PRODUCT INFORMATION

JEVTANA®

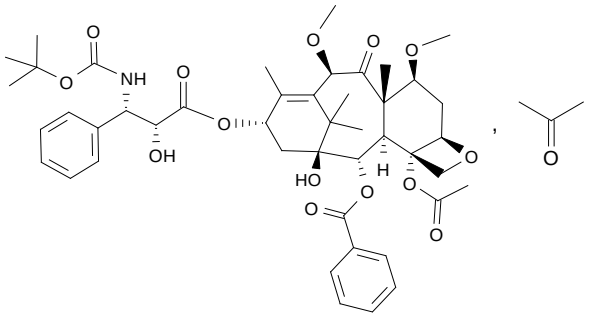
NAME OF THE MEDICINE

Non-proprietary Name

Cabazitaxel

Chemical Structure

The chemical structure of cabazitaxel is:



DESCRIPTION

Cabazitaxel belongs to the taxanes class. It is prepared by semi synthesis with a precursor extracted from yew needles.

Chemical name of cabazitaxel is (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate - propan-2-one (1:1).

Cabazitaxel is a white to off-white powder with a molecular formula of $C_{45}H_{57}NO_{14},C_3H_6O$ and a molecular weight of 894.01 (for the acetone solvate) / 835.93 (for the solvent free). It is lipophilic, practically insoluble in water and soluble in alcohol.

Jevtana (cabazitaxel) 60 mg/1.5 mL concentrate is a sterile, non-pyrogenic, clear yellow to brownish-yellow viscous solution and is available in single-use vials containing 60 mg (1.5 mL) cabazitaxel and 1.56 g polysorbate 80.

Each mL of concentrate contains 40 mg cabazitaxel (anhydrous), 1.04 g polysorbate 80 and citric acid.

Diluent for Jevtana is a clear, colourless, sterile, and non-pyrogenic, solution containing 13% (w/w) ethanol in water for injection, 4.5 mL.

Pharmacology

Class

Antineoplastic agent

ATC code: L01CD04

Site and Mode 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.

Pharmacodynamics

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

Pharmacokinetics

A population pharmacokinetic analysis was carried out in 170 patients including patients with advanced solid tumours (n=69), metastatic breast cancer (n=34) and metastatic prostate cancer (n=67). These patients received doses of cabazitaxel ranging from 10 to 30 mg/m^2 weekly or every 3 weeks.

Absorption

After a 1-hour IV administration dose of cabazitaxel at 25 mg/m^2, in patients with metastatic prostate cancer (n=67), the mean 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% to 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 (82.1%) 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.

Metabolism

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 from O-demethylation), with the main one accounting for approximately 5% of the 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 drugs that are mainly substrates of CYP3A. However, there is no potential risk of inhibition of drugs 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 drugs that are substrates of CYP1A, CYP2C9, and CYP3A.

Potent CYP3A inducers or inhibitors could affect cabazitaxel, as cabazitaxel is mainly metabolised by CYP3A.

Excretion

After a 1-hour IV 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 drug in urine).

Cabazitaxel has 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.

Cabazitaxel is minimally excreted via the kidney (2.3% of the dose excreted as the unchanged drug). 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 (see DOSAGE AND ADMINISTRATION and PRECAUTIONS sections).

Hepatic impairment

Cabazitaxel is eliminated primarily via hepatic 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 cabazitaxel dose (MTD) was 20 and 15 mg/m^2, respectively. In 3 patients with severe hepatic impairment (total bilirubin > 3 x 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 DOSAGE AND ADMINISTRATION). Cabazitaxel is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

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) and severe (9) renal impairment, who received several cycles of cabazitaxel in single IV infusion up to 25 mg/m^2.

CLINICAL TRIALS

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

Overall survival (OS) was the primary efficacy end-point of the study. Secondary endpoints included Progression Free Survival [PFS (defined as time from randomisation 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 randomized 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 with metastatic castration resistant prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Patients had to have neutrophils >1.5 cells x 10^9/L, platelets >100 cells x 10^9/L, haemoglobin >100 g/L, creatinine <1.5 x ULN, total bilirubin <1 x ULN, AST/SGOT <1.5 ULN, and ALT/SGPT <1.5 ULN.

Patients with a history of congestive heart failure, or myocardial infarction within the 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 to 92) and the racial distribution was 83.9% Caucasian, 6.9% Asian, 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 29.4% in the Jevtana group and 13.5% in the comparator group.

