For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory
This package insert is continually updated. Please read carefully before using a new pack.

Cabazitaxel Injection for Intravenous Infusion
JEVTANA®

COMPOSITION

Active ingredient: cabazitaxel

- One single-use vial Jevtana 60 mg /1.5 mL concentrate contains 60 mg cabazitaxel (solvent free and anhydrous) in a total volume of 1.5 mL
- One ml of Jevtana concentrate contains 40 mg cabazitaxel.

Excipients:

- concentrate vial: polysorbate 80, citric acid.
- solvent vial: ethanol 96% (573.3 mg), water for injection.

NATURE AND CONTENTS OF CONTAINER

One pack contains (2 vials):
Concentrate vial is a 15 mL clear glass vial (type I) closed with a grey chlorobutyl rubber closure sealed by an aluminum cap covered with a light green plastic flip-off cap. Each vial contains 60 mg Jevtana per 1.5 mL nominal volume (fill volume: 1.83 mL per 73.2 mg of Jevtana). This fill volume has been established during the development of Jevtana to compensate for liquid loss during preparation of the premix. This overfill ensures that after dilution with the ENTIRE content of the accompanying solvent for Jevtana, there is a minimal extractable premix volume of 6 mL containing 10 mg/mL Jevtana which corresponds to the labeled amount of 60 mg per vial.

Solvent vial is a 15 mL clear glass vial (type I) closed with a grey chlorobutyl rubber closure sealed by a gold color aluminum cap covered with a colourless plastic flip-off cap. Each vial contains 4.5 mL nominal volume (fill volume: 5.67mL). This fill volume has been established during the development and the overfill ensures, after the addition of the ENTIRE content of the solvent vial to the content of the Jevtana 60 mg concentration for solution vial, a concentration of the premix solution of the 10 mg/mL Jevtana.

INDICATIONS

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

DOSAGE AND ADMINISTRATION

General
The use of Jevtana should be confined to units specialized in the administration of cytotoxics and it should be administered under the supervision of a physician experienced in the use of anticancer chemotherapy (See section Preparation and Handling).

Premedication
Premedicate prior (at least 30 minutes before) to each administration of Jevtana with the following intravenous medications to reduce the incidence and severity of a hypersensitivity reaction:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent) and with
- H2 antagonist (ranitidine or equivalent) (See section Precautions).

Antiemetics prophylaxis is recommended and can be given orally or intravenously as needed.

Posology
The recommended dose of Jevtana is 25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout Jevtana treatment.

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

Table 1 - 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 > 1,500 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 > 1,500 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.

If patients continue to experience any of these reactions at 20mg/m^2, a further dose reduction to 15 mg/m^2 or discontinuation of Jevtana may be considered. Data in patients below the 20 mg/m^2 dose are limited.

Special Populations

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

Elderly Patients
No specific dose adjustment for the use of Jevtana in elderly patients is recommended (See section Precaution and Section Adverse Reactions).

Patients with Hepatic impairment
Jevtana is extensively metabolized by the liver.

- Patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN), should have cabazitaxel dose reduced to 20 mg/m^2. Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety.
- 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.
- Jevtana should not be given to patients with severe hepatic impairment [total bilirubin >3 x ULN (See section Contraindications and section Precautions)

Patients with Renal impairment
Jevtana is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting end-stage renal disease (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.

Concomitant drug use
Concomitant drugs that are strong CYP3A inducers or strong CYP3A inhibitors should be avoided (See section Interactions). However, if patients require co-administration of a strong CYP3A inhibitor, a 25% cabazitaxel dose reduction should be considered (See section Interactions).

Administration
Intravenous infusion.

CONTRAINDICATIONS

In patients with:

- a history of severe hypersensitivity reactions to cabazitaxel or other drugs formulated with polysorbate 80;
- neutrophil counts less than 1,500/mm^3;
  severe hepatic impairment (total bilirubin > 3 x ULN).

WARNINGS & PRECAUTIONS

WARNING: Monitoring of complete blood count is essential at appropriate intervals

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

Neutropenia
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). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

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

Neutropenia is the most common adverse reaction of Jevtana (See Section Adverse Reactions). 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 Section Dosage and Administration – General). Reduce dose in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment. Retreat only when neutrophils recover to a level ≥ 1,500/mm^3 (See section Contraindications).

Hypersensitivity reactions
All patients should be premedicated prior to the initiation of the infusion of Jevtana (See Section Dosage and Administration – General).
Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be

available. Severe reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy. Patients who have a history of severe hypersensitivity reactions should not be rechallenged with Jevtana (See section Contraindications).

