients ≥65 years of age compared to younger patients; neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinical neutropenia (23.8% versus 16.8%) and febrile neutropenia (8.3% versus 6.1%) (see sections 4.2 and 4.4).

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

4.9 Overdose

There is no known antidote to cabazitaxel. The anticipated complications of overdose would consist of exacerbation of adverse reactions as bone marrow suppression and gastrointestinal disorders.
In case of overdose, the patient should be kept in a specialised unit and closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Clinical efficacy and safety
The efficacy and safety of JEVTANA in combination with prednisone or prednisolone were evaluated in a randomised, open-label, international, multi-center, phase III study, in patients with hormone refractory metastatic prostate cancer previsouly 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 JEVTANA 25 mg/m^2 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/m^2 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 hormone refractory metastatic 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/mm^3, platelets >100,000/mm^3, 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 JEVTANA 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 JEVTANA 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 JEVTANA group and in the comparator group.

Overall survival was significant longer with JEVTANA 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).

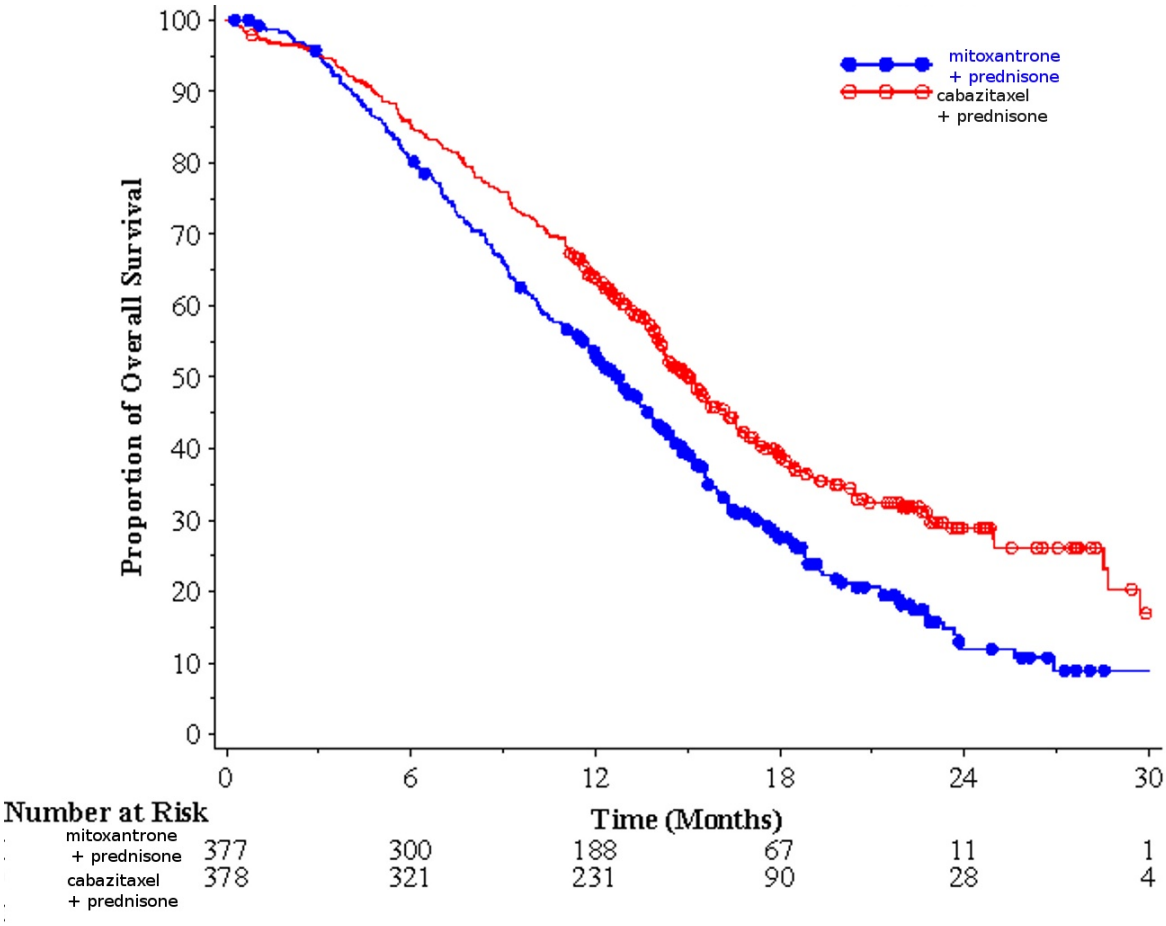
A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in JEVTANA arm, 30 patients in mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR (95%CI) 0.96 (0.49-1.86)).