Overall survival was significantly longer with Jevtana compared to mitoxantrone (15.1 months versus 12.7 months, respectively), with a 30% reduction in the risk of death compared to mitoxantrone (see Table Table 1 and Figure 1).

Table 1 - Efficacy of Jevtana in EFC6193 study in the treatment of patients with metastatic castration resistant prostate cancer (Intent-to-treat analysis) – Primary Endpoint

	Jevtana + prednisone	**mitoxantrone + prednisone**
	n=378	**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 (EFC6193)

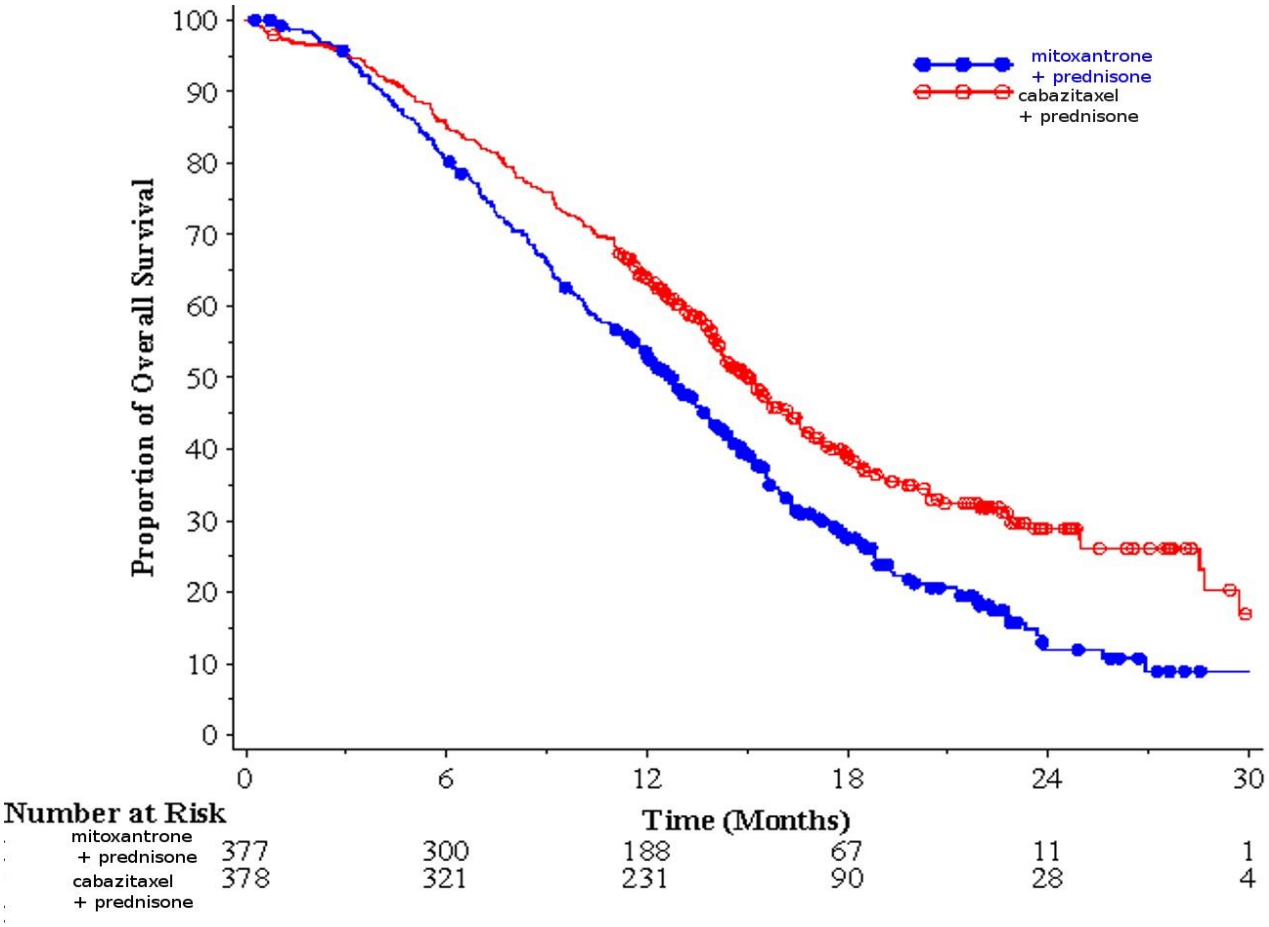


Table 2 - Efficacy of Jevtana in the treatment of patients with hormone refractory metastatic prostate cancer (Intent-to-treat analysis) – Secondary Endpoints

