PRODUCT MONOGRAPH

Pr JEVTANA®

Cabazitaxel for injection

Concentrated Solution 40 mg/mL
(60 mg/1.5 mL)

Antineoplastic Agent
L01CD04

sanofi-aventis Canada Inc.
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[Pr]JEVTANA®

(cabazitaxel for injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Concentrated solution/ 40 mg/mL	Polysorbate 80
	Diluent	13% (w/w) ethanol in water for injection

INDICATIONS AND CLINICAL USE

JEVTANA (cabazitaxel) in combination with prednisone or prednisolone is indicated for the treatment of patients with castration resistant (hormone refractory) metastatic prostate cancer previously treated with a docetaxel containing regimen.

JEVTANA should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy (see DOSAGE AND ADMINISTRATION and SPECIAL HANDLING INSTRUCTIONS sections).

Geriatrics (≥ 65 years of age):
Evidence from clinical studies suggests that use in the geriatric population is associated with differences in safety and a brief discussion can be found in the appropriate sections (see WARNINGS AND PRECAUTIONS, Special Populations, ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Special Populations, DOSAGE AND ADMINISTRATION, Special Populations, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Pediatrics (< 16 years of age):
The safety and the efficacy of JEVTANA in children have not been established.

CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- a history of severe hypersensitivity reactions to cabazitaxel or other drugs formulated with polysorbate 80, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage forms, Composition and Packaging section of the Product Monograph.

- neutrophil counts ≤ 1500/mm^3;

- hepatic impairment (bilirubin ≥ 1 x Upper Limit of Normal (ULN), or AST/SGOT and/or ALT/SGPT ≥1.5 × ULN).

- concomitant vaccination with yellow fever vaccine (see DRUG INTERACTIONS section).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions Box

- JEVTANA should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy (see INDICATION AND CLINICAL USE section).
- Severe hypersensitivity, pre-medication is recommended prior to treatment (see Immune section below and DOSAGE AND ADMINISTRATION).
- Neutropenic death/Neutrophil count (see WARNINGS AND PRECAUTIONS).
- Gastrointestinal (GI) hemorrhage and perforation, including fatal cases, particularly in patients most at risk of developing gastrointestinal complications (see WARNINGS AND PRECAUTIONS).

General

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, JEVTANA 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.

Cardiovascular

There is pre-clinical evidence that cabazitaxel may prolong the QT interval (see DETAILED PHARMACOLOGY, Cardiovascular Safety Pharmacology section). To further investigate the effect of cabazitaxel on QT interval, an open-label trial was conducted. No large changes in the mean QT interval (i.e., > 20 ms) from baseline based on Fridericia correction method were detected. However, a small increase in the mean QTc interval (i.e., < 10 ms) cannot be excluded due to study design limitations.

Cardiac arrhythmias have been reported in patients treated with JEVTANA, most commonly tachycardia and atrial fibrillation. During the randomized clinical trial, 4 fatal cases related to cardiac events were reported, although none was considered related to JEVTANA by the investigator (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Cardiac disorders and arrhythmias section).

Gastrointestinal

Gastrointestinal symptoms

If patients experience diarrhea following administration of JEVTANA they should be treated with commonly used anti-diarrheal medications. Appropriate measures should be taken to rehydrate the patients to avoid complications such as dehydration and electrolyte imbalance. Treatment delay or dosage reduction may be necessary for grade ≥3 diarrhea (see DOSAGE AND ADMINISTRATION section). During the randomized clinical trial, one fatal case was due to electrolyte imbalance (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Gastrointestinal section).

If patients experience nausea or vomiting, they may be treated with commonly used anti-emetics.

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

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.

Hematologic

Anemia

Caution is recommended in patients with anemia and appropriate measures should be taken as clinically indicated.

Neutropenia
During the randomized clinical trial, five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient death was attributed to neutropenia without a documented infection (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Abnormal Hematologic and Clinical Chemistry Findings section).

Neutropenia is the most common adverse reaction of JEVTANA (see ADVERSE REACTIONS section).

Ongoing patient monitoring is required from the first cycle and throughout treatment. Monitoring of complete blood count is essential on a weekly basis during cycle 1 and before each treatment cycle and as required thereafter so that the dose can be adjusted, if needed (See Monitoring and Laboratory Tests section). Reduce dose in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see DOSAGE AND ADMINISTRATION section). Re-treat only when neutrophils recover to a level > 1500/mm^3 (see CONTRAINDICATIONS section). Patients treated with JEVTANA 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). Patients may also receive antibiotics when appropriate. The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

Hepatic

JEVTANA is contraindicated in patients with hepatic impairment (bilirubin ≥ 1 x Upper Limit of Normal (ULN), or AST/SGOT and/or ALT/SGPT ≥ 1.5 × ULN).

JEVTANA is extensively metabolized in the liver, and hepatic impairment is likely to increase JEVTANA concentrations. Hepatic impairment is known to increase the risk of severe and life-threatening complications in patients receiving other drugs belonging to the same class as JEVTANA.

No formal pharmacokinetic studies in patients with hepatic impairment have been conducted. Effects on liver have been observed in pre-clinical settings (see DETAILED PHARMACOLOGY). Patients with impaired hepatic function (total bilirubin ≥ 1xULN, or AST and/or ALT ≥ 1.5x ULN) were excluded from the randomized clinical trial conducted in patients with metastatic hormone-resistant prostate cancer. Therefore, safety in this patient population is unknown.

Immune

Hypersensitivity reactions:
All patients should be premedicated prior to the initiation of the infusion of JEVTANA (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 JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of JEVTANA and appropriate therapy. Patients who have a history of severe hypersensitivity reactions should not be rechallenged with JEVTANA (see CONTRAINDICATIONS section).

Neurologic

Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving JEVTANA (see ADVERSE REACTIONS).

Renal

Renal disorders
Renal disorders have been reported in association with sepsis, severe dehydration due to diarrhea, vomiting and obstructive uropathy. Renal failure including 4 cases with fatal outcome has been observed during the randomized clinical trial (see ADVERSE REACTIONS, Clinical Trials Adverse Drug Reactions, Renal section). Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs.

Renal function should be monitored during JEVTANA therapy. Serum creatinine should be measured at baseline and with each blood count. JEVTANA treatment should be discontinued in case of renal failure ≥ grade 3 (see WARNINGS and PRECAUTIONS, Monitoring and Laboratory tests).

Reproduction

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 JEVTANA. Men being treated with JEVTANA are advised to seek advice on conservation of sperm prior to treatment.

Special Populations

Geriatrics (≥ 65 years of age):
Elderly patients may be more likely to experience certain adverse reactions including neutropenia and febrile neutropenia (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Special Populations section). However no specific dose adjustment for the use of JEVTANA in elderly patients is recommended (see DOSAGE AND ADMINISTRATION, Special populations).

Pregnant Women:
The effect of JEVTANA on human fertility is unknown. Animal studies showed that JEVTANA affected reproductive system in male rats and dogs (see TOXICOLOGY section).

There are no data from the use of JEVTANA in pregnant women. JEVTANA crosses the placenta barrier. In non-clinical studies in rats and rabbits, JEVTANA was embryotoxic, fetotoxic and abortifacient at exposures significantly lower than those expected at the recommended human dose level (see TOXICOLOGY section). JEVTANA is not recommended during pregnancy.

Nursing Women:
Available pharmacokinetics data in animals have shown excretion of JEVTANA and its metabolites in milk (see TOXICOLOGY section). JEVTANA should not be used during breast-feeding.

Pediatrics (< 16 years of age):
The safety and the efficacy of JEVTANA in children have not been established.

Patients with hepatic impairment:
Treatment with JEVTANA is contraindicated in patients with hepatic impairment. (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Special Populations sections). JEVTANA is extensively metabolized in the liver and hepatic impairment is likely to increase JEVTANA concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions section).