Table 3 - Efficacy of JEVTANA in the treatment of patients with hormone refractory metastatic prostate cancer

	JEVTANA + 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	

[1]HR estimated using Cox model; a hazard ratio of less than 1 favours JEVTANA

Figure 1: Kaplan Meier overall survival curves



There was an improvement in PFS in the JEVTANA 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 JEVTANA 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 JEVTANA arm. There was a median PSA progression of 6.4 months (95%CI: 5.1-7.3) for patients in JEVTANA 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 JEVTANA 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.

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

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/m^2 weekly or every 3 weeks.

Absorption
After 1-hour intravenous administration at 25 mg/m^2 cabazitaxel in patients with metastatic prostate cancer (n=67), the C_{max} was 226 ng/ml (Coefficient of Variation (CV): 107%) and was reached at the end of the 1-hour infusion (T_{max}). The mean AUC was 991 ng.h/ml (CV: 34%).
No major deviation to the dose proportionality was observed from 10 to 30 mg/m² in patients with advanced solid tumours (n=126).

Distribution
The volume of distribution (V_{ss}) was 4870 l (2640 l/m² for a patient with a median BSA of 1.84 m²) at steady state.
In vitro, the binding of cabazitaxel to human serum proteins was 89-92% and was not saturable up to 50,000 ng/ml, which covers the maximum concentration observed in clinical studies. Cabazitaxel is mainly bound to human serum albumin (82.0%) and lipoproteins (87.9% for HDL, 69.8% for LDL, and 55.8% for VLDL). The *in vitro* blood-to-plasma concentration ratios in human blood ranged from 0.90 to 0.99 indicating that cabazitaxel was equally distributed between blood and plasma.

Biotransformation
Cabazitaxel is extensively metabolised in the liver (>95%), mainly by the CYP3A isoenzyme (80% to 90%). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued 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/m^2. 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 [^{14}C]-cabazitaxel at 25 mg/m^2 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 JEVTANA 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/m^2, 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). JEVTANA 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/m^2.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in dogs after single dose, 5-day and weekly administation 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 JEVTANA 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

Concentrate
Polysorbate 80
Citric acid

Solvent
Ethanol 96%
Water for injections

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 vials
3 years.

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
Chemical and physical in-use stability has been demonstrated for 1 hour at ambient temperature (15°C-30°C). 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 hour at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

After final dilution in the infusion bag/bottle
Chemical and physical stability of the infusion solution has been demonstrated for 8 hours at ambient temperature (including the 1-hour infusion time) and for 48 hours at refrigerated conditions (including the 1-hour infusion time).
From a microbiological point of view, the infusion solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hour at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Do not refrigerate.

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

6.5 Nature and contents of container

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

- Concentrate: 1.5 ml of concentrate in a 15 ml clear glass vial (type I) closed with a grey chlorobutyl rubber closure sealed by an aluminium cap covered with a light green plastic flip-off cap. Each vial contains 60 mg cabazitaxel per 1.5 ml nominal volume (fill volume: 73.2 mg of cabazitaxel/1.83 ml). This fill volume has been established during the development of JEVTANA to compensate for liquid loss during preparation of the premix. This overfill ensures that after dilution with the **entire** content of the accompanying solvent for JEVTANA, there is a minimal extractable premix volume of 6 ml containing 10 mg/ml JEVTANA which corresponds to the labelled amount of 60 mg per vial.
- Solvent: 4.5 ml of solvent in a 15 ml clear glass vial (type I) closed with a grey chlorobutyl rubber closure sealed by a gold colour aluminium cap covered with a colourless plastic flip-off cap. Each vial contains 4.5 ml nominal volume (fill volume: 5.67 ml). This fill volume has been established during the development and the overfill ensures, after the addition of the **entire** content of the solvent vial to the content of JEVTANA 60 mg concentrate vial, a concentration of the premix solution of 10 mg/ml JEVTANA.

6.6 Special precautions for disposal and other handling

JEVTANA 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 JEVTANA solutions, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures. If JEVTANA, 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. JEVTANA requires **TWO** dilutions prior to administration. Follow the preparation instructions provided below.