	Jevtana + prednisone n=378	**Mitoxantrone + prednisone n=377**	**Hazard Ratio[3] [95% CI] or p-value of diff[4]**
PFS median mths	2.8	1.4	0.74 [0.64-0.86]
Overall Tumour Response [1]	14.4% n=201	4.4% n=204	p=0.0005
PSA Progression median mths	6.4	3.1	0.75 [0.63-0.90]
PSA Response[2]	39.2% n=329	17.8% n=325	p=0.0002

[1] Investigator-assessed in subjects with measurable disease. [2] Assessed in subjects with PSA > 20 ng/mL at baseline. [3] Cox model. [4] X^2 test.

There were no significant differences in pain progression or pain response between treatments.

In a non-inferiority, multicentre, multinational, randomised, open label phase III study (EFC11785 study), 1200 patients with metastatic castration resistant prostate cancer, previously treated with a docetaxel containing regimen, were randomized to receive either cabazitaxel 25 mg/m^2 (n=602) or 20 mg/m^2 (n=598) dose. Overall survival (OS) was the primary efficacy end-point.

The study met its primary objective of demonstrating the non-inferiority of cabazitaxel 20 mg/m^2 in comparison with 25 mg/m^2 (see table 3). A statistically significantly higher percentage (p<0.001) of patients showed a PSA response in the 25 mg/m^2 group (42.9%) compared to the 20 mg/m^2 group (29.5%). A statistically significantly higher risk of PSA progression in patients with the 20 mg/m^2 dose with respect to the 25 mg/m^2 dose was observed (HR 1.195 ; 95%CI: 1.025 to 1.393). There was no statistically difference with regards to the other secondary endpoints (PFS, tumour and pain response, tumour and pain progression, and four subcategories of FACT-P).

Table 3 - Overall survival in EFC11785 study comparing cabazitaxel 25 mg/m^2 arm versus cabazitaxel 20 mg/m^2 arm (Intent-to–treat analysis) – Efficacy primary endpoint

	CBZ20+PRED n=598	CBZ25+PRED n=602

Overall Survival		
Number of deaths, n (%) 497 (83.1 %) 501 (83.2%)	497 (83.1 %)	501 (83.2%)
Median survival (95% CI) (months)	13.4 (12.19 to 14.88)	14.5 (13.47 to 15.28)
Hazard Ratio[b]		
Versus CBZ25+PRED	1.024	-
1-sided 98.89% UCI	1.184	-
1-sided 95% LCI	0.922	-

CBZ20=Cabazitaxel 20 mg/m^2, CBZ25=Cabazitaxel 25 mg/m^2, PRED=Prednisone/Prednisolone
CI=confidence interval, LCI=lower bound of the confidence interval, UCI=upper bound of the confidence interval
a Refer to Kaplan-Meier curve
b Hazard ratio is estimated using a Cox Proportional Hazards regression model. A hazard ratio < 1 indicates a lower risk of Cabazitaxel 20 mg/m^2 with respect to 25 mg/m^2.

EFC11785 study demonstrated a better safety profile for the cabazitaxel 20 mg/m^2 dose. The safety profile of cabazitaxel 25 mg/m^2 observed in this study was qualitatively and quantitatively similar to that observed in the study EFC6193. The patients in the 20 mg/m^2 group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m^2 group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m^2 group, 128 patients (21.5%) had a dose reduced from 25 to 20 mg/m^2, 19 patients (3.2%) had a dose reduced from 20 to 15 mg/m^2 and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m^2. In the 20 mg/m^2 group, 58 patients (10.0%) had a dose reduced from 20 to 15 mg/m^2 and 9 patients (1.6%) had a dose reduced from 15 to 12 mg/m^2. All grade adverse reactions with an incidence higher than 10% were higher in patients treated at 25 mg/m^2 than in patients treated at 20 mg/m^2.

Table 4 - All grade adverse reactions with an incidence higher than 10% in patients treated with 25 mg/m^2 versus 20 mg/m^2

Adverse reactions	Patients treated at 25 mg/m^2	Patients treated at 20 mg/m^2
Diarrhoea	39.8%	30.7%
Nausea	32.1%	24.5%
Fatigue	27.1%	24.7%
Haematuria	20.8%	14.1%
Asthenia	19.7%	15.3%
Decreased appetite	18.5%	13.1%
Vomiting	18.2%	14.5%
Constipation	18.0%	17.6%
Back pain	13.9%	11.0%
Clinical neutropenia	10.9%	3.1%
Urinary tract infection	10.8%	6.9%
Peripheral sensory neuropathy	10.6%	6.6%
Dysgeusia	10.6%	7.1%

Grade ≥ 3 adverse reactions with an incidence higher than 5% were observed in patients treated at 25 mg/m^2 only.

