RANCANGAN LEAFLET/BROSUR

JEVTANA®
Cabazitaxel

SANOFI

QUALITATIVE AND QUANTITATIVE COMPOSITION
One ml of concentrate contains 40 mg cabazitaxel.
Each vial of 1.5 ml 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.
Excipients:
Each vial of solvent contains 573.3 mg of ethanol 96%.
For the full list of excipients, *see "List of excipients"*.

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.

CLINICAL PARTICULARS
Therapeutic indications
JEVTANA in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (see "Pharmacodynamic properties").
Due to high incidence of neutropenia, granulocyte-colony stimulating factor (G-CSF) should be administered within 24-72 hours since the first cycle of Jevtana administration.

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 "Special warnings and precautions for use"*).

Premedication
The recommended premedication regimen should be performed at least 30 minutes prior to each administration of JEVTANA with the following intravenous medicinal product 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 with
• H_2 antagonist (ranitidine or equivalent) (see "*Special warnings and precautions for use"*).

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.

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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 diarrhea despite appropriate treatment, including fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2.
Grade ≥2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2.

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.
No formal studies have been carried out in patients with hepatic impairment. As a precautionary measure, cabazitaxel should not be given to patients with hepatic impairment (bilirubin ≥1 x Upper Limit of Normal (ULN), or AST and/or ALT ≥1.5 x ULN) (see *"Contraindications"*, *"Special warnings and precautions for use"* and *"Pharmacokinetic properties"*).

Patients with renal impairment
Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance (CL_{CR}): 50 to 80 ml/min). Limited data are available for patients with moderate (CL_{CR}: 30 to 50 ml/min) and no data are available for patients with severe renal impairment (CL_{CR} <30 ml/min) or end stage renal disease; therefore, these patients should be treated with caution and monitored carefully during treatment (see *"Special warnings and precautions for use"* and *"Pharmacokinetic properties"*).
Elderly patients
No specific dose adjustment for the use of cabazitaxel in elderly patients is recommended (see *"Special warnings and precautions for use"*, *"Undesirable effects"*, *and "Pharmacokinetic properties"*).

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Concomitant medicinal products use
Concomitant medicinal products that are strong inducers or inhibitors of CYP3A should be avoided. (see *"Special warnings and precaution for use"* and *"Interaction with other medicinal products and other forms of interaction"*).

Paediatric population
The safety and the efficacy of JEVTANA in children and adolescents below 18 years of age have not been established.

Method of administration
For instructions on preparation and administration of the product, see *"Special precautions for disposal and other handling"*.
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 Special precautions for disposal and other handling.

Contraindications
- Hypersensitivity to cabazitaxel, to other taxanes, or to any excipients of the formulation including polysorbate 80.
- Neutrophil counts less than 1,500/mm^3.
- Hepatic impairment (bilirubin ≥ 1 × ULN, or AST and/or ALT ≥ 1.5 × ULN)
- Concomitant vaccination with yellow fever vaccine (see *"Interaction with other medicinal products and other forms of interaction"*).

Special warnings and precautions for use
Hypersensitivity reactions
All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel (see *"Posology and methode of administration"*).
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 *"Contraindications"*).

Bone marrow suppression
Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur (see *"Risk of neutropenia"* and *"Anaemia"* in section *"Special warnings and precautions for use"*).

Risk of neutropenia
Patients treated with cabazitaxel should 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). Due to high incidence of neutropenia, granulocyte-colony stimulating factor (G-CSF) should be administered within 24-72 hours since the first cycle of Jevtana administration. Patients who have high risk of increased complations from prolonged neutropenia are 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). The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

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Neutropenia is the most common adverse reaction of cabazitaxel (see *"Undesirable effects"*). 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 *"Posology and method of administration"*).
Patients should be re-treated only when neutrophils recover to a level ≥1,500/mm^3 (see *"Contraindications"*).

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 *"Posology and method of administration"*). 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 *"Undesirable effects"*). 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 *"Posology and method of administration"*).