Hepatic impairment increases the risk of severe and life-threatening complications in patients receiving other drugs belonging to the same class as JEVTANA. JEVTANA should not be given to patients with hepatic impairment (total bilirubin $\geq$ 1 x ULN, or AST/SGOT and/or ALT/SGPT $\geq 1.5 \times$ ULN) (see CONTRAINDICATIONS).

Patients with renal impairment:
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance (CL_{CR}): 50 to 80 mL/min). Data in patients with moderate (CL_{CR}: 30 to 50 mL/min) and severe renal impairment (CL_{CR}<30 mL/min) or end-stage renal failure is limited; therefore these patients should be treated with caution and monitored carefully during treatment (see also DOSAGE AND ADMINISTRATION, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions sections).

Monitoring and Laboratory Tests

Monitoring of complete blood count is essential on a weekly basis during cycle 1 and before each treatment cycle and as required thereafter so that the dose can be adjusted, if needed (see WARNINGS AND PRECAUTIONS, Hematologic section).

Renal function should be monitored during JEVTANA therapy. Serum creatinine should be measured at baseline and with each blood count. JEVTANA treatment should be discontinued in case of renal failure ≥ grade 3 (see WARNINGS and PRECAUTIONS, Renal).

ADVERSE REACTIONS

Adverse Reaction Overview

The Grade ≥ 3 adverse reactions reported in ≥ 5% of the patients in the phase III study including 371 patients in the JEVTANA group were neutropenia, leucopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia. The most common adverse reactions leading to treatment discontinuation were neutropenia and renal failure (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, Clinical Trial Adverse Reactions sections).

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Very common (≥ 10%) grade 1-4 adverse reactions were anemia, leucopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy (including peripheral sensory and motor neuropathy), pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia (see Table 1).

The grade 3-4 adverse reactions reported in ≥ 5% of the patients who received JEVTANA were neutropenia, leucopenia, anemia, febrile neutropenia, diarrhea, fatigue and asthenia (see Table 1).

Discontinuation of treatment due to adverse reactions occurred in 68 patients (18.3%) in the JEVTANA group and 31 patients (8.4%) in the mitoxantrone group. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (4.9%) JEVTANA-treated patients and 3 (< 1%) mitoxantrone-treated patients.

The most common fatal adverse reactions in JEVTANA-treated patients were due to infections (n=5). The majority (4 of 5 patients) of fatal infection-related adverse reactions in the randomized clinical trial occurred after a single dose of JEVTANA.

Table 1 provides the incidence of all adverse reactions and hematologic abnormalities occurring at higher rate (at least 2% higher) in patients receiving JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily (or prednisolone) compared to mitoxantrone 12 mg/m^2 every 3 weeks with prednisone 10 mg daily (or prednisolone) [TROPIC study]. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1. Incidence of reported adverse reactions and hematologic abnormalities in patients receiving JEVTANA in combination with prednisone (or prednisolone) and patients receiving mitoxantrone in combination with prednisone (or prednisolone) (at least 2% higher incidence rate in the JEVTANA group compared to mitoxantrone) [TROPIC study]

	JEVTANA at 25 mg/m^2 every 3 weeks in combination with prednisone 10 mg daily (or prednisolone)		Mitoxantrone at 12 mg/m^2 every 3 weeks in combination with prednisone 10 mg daily (or prednisolone)	
	n=371		n=371	
Body System / Preferred term	**All grades n (%)**	**grade 3/4 n (%)**	**All grades n (%)**	**grade 3/4 n (%)**
Blood and lymphatic system disorders				
Neutropenia[a]	347 (93.5%)	303 (81.7%)	325 (87.6%)	215 (58.0%)
Anemia[a]	361 (97.3%)	39 (10.5%)	302 (81.4%)	18 (4.9%)
Leucopenia[a]	355 (95.7%)	253 (68.2%)	343 (92.5%)	157 (42.3%)
Thrombocytopenia[a]	176 (47.4%)	15 (4%)	160 (43.1%)	6 (1.6%)
Febrile Neutropenia	---	28 (7.5%)	---	5 (1.3%)
Gastrointestinal disorders				
Diarrhea	173 (46.6%)	23 (6.2%)	39 (10.5%)	1 (0.3%)
Nausea	127 (34.2%)	7 (1.9%)	85 (22.9%)	1 (0.3%)
Vomiting	84 (22.6%)	7 (1.9%)	38 (10.2%)	0
Constipation	76 (20.5%)	4 (1.1%)	57 (15.4%)	2 (0.5%)
Abdominal Pain	43 (11.6%)	7 (1.9%)	13 (3.5%)	0
Dyspepsia	25 (6.7%)	0	6 (1.6%)	0
Abdominal Pain Upper	20 (5.4%)	0	5 (1.3%)	0
Hemorrhoids	14 (3.8%)	0	3 (0.8%)	0
Gastrooesophageal Reflux Disease	12 (3.2%)	0	3 (0.8%)	0
General disorders and administration site conditions				
Fatigue	136 (36.7%)	18 (4.9%)	102 (27.5%)	11 (3.0%)
Asthenia	76 (20.5%)	17 (4.6%)	46 (12.4%)	9 (2.4%)
Pyrexia	45 (12.1%)	4 (1.1%)	23 (6.2%)	1 (0.3%)
Mucosal Inflammation	22 (5.9%)	1 (0.3%)	10 (2.7%)	1 (0.3%)
Infections And Infestations				
Urinary Tract Infection	27 (7.3%)	4 (1.1%)	11 (3.0%)	3 (0.8%)
Metabolism and nutrition disorders				
Anorexia	59 (15.9%)	3 (0.8%)	39 (10.5%)	3 (0.8%)
Dehydration	18 (4.9%)	8 (2.2%)	10 (2.7%)	3 (0.8%)

Body System / Preferred term	JEVTANA at 25 mg/m^2 every 3 weeks in combination with prednisone 10 mg daily (or prednisolone) n=371		Mitoxantrone at 12 mg/m^2 every 3 weeks in combination with prednisone 10 mg daily (or prednisolone) n=371	
	All grades n (%)	grade 3/4 n (%)	All grades n (%)	grade 3/4 n (%)
Musculoskeletal and connective tissue disorders				
Back Pain	60 (16.2%)	14 (3.8%)	45 (12.1%)	11 (3.0%)
Arthralgia	39 (10.5%)	4 (1.1%)	31 (8.4%)	4 (1.1%)
Muscle Spasms	27 (7.3%)	0	10 (2.7%)	0
Nervous System Disorders				
Dysgeusia	41 (11.1%)	0	15 (4.0%)	0
Neuropathy Peripheral	30 (8.1%)	2 (0.5%)	4 (1.1%)	1 (0.3%)
Dizziness	30 (8.1%)	0	21 (5.7%)	2 (0.5%)
Headache	28 (7.5%)	0	19 (5.1%)	0
Peripheral Sensory Neuropathy	20 (5.4%)	1 (0.3%)	5 (1.3%)	0
Renal and urinary tract disorder				
Hematuria	62 (16.7%)	7 (1.9%)	14 (3.8%)	2 (0.5%)
Dysuria	25 (6.7%)	0	5 (1.3%)	0
Urinary Incontinence	9 (2.4%)	0	1 (0.3%)	0
Renal Failure Acute	8 (2.2%)	6 (1.6%)	0	0
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnea	44 (11.9%)	5 (1.3%)	17 (4.6%)	3 (0.8%)
Cough	40 (10.8%)	0	22 (5.9%)	0
Skin And Subcutaneous Tissue Disorders				
Alopecia	37 (10.0%)	0	18 (4.9%)	0
Vascular Disorders				
Hypotension	20 (5.4%)	2 (0.5%)	9 (2.4%)	1 (0.3%)

a based on laboratory values

Cardiac disorders and arrhythmias

All grade events among cardiac disorders were more common on JEVTANA of which 6 patients (1.6%) had grade ≥3 cardiac arrhythmias. The incidence of tachycardia on JEVTANA was 1.6%, none of which were grade ≥3. The incidence of atrial fibrillation was 1.1% in the JEVTANA group. Cardiac failure events were more common on JEVTANA, the event term being reported for 2 patients (0.5%). One patient in the JEVTANA group died from cardiac failure. Fatal

ventricular fibrillation was reported in one patient (0.3%), and cardiac arrest in 2 patients (0.5%). None were considered related by the investigator.