Table 5 - Grade ≥ 3 adverse reactions with an incidence higher than 5% in patients treated with 25 mg/m^2 versus 20 mg/m^2

Adverse reactions	Patients treated at 25 mg/m^2	Patients treated at 20 mg/m^2
Clinical neutropenia	9.6%	2.4%
Febrile neutropenia	9.2%	2.1%

There were fewer reported hematology abnormalities for patients treated at 20 mg/m^2 compared with patients treated at 25 mg/m^2 based on laboratory values:

Table 6 - Haematology abnormalities for patients treated at 20 mg/m^2 compared with patients treated at 25 mg/m^2

Adverse reactions	Patients treated at 25 mg/m^2	Patients treated at 20 mg/m^2
Grade ≥ 3 neutropenia	73.3%	41.8%
Grade ≥ 3 anaemia,	13.7%	9.9%
Grade ≥ 3 thrombocytopenia	4.2%	2.6%

INDICATIONS

Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen.

CONTRAINDICATIONS

- History of severe hypersensitivity reactions to cabazitaxel, any of the excipients of cabazitaxel or other drugs formulated with polysorbate 80
- neutrophil counts ≤1,500/mm^3
- severe hepatic impairment (total bilirubin > 3 x ULN)
- pregnancy and breast-feeding
- concomitant vaccination with yellow fever vaccine (see PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES)

PRECAUTIONS

Bone marrow suppression

Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia or pancytopenia may occur, (see additional information in the Neutropenia and Anaemia precautions below).

Neutropenia

Neutropenic deaths have been reported with cabazitaxel. Neutropenia is the most common adverse reaction of cabazitaxel (see ADVERSE EFFECTS section). Monitoring of complete blood count is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed (see DOSAGE AND ADMINISTRATION section).

Dose reduction is recommended in the case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see DOSAGE AND ADMINISTRATION section).

Restart treatment only when neutrophils recover to a level >1.5 cells x 10^9/L (see CONTRAINDICATIONS section).

The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

Patients treated with cabazitaxel may receive prophylactic G-CSF as per American Society of Clinical Oncology (ASCO) 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.

Hypersensitivity reactions

All patients should be premedicated prior to the initiation of the infusion of cabazitaxel (see DOSAGE AND ADMINISTRATION section).

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 who have a history of severe hypersensitivity reactions should not be rechallenged with cabazitaxel (see CONTRAINDICATIONS section).

Gastrointestinal symptoms

Nausea, vomiting and severe diarrhoea may occur. A death related to diarrhoea and electrolyte imbalance occurred with cabazitaxel in the efficacy trial. Intensive measures may be required for severe diarrhoea and electrolyte imbalance. Patients should be treated with rehydration, anti-diarrhoeal or anti-emetic medications as needed. Monitor and correct serum electrolyte levels particularly potassium. Delay in cabazitaxel treatment or reduction in dose may be necessary if patients experience Grade ≥ 3 diarrhoea (see DOSAGE AND ADMINISTRATION). Diarrhoea can also occur more frequently in patients who have received prior abdomino-pelvic irradiation. Dehydration is more common in patients aged 65 or older.

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

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

Peripheral Neuropathy

Cases of peripheral neuropathy, both sensory (e.g. paraesthesia, dysaesthesia) and motor, have been observed in patients treated with cabazitaxel. Patients should be advised to consult their doctor prior to continuing treatment if neuropathy symptoms such as pain, burning, tingling, numbness or weakness develop. Physicians should assess patients for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. For persistent Grade ≥2 peripheral neuropathy, the dose of cabazitaxel should be reduced (see DOSAGE AND ADMINISTRATION).

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 ADVERSE EFFECTS). Appropriate measures should be initiated. Interruption or discontinuation of cabazitaxel therapy may be necessary.

Renal Disorders

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. Ensure adequate hydration throughout treatment with cabazitaxel. Advise the patient to report any significant change in daily urine volume immediately. Measure serum creatinine at baseline, with each blood count and whenever the patient reports a change in urinary output. Discontinue cabazitaxel in case of renal failure ≥ Grade 3.