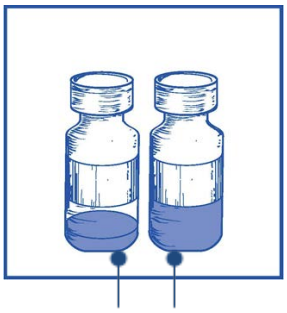
Note: Both the JEVTANA 60 mg/1.5 ml concentrate vial (fill volume: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (fill volume: 5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **ENTIRE** contents of the accompanying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

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

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

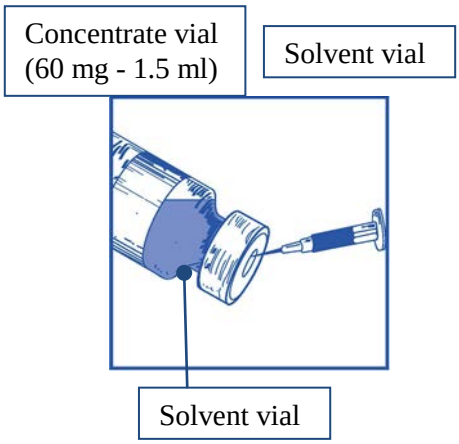
Step 1.1

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



Step 1.2

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

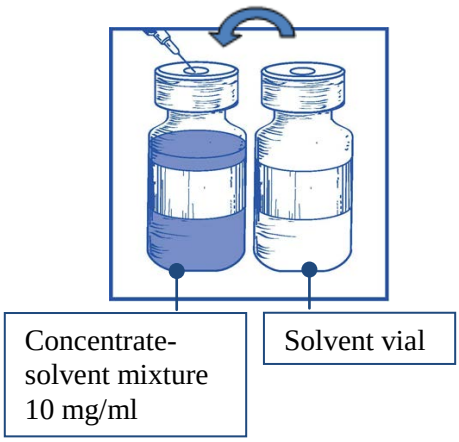


Step 1.3

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

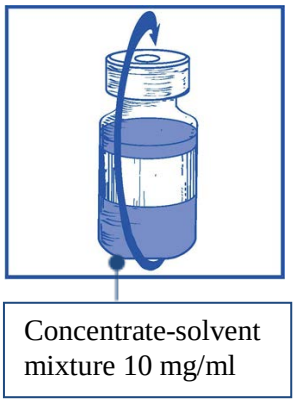
To limit foaming as much as possible when injecting the solvent, direct the needle onto the inside wall of the vial of concentrate solution and inject slowly.

Once reconstituted, the resultant solution contains 10 mg/ml of cabazitaxel.



Step 1.4

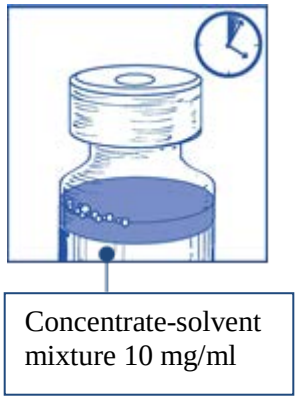
Remove the syringe and needle and mix manually and gently by repeated inversions until obtaining a clear and homogeneous solution. It could take approximately 45 seconds.



Step 1.5

Let this solution stand for approximately 5 minutes and check then that the solution is homogeneous and clear.

It is normal for foam to persist after this time period.



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

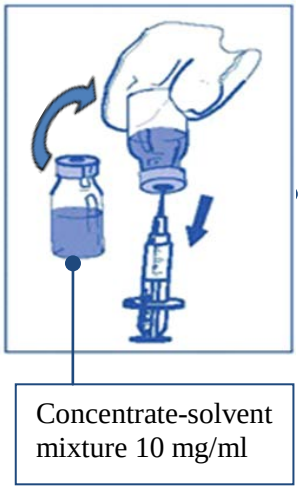
More than one vial of the concentrate-solvent mixture may be necessary to administer the prescribed dose.