Gastrointestinal disorders

Incidence of grade ≥ 3 diarrhea was 6.2%. No grade 4 diarrhea was reported and no fatal cases were reported. One case of grade 2 diarrhea was associated with a fatal electrolyte imbalance.

General disorders and administration site conditions

Peripheral oedema was observed at 9.2% incidence (all grades) in both groups, the incidence of grade ≥ 3 was 0.5% in JEVTANA arm and 0.3% in mitoxantrone arm.

Pain was observed at an incidence of 5.4% and 4.9% in all grades and 1.1% and 1.9% in grades ≥ 3 in the JEVTANA arm and mitoxantrone arm, respectively.

Investigations

Decreased weight was observed at 8.6% and 7.5% in all grades and 0% and 0.3% in grades ≥ 3 in the JEVTANA and mitoxantrone arms, respectively.

Nervous system disorders

Grade 3-4 peripheral neuropathy was reported in 0.5% of patients.

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. Four cases with fatal outcome were reported in the randomized clinical trial.

Hematuria: incidence of grade ≥3 hematuria was 1.9%. No fatal cases were reported in the JEVTANA-treated patients.

Abnormal Hematologic and Clinical Chemistry Findings

Neutropenia and associated clinical events:
The 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 respectively 21.3% and 7.5%. 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 (one case of fatal neutropenia, one case of fatal febrile neutropenia, 2 cases of fatal neutropenic infection).

The time to first occurrence of grade ≥ 3 neutropenia based on laboratory data showed that in most patients this event first occurred within the first 2 cycles of treatment.

The use of G-CSF has been shown to limit the incidence and severity of neutropenia (see DOSAGE AND ADMINISTRATION section).

Anemia
The incidence of grade ≥ 3 anemia based on laboratory abnormalities was 10.6% (54.2% of patients had any grade anemia at baseline). One fatal case was reported in the context of association with neutropenia and thrombocytopenia.

Liver function abnormalities
In the clinical study, the incidence of grade ≥3 increased AST, ALT, and bilirubin based on laboratory abnormalities were 0.7%, 0.9%, and 0.6%, respectively. Grade 4 increase in laboratory values of AST and ALT were reported in one patient each.

Special Populations

Geriatrics (≥ 65 years of age)

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: fatigue (40.4% vs. 29.8%), 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%), febrile neutropenia (8.3% vs. 6.1%), cardiac disorders (2.9% vs 0%), infections and infestations (13.3% vs 4.6%) (see WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Special Populations sections).

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

Post-Market Adverse Drug Reactions

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

DRUG INTERACTIONS

JEVTANA is extensively metabolized in the liver (≥ 95%), mainly by the CYP3A isoenzyme (80 to 90%). Therefore, concomitant drugs that are strong CYP3A inducers or inhibitors should be avoided and caution should be exercised in patients concurrently taking drugs known to be primarily metabolized through CYP3A (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section).

Overview

In vitro studies have shown that JEVTANA is mainly metabolized through CYP3A. The metabolism of JEVTANA is modified by the concomitant administration of compounds which are known to be strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir, voriconazole) or strong CYP3A inducers (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin).

Co-administration with strong CYP3A inhibitors should be avoided as they may increase cabazitaxel exposure (see Drug-Drug Interactions section below).

Co-administration with strong CYP3A inducers should be avoided as they may decrease cabazitaxel exposure.

A clinical drug-interaction study demonstrated that cabazitaxel (25 mg/m^2 administered as a single 1-hour infusion) did not modify the plasma levels of midazolam, a probe substrate of CYP3A. Therefore, JEVTANA at therapeutic doses when co-administered with CYP3A substrates in patients is not expected to have any clinical impact.

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 JEVTANA on drugs that are substrates of CYP1A, CYP2C9, and CYP3A.

In vitro JEVTANA did not inhibit the multidrug resistance proteins 1 and 2 (MRP1 and MRP2) or the organic cation transporter (OCT1). JEVTANA inhibited the transport of P-glycoprotein (P-gp) (digoxin, vinblastine), the breast cancer resistance protein (BCRP) (methotrexate) and the organic anion transporting polypeptides (OATP1B3) (CCK8) at concentrations at least 15 fold what was observed in clinical settings while it inhibited the transport of OATP1B1 (estradiol-17β-glucuronide) at concentrations only five fold what was observed in clinical settings. Therefore the risk of interaction with substrates of MRP, OCT1, P-gp, BCRP substrates and OATP1B3, is unlikely *in vivo* at the dose of 25 mg/m^2. The *in vitro* study has demonstrated that the risk of interaction with substrates of OATP1B1 (e.g. statins, valsartan, repaglinide) is possible *in vivo* at the dose of 25 mg/m^2. The risk of interaction with OATP1B1 transporter may be limited to the infusion duration (1 hour) and up to 20 minutes after the end of the infusion. However, this has not been confirmed by an *in vivo* drug-drug interaction study.

Drug-Drug Interactions

Prednisone/prednisolone administered at 10 mg daily did not affect the pharmacokinetics of JEVTANA.

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. Concomitant administration of aprepitant, a moderate CYP3A inhibitor, had no effect on cabazitaxel clearance or exposure.

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%.

JEVTANA did not inhibit *in vitro* the major biotransformation pathway of warfarin into 7-hydroxywarfarin, which is mediated by CYP2C9. Therefore, no pharmacokinetic interaction of JEVTANA on warfarin is expected *in vivo*.

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 JEVTANA. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The use of JEVTANA should be confined to units specialized in the administration of cytotoxics and it should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy (see Administration section below and SPECIAL HANDLING INSTRUCTIONS section).
- Premedication is recommended prior to treatment.

  Premedicate prior to each administration of JEVTANA with the following intravenous medications to reduce the incidence and severity of a hypersensitivity reaction:

  - antihistamine (diphenhydramine 25 mg or equivalent),
  - corticosteroid (dexamethasone 8 mg or equivalent) and with
  - H2 antagonist (ranitidine or equivalent) (see WARNINGS AND PRECAUTIONS section).

  Antiemetics prophylaxis is recommended and can be given orally or intravenously as needed.
- Dosage modifications may be required if patients experience neutropenia, febrile neutropenia, diarrhea or peripheral neuropathy (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment sections).
- Patients treated with JEVTANA 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).
- The patients may also receive antibiotics when appropriate.

Recommended Dose and Dosage Adjustment

Recommended Dose

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 JEVTANA treatment.

Dosage Adjustments

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

Table 2 - 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 > 1500 cells/mm^3, then reduce dosage of JEVTANA 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 > 1500 cells/mm^3, then reduce dosage of JEVTANA from 25 mg/m^2 to 20 mg/m^2.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA from 25 mg/m^2 to 20 mg/m^2.
Grade > 2 peripheral neuropathy	Delay treatment until improvement, then consider a dose reduction.

Discontinue JEVTANA treatment if a patient continues to experience any of these reactions at 20 mg/m^2.

Special Populations

Pediatrics (< 16 years of age): The safety and the efficacy of JEVTANA in children have not been established.

Geriatrics (≥ 65 years of age): No specific dose adjustment for the use of JEVTANA in elderly patients is recommended (see WARNINGS AND PRECAUTIONS, Special Populations, ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Special Populations, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions sections).

Patients with hepatic impairment
JEVTANA is extensively metabolized by the liver. No formal studies were conducted in patients with hepatic impairment. As a precautionary measure, JEVTANA should not be given to patients with hepatic impairment [bilirubin ≥ 1 x ULN, or AST/SGOT and/or ALT/SGPT ≥ 1.5 x ULN] (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions sections).

Patients with renal impairment
JEVTANA 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). Data in patients with moderate (CL_{CR}: 30 to 50 mL/min) and severe renal impairment (CL_{CR}<30 mL/min) or end stage renal disease is limited; therefore these patients should be treated with caution and monitored carefully during treatment (see WARNINGS AND PRECAUTIONS, Special Populations, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions sections).