Respiratory disorders

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome (see ADVERSE 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 improve the condition. The benefit of resuming cabazitaxel treatment must be carefully evaluated.

Eye disorders

Subcapsular lens fibre swelling/degeneration was observed in rats during a 10-cycle toxicity study at 10mg/kg (60mg/m^2 [approximately 2-fold the AUC in cancer patients at the recommended human dose]). The No-Observable Effect Level for microscopic lens findings was 5 mg/kg (30 mg/m^2 [approximately the AUC in cancer patients at the recommended human dose]). The clinical relevance of these findings is unknown. Adverse reactions were not observed in clinical studies.

Anaemia

Anaemia has been observed in patients receiving cabazitaxel (see ADVERSE 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 <100 g/L and appropriate measures should be taken as clinically indicated.

Risk of cardiac arrhythmias

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

Driving a Vehicle or Performing Other Hazardous Tasks

No studies on the effects on the ability to drive and use machines have been performed. However, 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 to not drive or use machines if they experience these adverse reactions during treatment.

Effects on Fertility

The effect of cabazitaxel on human fertility is unknown. Cabazitaxel did not affect mating performances or fertility of male or female rats at intravenous cabazitaxel doses of up to 0.2 mg/kg/day (resulting in AUCs below those in patients at the recommended dose). However, in multi-cycle toxicity studies following the clinically recommended dosing schedule in rats and dogs, the male reproductive system was identified as a target organ in both species and the female reproductive system was identified as a target organ in rats. Toxic effects, including seminiferous tubular atrophy and degeneration of seminal vesicles in males, and atrophy of the uterus and necrosis of corpora lutea in females, were observed at exposures (AUC) similar to or less than the AUC in patients at the recommended dose.

Animal studies showed that cabazitaxel affected the reproductive system in male rats and dogs without any functional effect on fertility. 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.

Use in Pregnancy

Category D

Cabazitaxel is not recommended during pregnancy.

Due to potential exposure via seminal liquid, men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of cabazitaxel.

There are no adequate and well-controlled studies in pregnant women using cabazitaxel. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with cabazitaxel.

Studies in rats have shown that cabazitaxel crosses the placenta barrier. When female rats were given cabazitaxel intravenously once daily during the period of organogenesis embryofoetal toxicity was observed at a dose of 0.16 mg/kg/day, (resulting in exposures (AUC) well below those in patients at the recommended dose) consisting of foetal deaths and decreased mean foetal weight associated with a delay in skeletal ossification. Similar findings have been reported with docetaxel or paclitaxel.

Cabazitaxel did not produce foetal abnormalities in rats and rabbits.

Use in Lactation

Cabazitaxel should not be used during breast-feeding.

Data in rats have shown excretion of cabazitaxel and/or its metabolites in milk.

Paediatric Use

The safety and the efficacy of cabazitaxel in children have not been established.

Use in the Elderly

Elderly patients (≥65 years of age) may be more likely to experience certain adverse reactions including neutropenia or febrile neutropenia with cabazitaxel (see ADVERSE EFFECTS).

In the randomized clinical trial, 3 of 131 (2%) patients < 65 years of age and 15 of 240 (6%) ≥ 65 years of age died of causes other than disease progression within 30 days of the last cabazitaxel dose.

In the population pharmacokinetic analysis in 70 patients of 65 years and older (57 from 65 to 75 and 13 ≥75), there was no age effect on the pharmacokinetics of Jevtana. No specific dose adjustment is recommended in the elderly.

Patients with Hepatic Impairment

Cabazitaxel is contraindicated in patients with severe hepatic impairment [total bilirubin > 3 Upper limit of Normal (ULN)] (see CONTRAINDICATIONS).

Cabazitaxel is extensively metabolised by the liver. 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 DOSAGE AND ADMINISTRATION, Pharmacokinetics).

Bile ductule hyperplasia, arteriolar/periarteriolar necrosis, and/or hepatocellular necrosis were observed in dogs after a single dose (0.25 mg/kg [5 mg/m^2]) 5-day (0.2 mg/kg [4 mg/m^2]) and weekly (0.325 mg/kg [6.5 mg/m^2]) administration. Kupffer cell pigmentation and bile duct degeneration/regeneration were observed in the liver at the highest tested dose of 10 mg/kg (60 mg/m^2) in a 10-cycle study in rats.