Anaemia
Anaemia has been observed in patients receiving cabazitaxel (see section Undesirable effects). 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.

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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 renal failure ≥CTCAE 4.0 Grade 3.

Urinary disorders
Cystitis due to radiation recall phenomenon has been reported with cabazitaxel therapy in patients who have previously received pelvic radiation therapy and docetaxel containing regimen (see section Undesirable effect). Appropriate measures should be initiated. Interruption or discontinuation of cabazitaxel therapy may be necessary.

Respiratory disorders
Interstitial pneumonia/pneumonitis and interstitial lung disease have been reported and may be associated with fatal outcome (see *"Undesirable effects"*). 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 *"Undesirable effects"*).

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

Patients with liver impairment
Treatment with JEVTANA is contraindicated (see *"Posology and method of administration"* and *"Contraindications"*).

Interactions
Co-administration with strong CYP3A4 inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel (see *"Posology and method of administration" and "Interaction with other medicinal products and other forms of interaction*). 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 CYP3A4 inducers should be avoided since they may lead to decreased plasma concentrations of cabazitaxel (see *"Posology and method of administration"* and *"Interaction with other medicinal products and other forms of interaction"*).

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.

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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 *Pharmacokinetics*).

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 *Posology* and *Special Warning and Precautions for use*). 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 see sections *Posology* and *Special Warning and Precautions for use*).

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.

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 *"Preclinical safety data"*) and that cabazitaxel crosses the placenta barrier (see *"Preclinical safety data"*). 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.

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Lactation
Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk (see *"Preclinical safety data"*). 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 *"Preclinical safety data"*). 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.

Effects on ability to drive and use machines

Based on the safety profile, cabazitaxel may have 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.

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 JEVTANA.

The most commonly (≥10%) occurring adverse reactions in all grades were anaemia (97.3%), leukopenia (95.6%), neutropenia (93.5%), thrombocytopenia (47.4%), and diarrhoea (46.6%). The most commonly (≥5%) occurring grade ≥3 adverse reactions in the JEVTANA 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 JEVTANA. The most common adverse reactions leading to JEVTANA discontinuation was neutropenia.

Tabulated summary 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).

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

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

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	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)

System Organ Class	**Adverse reaction**	**All grades n (%)**		**Grade>3 n (%)**
		Very common	**Common**	
Skin and subcutaneous tissue disorders	Alopecia	37 (10)		0
	Dry skin		9 (2.4)	0
	Erythema		5 (1.3)	0
Musculoskeletal and connective tissue disorders	Back pain	60 (16.2)		14 (3.8)
	Arthralgia	39 (10.5)		4 (1.1)
	Pain in extremity		30 (8.1)	6 (1.6)
	Muscle spasms		27 (7.3)	0
	Myalgia		14 (3.8)	1 (0.3)
	Musculoskeletal chest pain		11 (3)	1 (0.3)
	Flank pain		7 (1.9)	3 (0.8)
Renal and urinary disorders	Acute renal failure		8 (2.2)	6 (1.6)
	Renal failure		7 (1.9)	6 (1.6)
	Dysuria		25 (6.7)	0
	Renal colic		5 (1.3)	1 (0.3)
	Haematuria	62 (16.7)		7 (1.9)
	Pollakiuria		13 (3.5)	1 (0.3)
	Hydronephrosis		9 (2.4)	3 (0.8)
	Urinary retention		9 (2.4)	3 (0.8)
	Urinary incontinence		9 (2.4)	0
	Ureteric obstruction		7 (1.9)	5 (1.3)
Reproductive system and breast disorders	Pelvic pain		7 (1.9)	1 (0.3)
General disorders and administration site conditions	Fatigue	136 (36.7)		18 (4.9)
	Asthenia	76 (20.5)		17 (4.6)
	Pyrexia	45 (12.1)		4 (1.1)
	Peripheral oedema		34 (9.2)	2 (0.5)

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	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 *"Posology and method of administration"* and *"Special warnings and precautions for use"*).