Concomitant drug use
Concomitant drugs that are CYP3A inducers or potent CYP3A inhibitors should be avoided (see DRUG INTERACTIONS section)

Administration

- The final JEVTANA infusion solution should be administered intravenously as a 1-hour infusion at room temperature (see the two steps dilution process described below).

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

- Do not use PVC infusion containers or polyurethane infusion sets for the preparation and 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 section STORAGE AND STABILITY.

- Please also refer to the SPECIAL HANDLING INSTRUCTIONS section.

Dilution (2 steps process)

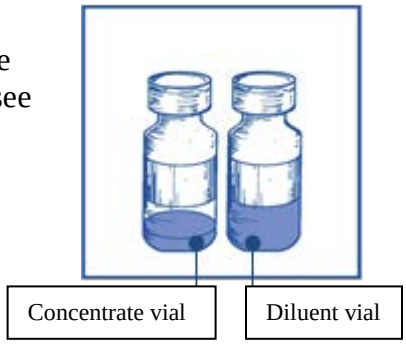
Read this ENTIRE section carefully before mixing and diluting. JEVTANA requires TWO dilutions prior to administration. Follow the preparation instructions provided below.
Note: Both the JEVTANA 60 mg/1.5 mL concentrate vial (fill volume: 73.2 mg cabazitaxel/1.83 ml) and the diluent vial (fill volume: 5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the ENTIRE content of the accompanying diluent, there is an initial diluted solution containing 10 mg/ml of JEVTANA (see DOSAGE FORM, COMPOSITION AND PACKAGING section).

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

Step 1: Initial dilution of JEVTANA 60 mg/1.5 mL concentrated solution with the supplied diluent.

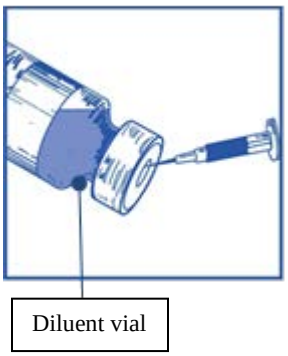
Step 1.1

Inspect the JEVTANA 60 mg/1.5 mL concentrate vial and the supplied diluent. The concentrated solution should be clear (see STORAGE AND STABILITY section).



Step 1.2

Using a syringe fitted with a needle, aseptically withdraw the ENTIRE content of supplied diluent by partially inverting the vial.

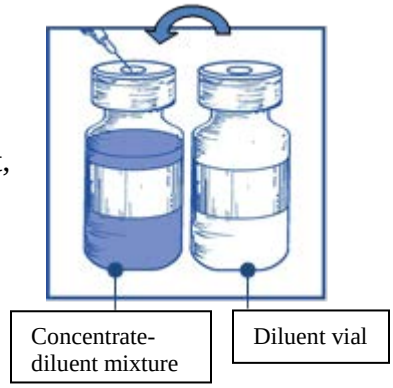


Step 1.3

Inject the ENTIRE content into the corresponding vial of JEVTANA 60 mg/1.5 mL concentrate.

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

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



Step 1.4

Remove the syringe and needle and mix manually and gently by repeated inversions for at least 45 seconds until obtaining clear and homogeneous solution. Do not shake.

Step 1.5

Let this solution stand for a few minutes (approximately 5 minutes) to allow any foam to dissipate and check that the solution is homogeneous and clear. It is normal for foam to persist after this time period. It is not required that all foam dissipates prior to continuing the preparation process.

This resulting concentrate-diluent solution contains 10 mg/mL of JEVTANA (at least 6 mL deliverable volume). It should be immediately diluted (within 1 hour) as detailed in Step 2.

The solution is stable for 1 hour if stored at room temperature (15°C to 30°C) (see STORAGE AND STABILITY section).

More than 1 vial of the initial diluted solution may be necessary to administer the prescribed dose.

Discard any unused portion.

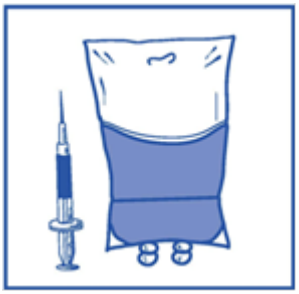
Step 2: Preparation of the dilution solution for infusion.

Step 2.1

Aseptically withdraw the required amount of initial diluted JEVTANA solution (10 mg/ml of JEVTANA), with a graduated syringe fitted with a needle. 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 the solution.

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

Step 2.2



Inject in a sterile PVC-free container of either 5% dextrose 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.

Step 2.3

Remove the syringe and needle and mix the content of the infusion by gently inverting the bag or bottle.

Step 2.4

As with all parenteral products, the resulting infusion solution should be inspected visually for particulate matter and discoloration prior to administration. Solution containing a precipitate or that is not clear should be discarded.

After final dilution in the infusion bag/bottle, the infusion solution may be stored up to 8 hours at room temperature (including the 1 hour infusion). Chemical and physical stability of the infusion solution has been demonstrated for 48 hours under refrigerated conditions (this includes the 1-hour infusion which should be administered at room temperature) (see STORAGE AND STABILITY section).

Discard any unused portion.

Table 3 - Two Steps Dilution Process

Step	Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
Step 1 **Initial dilution**	Concentrated solution JEVTANA 60 mg/1.5 mL	ENTIRE content of the supplied diluent	At least 6 mL deliverable volume	10 mg/mL of cabazitaxel
Step 2 **Preparation of the infusion solution**	Solution after initial dilution 10 mg/mL of cabazitaxel (at least 6 mL deliverable volume)	5% dextrose solution or 0.9% sodium chloride solution for infusion	Depends on the dosage	The concentration of the infusion solution should be between 0.10 mg/mL and 0.26 mg/mL

Incompatibilities / Compatibilities

- Always dilute JEVTANA 60 mg/1.5 mL concentrated solution with the ENTIRE content of the supplied diluent before adding to infusion solutions.
- JEVTANA must not be mixed with other drugs.
- JEVTANA contains polysorbate 80 which is known to increase the rate of di-(2-ethylhexyl) phtalate extraction (DEHP) from polyvinyl chloride (PVC). PVC infusion containers or polyurethane infusion sets should not be used for the preparation and administration of the infusion solution.

OVERDOSAGE

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

Management
There is no known antidote to JEVTANA. In case of overdose, the patient should be kept in a specialized 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

JEVTANA is an antineoplastic agent that acts by disrupting the microtubular network in cells.

JEVTANA binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

Pharmacodynamics

JEVTANA demonstrated a broad spectrum of antitumour activity against advanced human tumors xenografted in mice, including intracranial human glioblastomas.

JEVTANA is active in docetaxel-sensitive tumors. In addition JEVTANA demonstrated activity in tumor models resistant to chemotherapy, including docetaxel.

Pharmacokinetics

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

Table 4 Summary of JEVTANA's Pharmacokinetic Parameters in Patients with Metastatic Prostate Cancer

Dosage	C_{max}	$t_{½}$ (h)	AUC	Clearance	Volume of distribution
1-hour IV administration dose of JEVTANA at 25 mg/m^2	226 ng/mL (CV: 107%)	95 hours	991 ng.h/mL (CV: 34%)	48.5 L/h (26.4 L/h/m² for a patient with a median BSA of 1.84 m²)	4870 L (2640 L/m² for a patient with a median BSA of 1.84 m²) at steady state

Absorption:
After a 1-hour IV administration dose of JEVTANA 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 tumors (n=126).

Distribution:
The volume of distribution (Vss) was 4870 L (2640 L/m² for a patient with a median BSA of 1.84 m²) at steady state.

In vitro, the binding of JEVTANA 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. JEVTANA 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 JEVTANA was equally distributed between blood and plasma.

Metabolism:
JEVTANA is extensively metabolized in the liver (≥ 95%), mainly by the CYP3A isoenzyme (80 to 90%). JEVTANA 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 5% of parent exposure. Around 20 metabolites of JEVTANA are excreted into human urine and feces.