Patients with Renal impairment

Cabazitaxel is minimally excreted via the kidney (2.3% of the dose excreted as the unchanged drug). 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 (see DOSAGE AND ADMINISTRATION and Pharmacokinetics sections).

Carcinogenicity

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Jevtana.

Genotoxicity

Jevtana was negative in the bacterial reverse mutation (Ames) test. Jevtana was not clastogenic in an *in vitro* test in human lymphocytes (no induction of structural chromosomal aberrations) but it increased number of polyploid cells and it induced an increase of micronuclei in the *in vivo* micronucleus test in rats. However, these genotoxicity findings are inherent to the pharmacological activity of the compound (inhibition of tubulin depolymerisation) and have been observed with other compounds with the same pharmacological activity.

INTERACTIONS WITH OTHER MEDICINES

No formal clinical drug-drug interaction studies have been performed.

In vitro studies have shown that cabazitaxel is mainly metabolized through CYP3A (80% to 90%).

CYP3A Inhibitors: Though no formal drug interaction trials have been conducted for cabazitaxel, concomitant administration of potent CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) is expected to increase concentrations of cabazitaxel. Therefore, co administration with potent CYP3A inhibitors should be avoided.

If co-administration with a potent CYP3A inhibitor cannot be avoided, close monitoring for toxicity and a cabazitaxel dose reduction should be considered. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

CYP3A Inducers: Though no formal drug interaction trials have been conducted for cabazitaxel, the concomitant administration of CYP3A inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) is expected to decrease cabazitaxel concentrations. Therefore, co-administration with CYP3A inducers should be avoided (see Pharmacokinetics). In addition, patients should also refrain from taking St. John's Wort.

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, and may lead to an increase of exposure of OATP1B1 substrates.

Prednisone/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. Cabazitaxel inhibited the transport of P-glycoprotein (P-gp) (digoxin, vinblastine) and Breast Cancer Resistant Proteins (BRCP) (methotrexate), at concentrations at least 37 fold what is observed in clinical settings. Therefore the risk of interaction, with MRP, P-gp and BCRP substrates, is unlikely *in vivo* at the dose of 20 or 25 mg/m^2.

Vaccinations: Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapy may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving cabazitaxel (see CONTRAINDICATIONS). Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

ADVERSE EFFECTS

The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating is used, when applicable:

Very common ≥10%

Common ≥1 and <10%

Uncommon ≥0.1 and <1%

Rare ≥0.01 and <0.1%

Very rare <0.01%, not known (cannot be estimated from the available data)

The safety of Jevtana in combination with prednisone or prednisolone was evaluated in 371 patients with metastatic castration resistant prostate cancer, in a randomised open label, controlled phase III study (TROPIC). Patients received a median of 6 cycles of Jevtana or 4 of mitoxantrone.

The most commonly (≥5%) occurring Grade ≥3 adverse reactions in the Jevtana group were neutropenia (81.7%), febrile neutropenia (7.5%), diarrhoea (6.2%), leukopenia (68.2%) and anaemia (10.5%).

Discontinuation of treatment due to adverse drug reactions occurred in 68 patients (18.3%) in the cabazitaxel group and 31 patients (8.4%) in the mitoxantrone group. The most common adverse reaction leading to treatment discontinuation in the Jevtana group was neutropenia.

Table 7 - 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)
	Hypokalaemia		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)

System Organ Class	Adverse Reaction	All Grades n (%)		Grade≥3 n (%)
		Very common	Common	
	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)

[a] based on laboratory values

Neutropenia and associated clinical events:

Incidence of Grade ≥3 neutropenia based on laboratory data was 81.7%. The incidence of clinical neutropenia and febrile neutropenia adverse reactions were 21.3% and 7.5%, respectively. Neutropenia was the most common adverse reaction leading to drug 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 PRECAUTIONS section).

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, however an indirect relationship cannot be ruled out (e.g. electrolyte imbalance).

Renal and urinary tract disorders

Renal failure was observed at 2.2% in all grades and 1.6% in grades ≥3 in the Jevtana arm. Haematuria all grades was observed at 20.8% in EFC11785 study (see Clinical trial). 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/SGOT, increased ALT/SGPT, and increased bilirubin based on laboratory abnormalities were 10.6%, 0.9%, 1.1%, and 0.6%, respectively.

Post Marketing Experience

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made:

Gastrointestinal disorders:

Colitis, enterocolitis, gastritis, neutropenic enterocolitis have been observed. Gastrointestinal haemorrhage and perforation, ileus and intestinal obstruction have also been reported.