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

Haematuria
Haematuria all grades frequency was 20.8% at 25 mg/m2 in EFC11785 study (see section 5.1). Confounding causes such as disease progression, instrumentation, infection or anticoagulation/NSAID/aspirin therapy were identified in nearly two thirds of the cases.

Other laboratory abnormalities
The incidence of grade ≥3 anaemia, increased AST, ALT, and bilirubin based on laboratory abnormalities were 10.6%, 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 *"Special warnings and precautions for use")*.

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 *"Special warnings and precautions for use")*.

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Renal and urinary disorders
Cystitis due to radiation recall phenomenon, including haemorrhagic cystitis, were reported uncommonly. (see section *Special Warning and Precaution for use*)

Paediatric population
(see *"Posology and method of administration"*).

Other special populations

Elderly population
Among the 371 patients treated with JEVTANA 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 *"Posology and method of administration"* and *"Special warnings and precautions for use"*).

Overdose
There is no known antidote to JEVTANA. 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.

PHARMACOLOGICAL PROPERTIES
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

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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/mm3, haemoglobin >10 g/dL, creatinine <1.5 x ULN, total bilirubin <1 x ULN, AST and ALT <1.5 x ULN.

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

Demographics, including age, race, and ECOG performance status (0 to 2), were balanced between the treatment arms. In the JEVTANA group, the mean age was 68 years, range (46-92) and the racialdistribution 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/m^2 (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)).

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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 [1] (HR) (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

Figure1: Kaplan Meier overall survival curves

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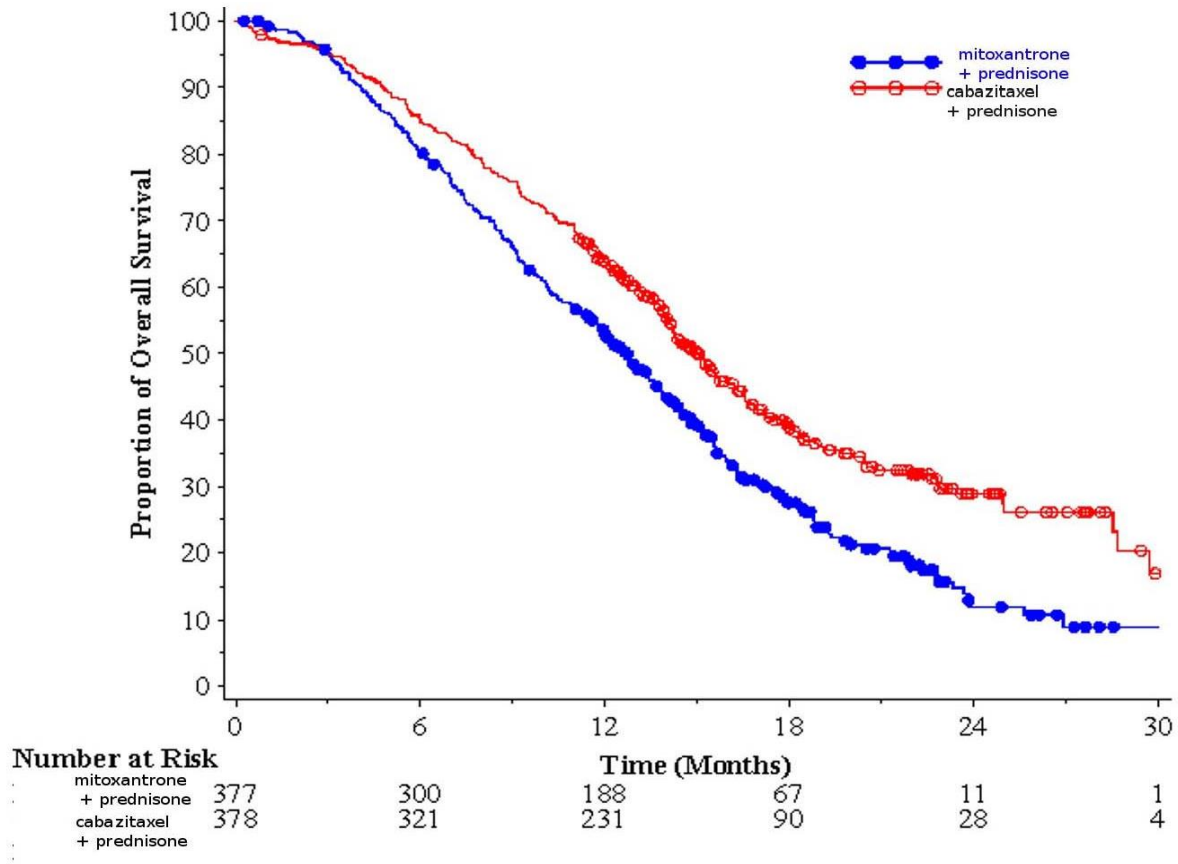