<u>Step 2: Second (final) dilution for infusion</u>

Step 2.1

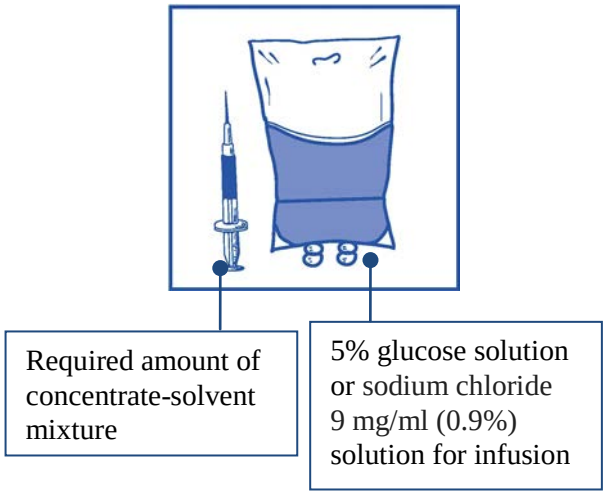
Aseptically withdraw the required amount of concentrate-solvent mixture (10 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 45 mg JEVTANA would require 4.5 ml of the concentrate-solvent mixture prepared following Step 1.

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



Step 2.2

Inject in a sterile PVC-free container of either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. The concentration of the infusion solution should be between 0.10 mg/ml and 0.26 mg/ml.



Step 2.3

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

Step 2.4

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

The infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned in section 6.3.
An in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) is recommended during administration.

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

JEVTANA 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

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/676/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 March 2011
Date of latest renewal: 19 November 2015

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
65926 Frankfurt am Main
Germany

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

JEVTANA 60 mg concentrate and solvent for solution for infusion
cabazitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml concentrate contains 40 mg cabazitaxel.
Each 1.5 ml vial of concentrate contains 60 mg cabazitaxel.
The concentrate vial (fill: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after **initial dilution with the ENTIRE content of the solvent vial**, the concentration of cabazitaxel is 10 mg/ml.

3. LIST OF EXCIPIENTS

Excipients
Concentrate vial: polysorbate 80 and citric acid;
Solvent vial: ethanol 96% and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate and solvent for solution for infusion.
1 vial of 1.5 ml concentrate and 1 vial of 4.5 ml solvent.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-use vials.

CAUTION: Two-step dilution required. Read the package leaflet before use.

For intravenous use (infusion) AFTER final dilution.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the diluted solution.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Do not refrigerate.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/676/001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL for CONCENTRATE

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

JEVTANA 60 mg sterile concentrate
cabazitaxel

2. METHOD OF ADMINISTRATION

Dilute with the ENTIRE supplied solvent.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 ml
10 mg/ml after first dilution.

6. OTHER

Solution for IV infusion after final dilution (see package leaflet).
Contains an overfill.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL for SOLVENT

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

SOLVENT for JEVTANA

2. METHOD OF ADMINISTRATION

Use the ENTIRE content for dilution (see package leaflet)**.**

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4.5 ml **(**ethanol 96% and water for injections**)**.

6. OTHER

This vial contains an overfill.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

JEVTANA 60 mg concentrate and solvent for solution for infusion
cabazitaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What JEVTANA is and what it is used for

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

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

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

2. What you need to know before you are given JEVTANA

Do not use JEVTANA if:

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

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

Warnings and precautions

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

Tell your doctor immediately if:
- you have fever. During treatment with JEVTANA, it is more likely that your white blood cell count may be reduced. Your doctor will monitor your blood and general condition for signs of

infections. He/she may give you other medicines to maintain the number of your blood cells. People with low blood counts can develop life-threatening infections. The earliest sign of infection may be fever, so if you experience fever, tell your doctor right away.

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

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

Other medicines and JEVTANA

Please tell your doctor, pharmacist or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription. This is because some medicines can affect the way JEVTANA works or JEVTANA can affect how other medicines work. These medicines include the following:
- ketoconazole, rifampicin (for infections);
- carbamazepine, phenobarbital or phenytoin (for seizures);
- St John's Wort (*Hypericum perforatum*) (herbal remedy for depression and other conditions);
- statins (such as simvastatin, lovastatin, atorvastatin, rosuvastatin, or pravastatin) (for reducing the cholesterol in your blood);
- valsartan (for hypertension);
- repaglinide (for diabetes).

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

Pregnancy, breast-feeding and fertility

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

JEVTANA should not be used during breast-feeding.

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

Driving and using machines

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

JEVTANA contains ethanol (alcohol)

This medicine contains 15% v/v ethanol (alcohol), equivalent to 14 ml of beer or 6 ml of wine. This medicine may be harmful for those suffering from alcoholism.