Respiratory disorders:

Cases of interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome, including cases with fatal outcomes have been reported (see PRECAUTIONS).

Renal and urinary disorders

Cystitis due to radiation recall phenomenon was reported uncommonly. (see PRECAUTIONS)

Elderly population:

Of 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 were: fatigue (40.4% vs. 29.8%), clinical neutropenia (24.2% vs. 17.6%), asthenia (23.8% vs. 14.5%), pyrexia (14.6% vs. 7.6%), dizziness (10.0% vs. 4.6%), urinary tract infection (9.6% vs 3.1%) and dehydration (6.7% vs. 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% vs. 73.3%), clinical neutropenia (23.8% vs. 16.8%) and febrile neutropenia (8.3% vs. 6.1%) (see PRECAUTIONS and Use in Elderly). Of the 595 patients treated with cabazitaxel 25 mg/m^2 in the prostate cancer EFC 11785 study, 420 patients were 65 years or over. The adverse reactions reported at rates of at least 5% higher in patients 65 years of age or greater compared to younger patients were diarrhoea (42.9% vs. 32.6%), fatigue (30.2% vs. 19.4%), asthenia (22.4% vs. 13.1%), constipation (20.2% vs. 12.6%), clinical neutropenia (12.9% vs. 6.3%), febrile neutropenia (11.2% vs. 4.6%) and dyspnoea (9.5% vs. 3.4%)

DOSAGE AND 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.

Do not use PVC infusion containers (bags or bottles) for the preparation of the infusion solution.

Do not use polyurethane infusion sets (tubing, filter, pumps) for the administration of the infusion solution.

Premedication

Premedicate at least 30 minutes prior to each administration of Jevtana with the following intravenous medications to reduce the risk and severity of a hypersensitivity reaction:

antihistamine (equivalent to dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),

corticosteroid (dexamethasone 8 mg or equivalent) and with

H_2 antagonist (ranitidine or equivalent).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed (see PRECAUTIONS section).

Preparation Process

As for any other antineoplastic agent, caution should be exercised when handling and preparing Jevtana solutions. The use of gloves is recommended.

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. Jevtana is for single use in one patient only. Discard any residue.

Read this ENTIRE section carefully before mixing and diluting. Jevtana requires a TWO step dilution process prior to administration. Follow the preparation instructions provided below. Note: Both the Jevtana concentrate vial and the diluent vial contain an overfill to compensate for liquid loss during preparation. The overfill ensures that the pre-mix concentration will be 10mg/mL Jevtana provided that the ENTIRE contents of the diluent are transferred into the Jevtana concentrate vial.

The following 2-step dilution process must be carried out in an aseptic manner for preparing the solution for infusion:

Step 1: Preparation of pre-mix (Initial dilution of Jevtana 60 mg/1.5 mL concentrate with the supplied diluent)

Inspect the Jevtana 60 mg/1.5 mL concentrate vial and the supplied diluent. The concentrate solution should be clear (see PRESENTATION AND STORAGE SECTION).

Withdraw the ENTIRE content of the supplied diluent using a syringe, by partially inverting the vial, and inject it into the corresponding Jevtana 60 mg/1.5 mL concentrate vial. To limit foaming as much as possible when injecting the diluent, direct the needle onto the inside wall of the vial of concentrate and inject slowly.

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

Let the 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 pre-mix (concentrate-diluent mixture) contains 10 mg/mL of cabazitaxel (at least 6 mL deliverable volume). It should be immediately diluted as detailed in step 2.

Unused pre-mix should be discarded.

Step 2: Preparation of the infusion solution

Withdraw the required amount of initial diluted (pre-mix) Jevtana solution (10 mg/mL of cabazitaxel), with a graduated syringe and inject into a sterile PVC-free container (bags or bottles) of either 5% glucose solution or 0.9% sodium chloride solution for infusion. The concentration of the infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

As an example, a dose of 45 mg Jevtana would require 4.5 mL of the concentrate-diluent mixture prepared following step 1. More than one vial of the initial diluted solution may be necessary to administer the prescribed 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.

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

As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. Solution containing a precipitate should be discarded.

Administration

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

Do not use polyurethane infusion sets (tubing, filter, pumps) for the administration of the infusion solution.

The Jevtana infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned in the Presentation and Storage section.

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

Recommended Dosage

The recommended dose of Jevtana is 20 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 Jevtana treatment.

A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider (See PRECAUTIONS, ADVERSE EFFECTS and Clinical trials).