Based on *in vitro* studies, the potential risk of inhibition by JEVTANA at clinically relevant concentrations is possible towards drugs that are mainly substrate of CYP3A. JEVTANA does not inhibit other CYP enzymes. In addition, JEVTANA did not induce CYP isozymes (CYP1A, CYP2C, and CYP3A) *in vitro*.

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. JEVTANA is mainly excreted in the feces as

numerous metabolites (76% of the dose); while renal excretion of JEVTANA and metabolites account for less than 3.7% of the dose (2.3% as unchanged drug in urine).

Following a one-hour intravenous infusion, plasma concentrations of JEVTANA can be described by a three-compartment pharmacokinetic model characterized by rapid initial and intermediate phases with half-lives of 4 minutes and 2 hours respectively and by a long terminal phase with a half-life of 95 hours.

JEVTANA 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).

Special Populations and Conditions

Pediatrics: Safety and effectiveness of JEVTANA have not been established in children.

Geriatrics: In the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of JEVTANA between patients ≤ 65 years (n=100) and older (n=70; 57 patients from 65 to 75 years and 13 patients above 75 years) (see WARNINGS AND PRECAUTIONS, Special Populations, ADVERSE REACTIONS, Clinical Trial Adverse Reactions, DOSAGE AND ADMINISTRATION, Special Populations).

Hepatic Insufficiency: No formal studies in patients with hepatic impairment have been conducted (see CONTRAINDICATIONS section). However, as JEVTANA is eliminated primarily via hepatic metabolism, increased exposure may be expected.

Renal Insufficiency: JEVTANA is minimally excreted via the kidney (2.3% of the dose). No formal pharmacokinetic studies were conducted with JEVTANA 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 JEVTANA (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION, Special Populations sections).

STORAGE AND STABILITY

Before dilution

Store the unopened vials at room temperature (15°C to 30°C). Do not refrigerate.

After dilutions:

For storage conditions of the initial diluted solution (step 1) and the final infusion solution (step 2), see below.

Step 1: Stability of the initial diluted solution in the vial:

After initial dilution of JEVTANA 60 mg/1.5 mL concentrated solution with the diluent, the resulting concentrate-diluent solution (10 mg/mL) should be used immediately. The solution is stable for 1 hour if stored at room temperature (15°C to 30°C).

Discard any unused portion.

Step 2: Stability of the solution in the infusion bag/bottle:

After final dilution in the infusion bag/bottle (in either 0.9% sodium chloride or 5% dextrose solution), the infusion solution may be stored up to 8 hours (including the 1 hour infusion) at room temperature (15°C to 30°C).

Chemical and physical stability of the infusion solution has been demonstrated for 48 hours under refrigerated conditions (2°C to 8°C) (this includes the 1-hour infusion which should be administered at room temperature).

Discard any unused portion.

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

SPECIAL HANDLING INSTRUCTIONS

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.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Two-vial formulation:

- One single-use concentrate vial of JEVTANA 60 mg /1.5 mL (40 mg/mL). The concentrated solution is a clear yellow to brownish-yellow oily solution.

- One single-use diluent vial. The diluent is a clear and colorless solution.

Composition

JEVTANA 60 mg /1.5 mL Concentrated Solution

- JEVTANA 60 mg/1.5 mL concentrated solution contains 60 mg cabazitaxel (anhydrous and solvent free) and 1.56 mg polysorbate 80 (including citric acid for pH adjustment) in a total volume of 1.5 mL (nominal volume).
- Each mL of the concentrated solution contains 40 mg cabazitaxel (anhydrous) and 1.04 mg polysorbate 80.

Diluent

- The diluent for JEVTANA contains 13% (w/w) ethanol in water for injection, 4.5 mL (nominal volume).

Note: The JEVTANA 60 mg/1.5 mL concentrate vials are filled with a 22% excess (corresponding to 73.2 mg cabazitaxel for a total fill volume of 1.83 mL) and the diluent vials with a 26% excess (total fill volume 5.67 mL).

Table 5– Nominal and actual fill volumes for Jevtana diluent and concentrate vials

	Diluent vial	**Concentrate vial**
Nominal volume	4.5 mL	1.5 mL (60 mg cabazitaxel)
Actual fill volume	5.67 mL	1.83 mL (73.2 mg cabazitaxel)

This fill volume has been established during the development of JEVTANA to compensate for liquid loss during preparation of the initial diluted solution. This overfill ensures that after dilution with the ENTIRE content of the accompanying diluent for JEVTANA, there is a minimal extractable premix volume of 6 mL containing 10 mg/mL which corresponds to the labeled amount of 60 mg per vial.

Packaging

One pack contains (2 vials):

- One concentrate vial: 1.5 mL (nominal volume) of JEVTANA 60 mg concentrated solution in 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.
- One diluent vial: 4.5 mL (nominal volume) of diluent in 15 mL clear glass vial (type I) closed with a grey chlorobutyl rubber closer sealed by a gold color aluminium cap covered with a colourless plastic flip-off cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

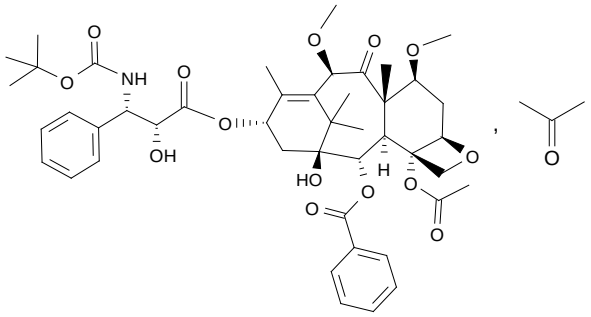
Common name: Cabazitaxel

Chemical name: (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)

Molecular formula: $C_{45}H_{57}NO_{14},C_3H_6O$

Molecular mass: 894.01 (acetone solvate), 835.93 (solvate free)

Structural formula:



Physicochemical properties:

- White to almost white powder
- Practically insoluble in water and soluble in alcohol
- Lipophilic

CLINICAL TRIALS

Study demographics and trial design

The efficacy and safety of JEVTANA in combination with prednisone or prednisolone were evaluated in a randomized, open-label, international, multi-center, phase III study, in patients with castration resistant (hormone refractory) metastatic prostate cancer previously treated with a docetaxel-containing regimen (TROPIC study, EFC6193).[1, 2]

Table 6 - Summary of patient demographics for EFC6193 in patients with castration resistant metastatic prostate cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
TROPIC EFC6193	Phase III study Randomized Open-label International Multi-center	JEVTANA 25 mg/m^2 IV every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily Mitoxantrone 12 mg/m^2 IV every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily	755 patients were randomized 378 in the JEVTANA arm 377 in the mitoxantrone arm	68 years (range 46-92) in the JEVTANA arm 67 years (range 47-89) in the mitoxantrone arm	Men

Overall survival (OS) was the primary efficacy endpoint of the study. The objective was to detect a 25% reduction in hazard rate in the JEVTANA arm relative to the comparator with a power of 90% at a 2-sided 5% alpha level.

Secondary endpoints included:

- Progression free survival (PFS) (defined as time from randomization to tumor progression, Prostatic Specific Antigen (PSA) progression, pain progression, or death due to any cause, whichever occurred first),
- Tumor response rate based on Response Evaluation Criteria in Solid Tumors (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 defined as an increase of ≥1 point in the median PPI from its nadir noted on 2 consecutive three-week-apart visits or ≥25% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits or a requirement for local palliative radiotherapy),

- 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).

Once a patient had progressed or started another anticancer therapy, the follow-up visits were planned to be performed every 3 months until death or study cut-off for a maximum of 2 years.

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 castration resistant metastatic prostate cancer previously treated with docetaxel with either measurable disease with documented progression 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 > 1500/mm^3, platelets > 100 000/mm^3, hemoglobin > 10 g/dL, creatinine < 1.5 x ULN, total bilirubin < 1 x ULN, AST/SGOT < 1.5 x ULN, and ALT/SGPT < 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 years) and the racial distribution was 83.9% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others.