To be taken into account if you are in a high-risk group such as patients with liver disease, or epilepsy.

3. How to use JEVTANA

Instructions for use

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

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

How much and how often to have

- The usual dose depends on your body surface area. Your doctor will calculate your body surface area in square meters (m^2) and will decide the dose you should have.
- You will usually have an infusion once every 3 weeks.

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

4. Possible side effects

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

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

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

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

Other side effects include:

Very common (may affect more than 1 in 10 people):
- decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection)
- decrease in the number of platelets (which results in increased risk of bleeding)
- loss of appetite (anorexia)
- alteration in sense of taste
- shortness of breath
- cough
- stomach upsets including feeling sick (nausea), being sick (vomiting), diarrhoea or constipation
- abdominal pain
- short term hair loss (in most cases normal hair growth should return)
- back pain
- joint pain
- blood in the urine
- feeling tired, weak or lack of energy.

Common (may affect up to 1 in 10 people):
- urinary tract infection
- lack of white blood cells associated with fever and infection
- feeling of numbness, tingling, burning or decreased sensations in hands and feet
- dizziness
- headache
- decrease or increase in blood pressure
- uncomfortable feeling in the stomach, heart burn or belching
- stomach pain
- haemorrhoids
- muscle spasm
- painful or frequent urination
- urinary incontinence
- kidney disease or problems
- sore in the mouth or on lips
- infections or risk of infections
- high blood sugar
- low blood potassium
- mental confusion
- feeling anxious
- abnormal feeling or loss of sensation or pain in hands and feet
- ringing in the ear
- trouble with balance
- rapid or irregular heartbeat
- blood clot in the leg
- skin feeling hot or flushed
- pain in mouth or throat
- rectal bleeding
- redness of the skin
- muscle discomfort, aches or pain
- swelling of the feet or legs
- chills.

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

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

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

5. How to store JEVTANA

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

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

Do not store above 30°C. Do not refrigerate.

Information about storage and the time to use JEVTANA, once it has been diluted and is ready to use, are described in the section "PRACTICAL INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS ON PREPARATION, ADMINISTRATION AND HANDLING OF JEVTANA".

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

6. Contents of the pack and other information

What JEVTANA contains
The active substance is cabazitaxel. One ml of concentrate contains 40 mg cabazitaxel. Each vial of concentrate contains 60 mg cabazitaxel.
The other ingredients are polysorbate 80 and citric acid in the concentrate, and ethanol 96% and water for injections in the solvent (see section 2 "JEVTANA contains alcohol").
Note: Both the JEVTANA 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.

What JEVTANA looks like and contents of the pack
JEVTANA is a concentrate and solvent for solution for infusion (sterile concentrate).
The concentrate is a clear yellow to brownish-yellow oily solution.
The solvent is a clear and colourless solution.

One pack of JEVTANA contains:

- One single useclear glass vial, closed with a grey chlorobutyl rubber closure sealed by an aluminium cap with a light green plastic flip-off cover, containing 1.5 ml (nominal volume) concentrate.
- One single use clear glass vial, closed with a grey chlorobutyl rubber closure sealed by a gold colour aluminium cap with a colourless plastic flip-off cover, containing 4.5 ml (nominal volume) solvent.

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Manufacturer

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Other sources of information

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

The following information is intended for healthcare professionals only.

PRACTICAL INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS ON PREPARATION, ADMINISTRATION AND HANDLING OF JEVTANA 60 mg CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION

This information supplements sections 3 and 5 for the user.
It is important that you read the entire content of this procedure prior to the preparation of the infusion solution.

Incompatibilities

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

Shelf life and special precautions for storage

For the pack of JEVTANA 60 mg concentrate and solvent
Do not store above 30°C.
Do not refrigerate.

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. From a microbiological point of view, the two-step dilution process must take place in controlled and aseptic conditions (see below "Preparation and administration precautions").

After initial dilution of JEVTANA 60 mg concentrate with the **entire** contents of the solvent vial chemical and physical in-use stability has been demonstrated for 1 hour at ambient temperature.

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

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

Preparation and administration precautions

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

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

Always dilute the concentrate for solution for infusion with the **entire** supplied solvent before adding to infusion solutions.

Preparation steps

Read this **ENTIRE** section carefully before mixing and diluting. JEVTANA requires **TWO** dilutions prior to administration. Follow the preparation instructions provided below.