Dosage Adjustments

Dosage modifications should be made if patients experience the following adverse reactions.

Table 8 - Recommended Dosage Modifications for adverse reaction in patients treated with Jevtana

Adverse reactions	Dosage Modification
Prolonged Grade ≥3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF	Delay treatment until neutrophil count is >1.5 cells x 10^9/L, then reduce dosage of Jevtana by one dose level.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1.5 cells x 10^9/L, then reduce dosage of Jevtana by one dose level.
Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of Jevtana from by one dose level.
Grade ≥2 peripheral neuropathy	Delay treatment until improvement, then reduce dosage of Jevtana from by one dose level.

Patients at a 20 mg/m^2 dose who require dose reduction should decrease dosage of Jevtana to 15 mg/m^2 (see ADVERSE EFFECTS)

Patients at a 25 mg/m^2 dose who require dose reduction should decrease dosage of Jevtana to 20 mg/m^2. One additional dose reduction to 15 mg/m^2 may be considered (see ADVERSE EFFECTS).

Data in patients below the 20 mg/m^2 dose are limited.

Special Populations

Patients with Hepatic Impairment

Cabazitaxel is extensively metabolised by the liver.

Administer Jevtana at a dose of 20 mg/m^2 in patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN). Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety. Limited efficacy data for cabazitaxel at 15 mg/m^2, the maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3.0 x ULN), are available to recommend this dose in this population. (see Pharmacokinetics)

Cabazitaxel should not be given to patients with severe hepatic impairment (total bilirubin >3 x Upper Limit of Normal (ULN), see CONTRAINDICATIONS, PRECAUTIONS and Pharmacokinetics).

Concomitant Medicinal Products Use

Concomitant medicines that are strong inducers or inhibitors of CYP3A should be avoided (see INTERACTIONS WITH OTHER MEDICINES). However if patients require co-administration of a potent CYP3A inhibitor, a cabazitaxel dose reduction should be considered.

Patients with Renal Impairment

Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment not requiring haemodialysis. Patients presenting end-stage renal disease (CL_{CR} <15 mL/min/1.73m^2) by their condition and the limited amount of available data; should be treated with caution and monitored carefully during treatment. (see Pharmacokinetics)

Elderly

No specific dose adjustment for the use of cabazitaxel in elderly patients is recommended (see PRECAUTIONS, ADVERSE EFFECTS).

Children

The safety and efficacy of cabazitaxel in children have not been established.

OVERDOSAGE

Signs and Symptoms

The anticipated complications of overdose would be exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders.

Management

There is no known antidote to cabazitaxel. 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Jevtana Injection concentrate 60 mg/1.5 mL is supplied as a pack consisting of the following:

- Concentrate: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80

Each vial contains 60mg of Jevtana per 1.5mL nominal volume. The actual fill volume is 1.83mL (containing 73.2 mg Jevtana). This fill volume compensates for liquid loss during preparation of the premix. This overfill ensures that after dilution with the ENTIRE content of the accompanying diluent for Jevtana, there is a minimal extractable premix volume of 6mL containing 10mg/mL Jevtana which corresponds to the labeled amount of 60mg per vial.

- Diluent: contains 4.5 mL of 13% (w/w) ethanol in Water for Injection.

Each vial has a 4.5mL nominal volume and an actual fill volume of 5.67mL. The ENTIRE contents of the diluent vial need to be transferred into the Jevtana concentrate vial. This ensures that the premix solution will have a concentration of 10mg/mL Jevtana.

Do not refrigerate undiluted Jevtana concentrate.

Stability of the initial diluted solution in the vial:

After initial dilution (pre-mix) of Jevtana 60 mg/1.5 mL concentrate with the diluent (pre-mix), the resulting concentrate-diluent mixture is stable for 1 hour if stored below 30ºC.

Stability of the final dilution solution in the infusion bag:

After final dilution in the infusion bag/bottle, the infusion solution may be stored up to 8 hours below 30ºC (including the 1 hour infusion).

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, the infusion solution may be stored for up to 8 hours below 30ºC (including the 1 hour infusion) or for not more than 24 hours at 2º-8ºC.

As the infusion solution is supersaturated, it may crystallise over time. In this case, the infusion solution must not be used and should be discarded.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd

12-24 Talavera Road
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN ARTG

8th December 2011

DATE OF MOST RECENT AMENDMENT

11 May 2018

Jevtana is a registered trademark of sanofi-aventis.