In the JEVTANA group, 53.2% of the patients had a measurable disease. As for prior anticancer therapies and procedures, 25.9% and 35.4% had been previously exposed to curative and palliative radiation respectively and all patients had previously received chemotherapy regimens (68.8%, 24.9% and 6.3% for 1, 2 or ≥ 3 regimens respectively). In the JEVTANA group, the majority of patients (66.7%) had received ≥ 450 mg/m^2 (≥ 6 cycles) of prior docetaxel-based therapy and 87.5% of the patients had progressed during or within 6 months of prior docetaxel-based therapy.

Table 7- Summary of baseline and demographic characteristics – ITT population

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Age, in years		
Median	67.0	68.0
Minimum	47	46
Maximum	89	92
Age		
18 to 64	162 (43.0%)	133 (35.2%)
65 to 74	145 (38.5%)	176 (46.6%)
75 and above	70 (18.6%)	69 (18.3%)
Race		
Caucasian/White	314 (83.3%)	317 (83.9%)
Black	20 (5.3%)	20 (5.3%)
Asian/Oriental	32 (8.5%)	26 (6.9%)
Other	11 (2.9%)	15 (4.0%)
ECOG PS[a]		
0 or 1	344 (91.2%)	350 (92.6%)
0	120 (31.8%)	141 (37.3%)
1	224 (59.4%)	209 (55.3%)
2	33 (8.8%)	28 (7.4%)
ECG		
Normal	251 (66.6%)	268 (70.9%)
Abnormal	98 (26.0%)	86 (22.8%)
Missing	28 (7.4%)	24 (6.3%)
Echocardiography (Left ventricular ejection fraction) %		
Number of patients	243	235
Median	64.00	63.00
Minimum	42.0	38.0
Maximum	80.0	86.0
Radionuclide Ventriculography (LVEF) %		
Number of patients	129	140
Median	63.00	62.00
Minimum	50.0	50.2
Maximum	80.0	81.0
PSA (in ng/mL)		
Number of patients	370	371
Median	127.5	143.9
Minimum	2	2
Maximum	11220	7842
Measurable Disease		
Measurable Disease	204 (54.1%)	201 (53.2%)
Not Measurable Disease	173 (45.9%)	177 (46.8%)
Extent of disease		
Metastatic	356 (94.4%)	364 (96.3%)
Loco Regional Recurrence	20 (5.3%)	14 (3.7%)
Missing	1 (0.3%)	0

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone

CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

[a]According to the protocol, patients were stratified according to ECOG PS 0-1, versus 2.

The median number of cycles was 6 in the JEVTANA group and 4 in the mitoxantrone group.

The median relative dose intensity was 96.12% in the JEVTANA group. Treatment discontinuation due to adverse reaction occurred in 18% of patients who received cabazitaxel and 8% in patients who received mitoxantrone. Among patients in the JEVTANA arm, 9.8% of cycles were administered at a reduced level (12% of patients) compared with 5.1% on the mitoxantrone arm (4% of patients). The majority of these dose reductions were performed as planned by the study protocol (i.e., 20% dose reductions). Dose delays were reported in 28% of cabazitaxel-treated patients (9.2% of cycles) and 15% of mitoxantrone-treated patients (7.9% of cycles). The number of patients who completed the study treatment (10 cycles) was 2-fold higher in the JEVTANA group than in the comparator group (29.4% vs. 13.5%).

Study results

Overall survival was significantly longer in the JEVTANA arm with JEVTANA-treated patients having a 30% relative reduction in the risk of death compared to mitoxantrone [hazard ratio =0.70, 95% CI (0.59 – 0.83)] (see Table 8 and Figure 1). At 12 months and 18 months, overall survival was 64% and 39% in the JEVTANA arm and 53% and 28% in the mitoxantrone arm.

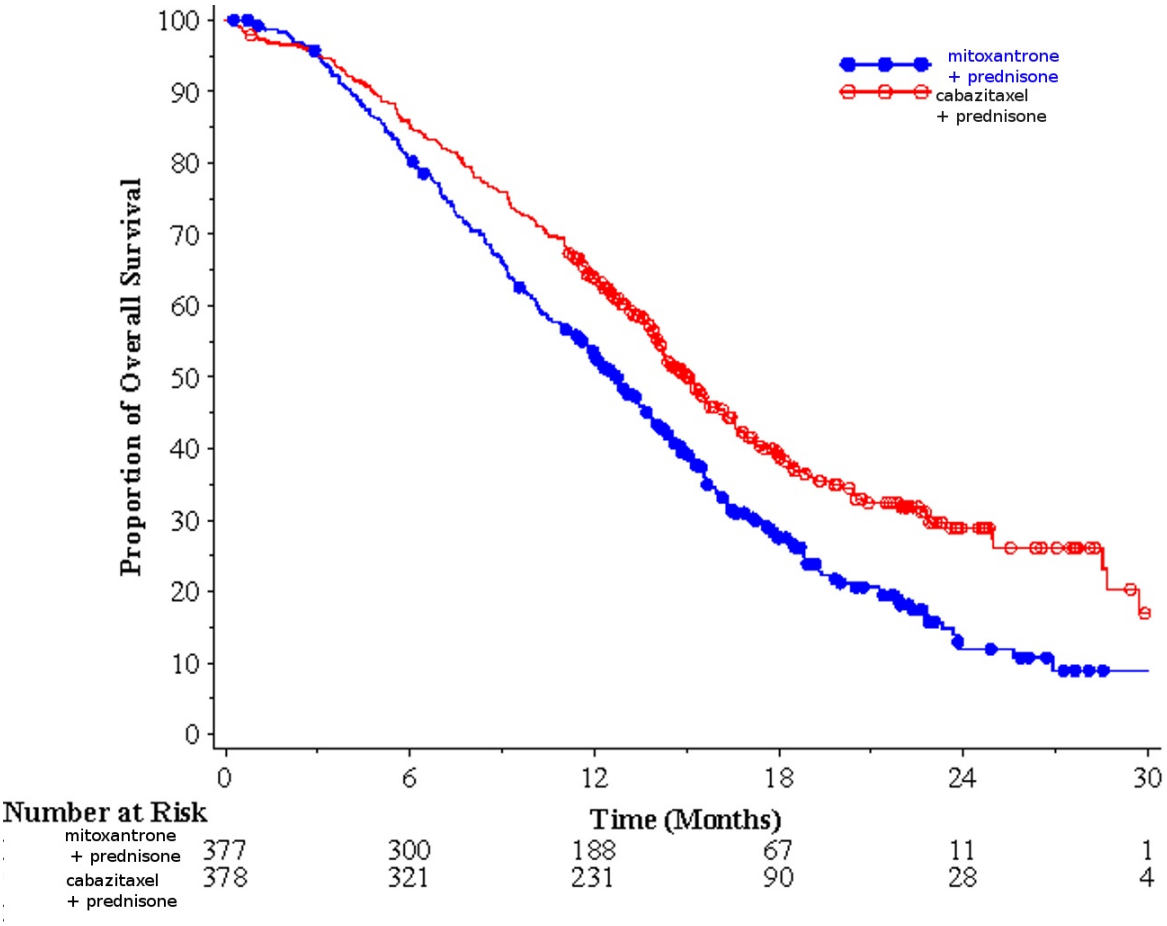
Table 8- Efficacy of JEVTANA in the treatment of patients with castration resistant metastatic prostate cancer (Intent-to–treat analysis) – Primary Endpoint

	JEVTANA + prednisone* n=378	**mitoxantrone + prednisone* n=377**
Overall Survival		
Number of patients with deaths (%)	234 (61.9 %)	279 (74%)
Median survival (months) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio (HR)[1] (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

[1]HR estimated using Cox model; a hazard ratio of less than 1 favors JEVTANA
* prednisone or prednisolone

A sub-group of 59 patients received prior cumulative dose of docetaxel <225mg/m^2 (29 patients in the JEVTANA arm, 30 patients in the mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR=0.96, 95% CI 0.49-1.86).