There was an improvement in PFS in the JEVTANA arm compared to mitoxantrone arm, 2.8 (2.4-3.0) months versus 1.4 (1.4-1.7) respectively, HR (95%CI) 0.74 (0.64-0.86), p<0.0001.

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.

Pediatric 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 *"Posology and method of administration"*).

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.

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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/m^2 in patients with advanced solid tumours (n=126).

Distribution
The volume of distribution (Vss) was 4870 l (2640 l/m^2 for a patient with a median BSA of 1.84 m^2) 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 CYP3A4 isoenzyme (80% to 90%). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued 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*. Potent CYP3A inductor or inhibitor could affect the plasma concentration of cabazitaxel, as cabazitaxel is mainly metabolised by CYP3A. Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.
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) and Breast-Cancer-Resistant-Proteins (BRCP) (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 *Interactions*)

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

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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/m^2 for a patient with a median BSA of 1.84 m^2) and a long terminal half-life of 95 hours.

Special populations
Elderly
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
No formal studies in patients with hepatic impairment have been conducted. However, as cabazitaxel is eliminated primarily via metabolism, increased exposure may be expected.

Renal impairment
Cabazitaxel is minimally excreted via the kidney (2.3% of the dose). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. 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.

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 *"Posology and method of administration"*).

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.

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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 *"Special precautions for disposal and other handling"* for disposal of unused product).

PHARMACEUTICAL PARTICULARS

List of excipients

Concentrate
Polysorbate 80
Citric acid
Solvent
Ethanol 96%
Water for injections

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section *"Special precautions for disposal and other handling"*.
PVC infusion containers and polyurethane infusion sets should not be used for the preparation and administration of the infusion solution.

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:

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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.
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.

Special precautions for storage
Do not store above 30ºC.
Do not refrigerate.
For storage conditions of the diluted medicinal product, see section *"Shelf Life"*.

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.

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 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

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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.

- Set aside the JEVTANA concentrate vial (fill volume: 1.83 ml) and the supplied solvent (fill volume: 5.67 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.
- Withdraw the entire content of the supplied solvent using a syringe, by partially inverting the vial, and inject it into the corresponding vial of JEVTANA concentrate. 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.
- 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.
- Let this solution stand for approximately 5 minutes and then check 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). It should be immediately diluted (within 1 hour) as detailed in step 2.

Step 2: Preparation of the infusion solution.

- Based on the required dose for the patient, withdraw the corresponding volume of the concentrate-solvent mixture containing 10 mg/ml of JEVTANA, with a graduated syringe. As an example, a dose of 45 mg JEVTANA would require 4.5 ml of the concentrate-solvent mixture prepared following step 1. More than one vial of the concentrate-solvent mixture may be necessary for preparing the appropriate dose.
- 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.
- Use PVC-free infusion containers and inject the withdrawn volume into 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.
- Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion.

The JEVTANA infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned in section *"Shelf Life"*. 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.
An in-line filter of 0.22 micrometer nominal pore size is recommended during administration.

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

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

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

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

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