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. Treatment delay or dosage reduction may be necessary for grade ≥3 diarrhea (See Section Dosage and Administration – General). 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.

Anemia
Anemia has been observed in patients receiving cabazitaxel (see Section Adverse Reactions).Hemoglobin and hematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anemia or blood loss. Caution is recommended in patients with hemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated.

Renal disorders
Renal disorders, have been reported in association with sepsis, severe dehydration due to diarrhea, 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. Renal function should be monitored.

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

Respiratory disorders
Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome (see Section Adverse event).
If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of cabazitaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming cabazitaxel treatment must be carefully evaluated.

Cardiac arrhythmias
Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation (See section Adverse Event).

Elderly patients
Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions including neutropenia or febrile neutropenia (See section Adverse Event).

Patients with hepatic impairment
Cabazitaxel is extensively metabolized in the liver.
Jevtana is contraindicated in patients with severe hepatic impairment (total bilirubin> 3 ULN(See section Contraindications).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 section Special Populations).

INTERACTIONS

The metabolism of cabazitaxel is modified by the concomitant administration of compounds which are known to be strong inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, vorconazole) or strong inducers (e.g., rifampicin, carbamazepine, or phenytoin) of CYP3A. Co-administration with strong CYP3A inhibitors should be avoided. If co-administration with a strong CYP3A inhibitor cannot be avoided, close monitoring for toxicity and a cabazitaxel dose reduction should be considered (See Section Dosage and Administration – Special Population).

Co-administration with strong CYP3A inducers should be avoided as they may decrease cabazitaxel exposure (See section Dosage and Administration – Special Populations).

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 administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.

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

PREGNANCY

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.

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

LACTATION

Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk. Jevtana should not be used during breast-feeding.

FERTILITY

The effect of Jevtana on human fertility is unknown. Animal studies showed that cabazitaxel affected reproductive system in male rats and dogs.

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 to not drive or use machines if they experience these adverse reactions during treatment.

ADVERSE EVENTS

The following 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).

CLINICAL STUDIES

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

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

Common (≥ 5%) Grade ≥ 3 adverse reactions in patients who received cabazitaxel were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

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 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 TROPIC occurred after a single dose of Jevtana.

Table 2. Incidence of reported adverse reactions and hematologic abnormalities in patients receiving Jevtana in combination with prednisone and patients receiving mitoxantrone in combination with prednisone (at least 2% higher incidence rate in the Jevtana group compared to mitoxantrone)

	Jevtana at 25 mg/m² every 3 weeks in combination with prednisone 10 mg daily		**Mitoxantrone at 12 mg/m² every 3 weeks in combination with prednisone 10 mg daily**	
	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%)
Anaemia[a]	361 (97.3%)	39 (10.5%)	302 (81.4%)	18 (4.9%)
Leukopenia[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				
Diarrhoea	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
Haemorrhoids	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%)
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
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 n=371		Mitoxantrone at 12 mg/m^2 every 3 weeks in combination with prednisone 10 mg daily n=371	
	All grades n (%)	**grade 3/4 n (%)**	**All grades n (%)**	**grade 3/4 n (%)**
Renal and urinary tract disorder				
Haematuria	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				
Dyspnoea	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
Infections And Infestations				
Urinary Tract Infection	27 (7.3%)	4 (1.1%)	11 (3.0%)	3 (0.8%)
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
Vascular Disorders				
Hypotension	20 (5.4%)	2 (0.5%)	9 (2.4%)	1 (0.3%)

a based on laboratory values

Description of selected adverse reactions:
General disorders and administration site conditions
Peripheral oedema was observed at an incidence of 9.2% in all grades, and an incidence of 0.5% and 0.3% in grade ≥ 3 in the Jevtana arm and mitoxantrone arm, respectively.

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.

Neutropenia and associated clinical events:
Incidence of grade ≥ 3 neutropenia based on laboratory data was 81.7%. The incidence grade ≥ 3 of 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.
The use of G-CSF has been shown to limit the incidence and severity of neutropenia (See Section Dosage and Administration – General).

Cardiac disorders and arrhythmias:
All Grade events among cardiac disorders were more common in Jevtana group of which 6 patients (1.6%) had Grade ≥ 3 cardiac arrhythmias. The incidence of tachycardia in Jevtana group was 1.6%, none of which were Grade ≥ 3. The incidence of atrial fibrillation was 1.1% in the Jevtana group.