Figure 1 - Kaplan Meier Overall Survival Curves



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

There was a significantly higher rate of overall tumor 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. The median time to tumor progression was 8.8 months (95% CI: 7.4 – 9.6) in the JEVTANA arm and 5.4 months (95% CI: 4.7 – 6.5) in the mitoxantrone arm, p<0.0001.

PSA secondary endpoints were positive in the JEVTANA arm. There was a median PSA progression free of 6.4 months (95% CI: 5.1-7.3) for patients in the JEVTANA arm, compared to 3.1 months (95% CI: 2.2-4.4) in the mitoxantrone arm, HR 0.75 (95% CI 0.63-0.90), p=0.0010. The PSA response was 39.2% in patients on JEVTANA (95% CI: 33.9-44.5) versus 17.8% in patients on mitoxantrone (95% CI: 13.7-22.0), p=0.0002. PSA-based endpoints are not validated surrogate endpoints in this patient population.

The present pain intensity (PPI) scores, evaluating time to pain progression and pain response of patients in the two treatment groups were comparable. There was no statistically significant difference between treatment arms in the time to pain progression and in pain response.

DETAILED PHARMACOLOGY

Cabazitaxel is a semi-synthetic taxane derived from the 10-deacetyl Baccatin III, which is extracted from European yew needles.

Tubulin, the protein component of microtubules, is the main target of taxanes, such as docetaxel and paclitaxel. Cabazitaxel is as potent as docetaxel in stabilizing microtubules.

In vivo, cabazitaxel is as potent as docetaxel against docetaxel-sensitive tumors. It has a broad spectrum of antitumor efficacy in murine tumors (B16 melanoma, colon C51, mammary MA16/C, MA17/A) including efficacy on measurable diseases (colon C38, pancreas P03).

Cabazitaxel also has a good antitumor activity in human tumor models xenografted in nude mice, including not only prostate DU 145, but other tumor types, such as colon HCT 116, lung A549, pancreas MIA PaCa-2, head and neck SR475 and kidney Caki-1.

Finally, cabazitaxel is active *in vivo* in tumor models poorly or not sensitive as well as resistant to docetaxel or other chemotherapeutic agents, i.e. in 3 aggressive murine tumors (Lewis lung carcinoma, pancreas P02 adenocarcinoma and B16/TXT melanoma, a tumor model with *in vivo* acquired resistance to docetaxel) and also in 3 human tumor models (colon HCT-8, gastric GXF-209 and mammary UISO BCA-1).

In addition, this compound was found to penetrate the blood brain barrier and marked antitumor activity was obtained in nude mice bearing-intracranial glioblastomas.

Absorption

The disposition of cabazitaxel has been assessed in various animal species selected for the toxicology and pharmacology evaluation of the compound. Overall in all species, after IV administration, cabazitaxel exposure increased with dose, with no deviation from dose proportionality in mice while exposure increased in a greater than dose proportional manner in rats and dogs. No gender effect was observed in rats and dogs. No accumulation was observed in mice, rats or dogs after five-daily or weekly administrations or after administration every 3 weeks.

Distribution

Plasma protein binding of cabazitaxel was very high in mice (99.3%) and high in rats (95.5%), rabbits (91.4%), dogs (97.1%) and humans (91.9%) with no trend of saturation in the concentration range of 50 to 1000 ng/mL. At higher concentrations (up to 50 000 ng/mL) a trend toward saturation was observed in rabbits (above 1000 ng/mL), in mice (above 5000 ng/mL) and

in dogs (above 10 000 ng/mL) and not in rats and humans. A trend toward saturation was observed in rabbits (above 1000 ng/mL), in mice (above 5000 ng/mL) and in dogs (above 10 000 ng/mL) and not in rats and humans.

Cabazitaxel exhibited a large volume of distribution in mice (2.5 to 3.7 L/kg), in tumor bearing mice (8.8 L/kg), in rats (22.7 L/kg) and in dogs (3.3 to 14.5 L/kg). In tumor-free and tumor-bearing mice and in rats, cabazitaxel was rapidly and widely distributed into most organs, including brain and tumor, with no specific affinity for any organ nor for melanin. However, a slow elimination of the radioactivity from the testes was noted in rats. Low placental transfer of radioactivity (66% being cabazitaxel) was observed in rats fetuses.

Metabolism

In vitro and *in vivo* metabolism studies showed similar biotransformation pathways between rodent species, dogs, and humans, with quantitative differences. The metabolic pathways involved Phase I reactions including O-demethylations, hydroxylation on t-butyl group of the lateral chain, followed by a cyclization of the lateral chain and finally cleavage of cabazitaxel leading to the loss of the taxane ring. Numerous combinations of these metabolic pathways were observed. *In vivo*, the parent drug was the main circulating compound in mouse, rat, dog and human plasma (≥ 65% of the total radioactivity). Metabolism was the main elimination pathway of cabazitaxel in all species and almost no parent drug was excreted in urine or feces (<2.5% dose).

Seven metabolites were detected in human plasma but none of them accounted individually for more than 10% on average of systemic exposure of parent drug. All metabolites detected in human plasma were identified and detected in plasma and/or excreta of at least one animal species.

Excretion

Cabazitaxel exhibited a high plasma clearance in rats (4.8 L/h/kg) and dogs (2.5 to 5.3 L/h/kg) and moderate clearance in normal (0.9 to 1.1 L/h/kg) and tumor bearing mice (1.7 L/h/kg).
• Following intravenous dosing in mice, rats and dogs, radioactivity was mainly excreted in the feces via the bile (≥ 87% of the dose) and urinary excretion was minimal (≤ 4% of the dose).
• Following intravenous dosing [14C]-cabazitaxel to lactating rats, a small amount of radioactivity was excreted into milk (between 0.23% and 1.5% of the dose).

Cardiovascular safety pharmacology

The effects of cabazitaxel on the cardiovascular system were evaluated in pentobarbitone-anesthetized male dogs (N=4/group) with conventional ECG leads that received single intravenous doses of either cabazitaxel at a dose of 0.45 mg/kg (corresponding to 9 mg/m^2), vehicle (0.1% PS80/0.04% ethanol in 5% glucose, corresponding to the concentration of PS80 and ethanol contained in the cabazitaxel-treated group) or an aqueous solution of 5% glucose as 60 min infusions, according to a parallel group design. At the end of the 60 min infusion, heart rate was increased by 13 bpm in the vehicle control group and decreased by 29 bpm in the cabazitaxel group. At the 60 min time point, the

QTc interval was increased by 12 ms in the vehicle control group and by 54 ms in the cabazitaxel group.

ECG evaluations have been performed in a 13-cycle intravenous toxicity study conducted in non anesthetized dogs (N=40) up to 0.5 mg/kg/adm (10 mg/m^2/adm). There were no compound-related changes in heart rate, PR, QT corrected or not, and QRS values throughout the study at any dose level and after multiple intravenous treatments with cabazitaxel.

TOXICOLOGY

Effects on the liver

Bile ductule hyperplasia, arteriolar/periarteriolar necrosis, and/or hepatocellular necrosis were observed in dogs after 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 at exposure levels lower than clinical exposure levels. Kupffer cells pigmentation and bile ducts degeneration/regeneration were observed in the liver at the highest lethal dose of 10 mg/kg (60 mg/m^2) in a 10-cycle study in rats.

Neurotoxicity

Non-reversible peripheral neurotoxicity characterized histopathologically by degeneration in the sciatic nerves and lumbosacral nerve roots was observed in mice after 10 or 20 weeks following a single administration. The No-Observable Effect Level was 15 mg/kg (45 mg/m^2) after single intravenous administration over 1 hour.

Central neurotoxicity characterized histopathologically by neuron necrosis and/or vacuolation in the brain, axonal swelling and degeneration in the cervical spinal cord was noted in mice after a single 1-hour intravenous administration at 15 mg/kg (45 mg/m^2) considered sufficiently in excess of the maximum human exposure. The No-Observable Effect Level was 10 mg/kg (30 mg/m^2) (approximately 7-fold the AUC in cancer patients at the recommended human dose) after single intravenous administration over 1 hour.