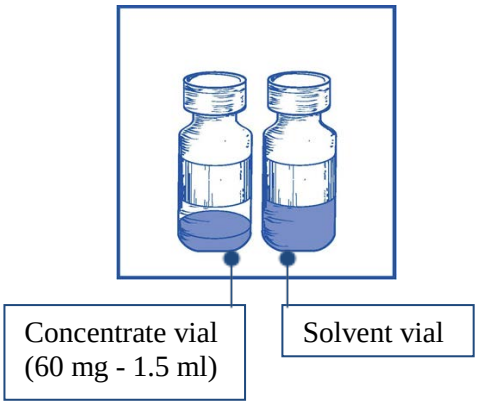
Note: Both the JEVTANA 60 mg/1.5 ml concentrate vial (fill volume: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (fill volume: 5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **ENTIRE** contents of the accompanying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

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

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

Step 1.1

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



Step 1.2

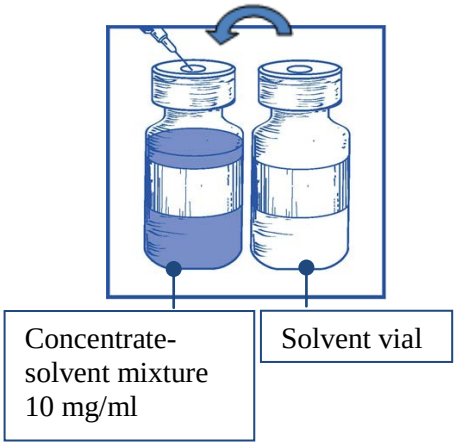
Using a syringe fitted with a needle, aseptically withdraw the **entire** contents of the supplied solvent by partially inverting the vial.

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.

Concentrate-solvent mixture 10 mg/ml

Step 1.5

Let this solution stand for approximately 5 minutes and check then that the solution is homogeneous and clear.

It is normal for foam to persist after this time period.

Concentrate-solvent mixture 10 mg/ml

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.

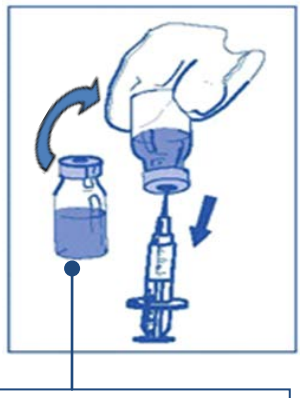
More than one vial of the concentrate-solvent mixture may be necessary to administer the prescribed dose.

<u>Step 2: Second (final) dilution for infusion</u>

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 JEVTANA would require 4.5 ml of the concentrate solvent mixture prepared following Step 1.

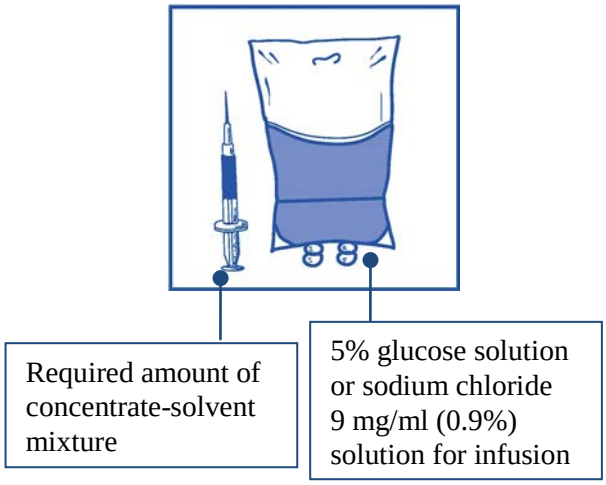
Since foam may persist on the wall of the vial of this solution, following its preparation described in Step 1, it is preferable to place the needle of the syringe in the middle when extracting.



Concentrate-solvent mixture 10 mg/ml

Step 2.2

Inject in a sterile PVC-free container of either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. The concentration of the infusion solution should be between 0.10 mg/ml and 0.26 mg/ml.



Step 2.3

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

Step 2.4

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 and special precautions for storage** above.

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

Method of administration

JEVTANA is administered as a 1 hour infusion.
An in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) is recommended during administration.
PVC infusion containers or polyurethane infusion sets should not be used for the preparation and administration of the infusion solution.