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.
Hematuria all grades was observed at 20.8% in EFC11785 study. Confounding causes such as disease progression, instrumentation, infection or anticoagulation/NSAID/aspirin therapy were identified in nearly two thirds of the cases.

Gastrointestinal Disorders:
Colitis, enterocolitis, gastritis, neutropenic enterocolitis have been observed. Gastrointestinal hemorrhage 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 outcome have been reported (see Section Precautions).

Investigations:
The incidence of grade ≥ 3 anemia, increased AST/SGOT, increased ALT/SGPT, and increased bilirubin based on laboratory abnormalities were 10.6%, 0.9%, 1.1%, and 0.6%, respectively.

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

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 Section Dosage and Administration – Special population and Section Precautions).
Of the 595 patients treated with cabazitaxel 25 mg/m2 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%).

POST MARKETING EXPERIENCES
• Renal and urinary disorders
Cystitis due to radiation recall phenomenon was reported uncommonly. (See section Precautions)

OVERDOSE

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.

INCOMPATIBILITIES / COMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section Preparation and handling.

Always dilute Jevtana 60 mg/1.5 mL concentrate for solution for infusion with the supplied solvent before adding to infusion solutions.

Jevtana contains polysorbate 80 which is known to increase the rate of di-(2-ethylhexyl) phtalate extraction (DEHP) from polyvinyl chloride (PVC).

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

STORAGE CONDITIONS AND SHELF-LIFE

Storage:
Before dilution
Store below 30 °C
Do not refrigerate.

After dilutions:
For storage conditions of the diluted medicinal product (See section Preparation and Handling).

Shelf-life:
See outer carton

Stability of the initial diluted solution in the vial:
After initial dilution of Jevtana 60 mg/1.5 mL concentrate with the solvent, the resulting concentrate-solvent mixture is stable for 1 hour if stored at ambient temperature.

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 at ambient temperature (including the 1 hour infusion).

Chemical and physical stability of the infusion solution has been demonstrated for 48 hours under refrigerated conditions (including the 1 hour infusion).

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

PREPARATION AND HANDLING

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.

Preparation steps

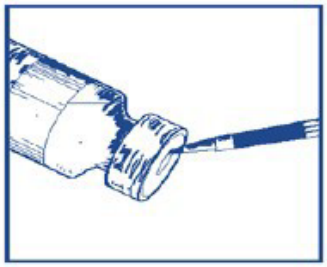
Read this ENTIRE section carefully before mixing and diluting. Jevtana requires TWO dilutions prior to administration. Follow the preparation instructions provided below.

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

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

Step 1: First dilution

Step 1.1
Inspect the Jevtana 60 mg/1.5 ml concentrate vial and the supplied solvent. The concentrate solution should be clear.



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

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

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

Step 1.5
Let this solution stand for approximately 5 minutes and check then that the solution is homogeneous and clear.

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

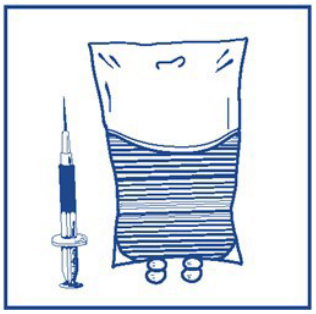
This resulting concentrate-solvent mixture contains 10 mg/ml of Jevtana (at least 6 ml deliverable volume. The second dilution should be done immediately (within 1 hour) as detailed in Step 2.

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

Step 2: Second (final) dilution for infusion

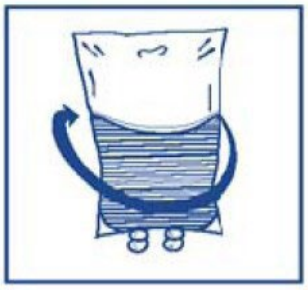
Step 2.1
Aseptically withdraw the required amount of initial diluted Jevtana solution (10 mg/ml of Jevtana), with a graduated syringe fitted with a needle.

Step 2.2
Inject in a sterile PVC-free container 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.



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

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



Step 2.4
As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. Solution containing a precipitate should be discarded.

Preparation and administration

- Jevtana is administered as a 1 hour Infusion.
- Do not use PVC infusion containers.
- Do not use polyurethane infusion sets.

Use an in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) during administration.
The Jevtana infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions (See Section Storage and Shelf life).

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

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

Jevtana must not be mixed with any other medicines.

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