Eye disorders

Subcapsular lens fiber swelling/degeneration was observed in rats during a 10-cycle toxicity study at 10-20 mg/kg (60-120 mg/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]). These effects were not reversible after 8 weeks.

Carcinogenicity

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

Mutagenicity

Cabazitaxel was found negative in the bacterial reverse mutagenic (Ames) test.

Genotoxicity

Cabazitaxel 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 at doses of 0.5, 1 and 1.5 mg/kg. However, these genotoxicity findings are inherent to the pharmacological activity of the compound (inhibition of tubulin depolymerization) and have been observed with compounds with the same pharmacological activity.

Teratogenicity

Non-clinical studies in rats and rabbits have shown that cabazitaxel is embryotoxic, fetotoxic, and abortifacient. When female rats were given cabazitaxel intravenously once daily from gestational days 6 through 17, embryofetal toxicity was observed at exposures lower than those seen in humans receiving clinically relevant doses of cabazitaxel (at a dose of 0.16 mg/kg/day; approximately one-tenth to one-twentieth the AUC in cancer patients at the recommended human dose) consisting of fetal deaths and decreased mean fetal weight associated with a delay in skeletal ossification. Similar findings have been reported with docetaxel or paclitaxel.

Cabazitaxel did not produce fetal abnormalities in rats and rabbits. Cabazitaxel crossed the placenta barrier in rats.

After a single intravenous administration of [^{14}C]-cabazitaxel at a dose of 0.08 mg/kg to lactating female rats, less than 1.5% of the dose was found in the maternal milk over 24 hours.

Impairment of fertility

Cabazitaxel did not affect mating performances or fertility of treated male rats at doses of 0.05, 0.1 and 0.2 mg/kg/day. However, in repeat dose toxicity studies, degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats treated intravenously with cabazitaxel at a dose of 5 mg/kg (approximately the AUC in cancer patients at the recommended human dose), and minimal testicular degeneration in dogs (minimal epithelial single cell necrosis in epididymis) treated at a dose of 0.5 mg/kg (approximately one-tenth of the AUC in cancer patients at the recommended human dose). Exposures in animals were similar or lower than those seen in humans receiving clinically relevant doses of cabazitaxel.

Phototoxicity

Taking into account the spectrum of ultra-violet absorption of cabazitaxel (no absorption within the 290-700 nm range) no phototoxicity study was performed.

REFERENCES

1. Sartor AO. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). Meeting: 2010 Genitourinary Cancers Symposium. San Francisco, California. Abstract No: 9.
2. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. Lancet 2010; 376(9747):1147-54.

PART III: CONSUMER INFORMATION

[Pr]JEVTANA®
Cabazitaxel for injection

This leaflet is part III of a three-part "Product Monograph" published when JEVTANA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JEVTANA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
JEVTANA, in combination with prednisone or prednisolone, is used to treat patients with metastatic prostate cancer who have received prior cancer treatment with docetaxel.

What it does:
Every cell in your body contains a supporting structure (almost like a "skeleton"). If this "skeleton" is damaged, the cell can not grow or divide.

JEVTANA makes the "skeleton" in cells unnaturally stiff, so the cancer cells then can no longer grow or divide.

When it should not be used:
- if you experienced severe allergy (hypersensitivity) to:
  - JEVTANA or any of the other ingredients in the formulation or components of the container; or
  - to other medicine containing the same nonmedicinal ingredients (polysorbate 80).
- if the number of your white blood cells is too low.
- if you have a liver disease.
- if you have recently received or you are about to receive a live vaccine such as yellow fever vaccine.

What the medicinal ingredient is:
Cabazitaxel

What the important nonmedicinal ingredients are:
Polysorbate 80 (including citric acid) and ethanol.

What dosage forms it comes in:
JEVTANA is a concentrated solution for injection and is available in a vial. Each vial contains 60mg/1.5 ml cabazitaxel. JEVTANA is to be diluted with a diluent provided with the product.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
JEVTANA should only be administered by a qualified healthcare professional experienced in the use of anticancer treatments.

Possible serious side effects with the use of JEVTANA include:
- Serious allergic reactions
- Low white blood cell count that may result in life-threatening infection and death
- Gastrointestinal reactions (such as bleeding and perforation) that may result in death

BEFORE or WHILE you use JEVTANA talk to your doctor, nurse or pharmacist if:

- You have a fever. A fever is the earliest sign of infection which may be caused by reduced white blood cell count.
- You have any allergies. Antiallergic medicines will be given to you to reduce the risk of an allergic reaction, as JEVTANA may also cause serious allergic reactions (hypersensitivity).
- You have severe or persistent diarrhea, nausea or vomiting which may result in dehydration.
- You have liver or kidney problems.
- You have heart problem or irregular heart rate.
- You are going to have any vaccines. JEVTANA should not be used if you have recently received or you are about to receive a live vaccine (such as yellow fever vaccine), since concomitant use may result in serious life-threatening infections.

JEVTANA might be present in your semen. Use a condom every time you have sexual intercourse with a woman who is pregnant or can get pregnant while you are taking JEVTANA and for 6 months after your last dose of JEVTANA.

JEVTANA may cause fatigue or dizziness. If you experience these symptoms, do not drive or use any tools or machines.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or your hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Some medicines may affect the way JEVTANA works or JEVTANA may affect how other medicines work.

These medicines include the following:
- medicines used to treat infections, such as: ketoconazole, rifampicin, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir, voriconazole
- medicines used to treat seizures, such as: carbamazepine, phenytoin, phenobarbital.

PROPER USE OF THIS MEDICATION

Usual dose:

JEVTANA will be given to you as an infusion into the vein (intravenous infusion) by a healthcare professional.

Usual dose: 25 mg/m^2 (body surface area) given as an intravenous infusion once every 3 weeks.

The infusion will take about 1 hour.

During treatment with JEVTANA you will also need to take prednisone by mouth every day.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

This medicine needs to be given on a fixed schedule. If you miss an appointment, call your doctor or nurse for instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, JEVTANA can cause side effects.

Very common side effects may include:
- low white blood cell count, which may cause infections and fever
- low red blood cell count (anemia), which may cause shortness of breath and fatigue
- low blood platelets that may lead to bleeding
- diarrhea, nausea, vomiting, constipation, abdominal pain
- decreased appetite
- change in the sense of taste
- blood in the urine (hematuria)
- allergic reactions
- hair loss
- tiredness
- muscle or joint pain
- back pain
- weakness
- cough
- shortness of breath
- fever

Common side effects may include:
- low blood pressure
- decreased amount of urine and swelling of the face, legs or body (kidney failure)
- headache
- dizziness
- numbness, tingling, burning or decreased sensation in the hands and feet
- muscle spasms
- dehydration
- urinary tract infection

Tell your doctor about any side effects that you might have during treatment with JEVTANA.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Fever, chills or signs of infection, like redness or swelling at the injection site, a cough that brings up mucus, or a sore throat		√	
Persistent vomiting or diarrhea; abdominal pain, abdominal tenderness, persistent constipation, dark stool or blood in stool.		√	
Kidney symptoms such as blood in the urine, urinary incontinence, decreased amount of urine, pain while urinating, swelling, especially in legs and feet, feeling confused, anxious, restless or sleepy, pain in the back just below the rib cage.		√	
Unusual bleeding or bruising, black or tarry stools, blood in the urine		√	
Extreme weakness or fatigue		√	
Uncommon			
Allergic reactions such as trouble breathing, tightness in the throat, rash, hives, swelling of the lips or tongue or low blood pressure		√	

This is not a complete list of serious side effects. For any unexpected effects while taking JEVTANA, contact your doctor or pharmacist.

HOW TO STORE IT

The unopened vials should be stored at room temperature between 15°C to 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701 E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.sanofi.ca, or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927

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