PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] CABAZITAXEL FOR INJECTION

Concentrated Solution 10 mg/mL, Intravenous
(45 mg/4.5 mL & 60 mg/6 mL)

Manufacturer's Standard

Antineoplastic Agent

L01CD04

Sandoz Canada Inc.
110, de Lauzon Street
Boucherville, QC J4B 1E6
Canada

Date of Initial Authorization

December 17, 2019

Date of Revision:
February 14, 2023

Submission Control No: 268715

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	02/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Cabazitaxel for Injection (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.

Cabazitaxel for Injection should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy (see 3 SERIOUS WARNINGS AND PRECAUTIOUS BOX, 4 DOSAGE AND ADMINISTRATION and 12 SPECIAL HANDLING INSTRUCTIONS).

1.1 Pediatrics (<18 years of age)

There is no indication for the use of Cabazitaxel for Injection in the pediatric population. The safety and the efficacy of cabazitaxel in children have not been established (see 10 CLINICAL PHARMACOLOGY – Special Populations and Conditions).

1.2 Geriatrics (≥ 65 years 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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

2 CONTRAINDICATIONS

Cabazitaxel for Injection 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 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING.
- neutrophil counts ≤ 1500 / mm^3;
- severe hepatic impairment (total bilirubin > 3 x Upper Limit of Normal (ULN)).
- concomitant vaccination with yellow fever vaccine (see 9 DRUG INTERACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Cabazitaxel for Injection should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy (see 1 INDICATIONS).
- Severe hypersensitivity, pre-medication is recommended prior to treatment (see 4 DOSAGE AND ADMINISTRATION).
- Neutropenic death/Neutrophil count (see 7 WARNINGS AND PRECAUTIONS).
- Gastrointestinal (GI) hemorrhage and perforation, including fatal cases, particularly in patients most at risk of developing gastrointestinal complications (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The use of Cabazitaxel for Injection 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 4.4 Administration and 12 SPECIAL HANDLING INSTRUCTIONS).

- Premedication is recommended prior to treatment.

  Premedicate prior to each administration of Cabazitaxel for Injection 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 7 WARNINGS AND PRECAUTIONS).

  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 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

- Patients treated with Cabazitaxel for Injection 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) (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

- The patients may also receive antibiotics when appropriate.

Hepatic insufficiency

Cabazitaxel is extensively metabolized in 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 for Injection dose reduced to 20 mg/m^2. Administration of Cabazitaxel for Injection to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety.
- In patients with moderate hepatic impairment (total bilirubin >1.5 to ≤ 3.0 x ULN), the maximum tolerated dose (MTD) was 15 mg / m^2. If the treatment is considered in patients with moderate hepatic impairment, the dose of cabazitaxel should not exceed 15 mg/m^2. However, limited efficacy data are available and the efficacy of cabazitaxel at this dose is unknown. Patients should be treated with caution and monitored carefully during treatment.
- Cabazitaxel for Injection is contraindicated in patients with severe hepatic impairment (total bilirubin >3 x ULN) (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal insufficiency

Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting end stage renal disease (CL_{CR} <15 mL/min/1.73m^2), by their condition and the limited amount of available data; should be treated with caution and monitored carefully during treatment (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Concomitant drug

Concomitant drugs that are CYP3A inducers or potent CYP3A inhibitors should be avoided (see 9 DRUG INTERACTIONS)

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of Cabazitaxel for Injection is 20 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout Cabazitaxel for Injection treatment (see 14 CLINICAL TRIALS, Study EFC11785 [PROSELICA]).

A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, and 14 CLINICAL TRIALS, Study EFC6193 [TROPIC]).

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 Cabazitaxel for Injection

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 Cabazitaxel for Injection by one dose level.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is > 1500 cells/mm^3, then reduce dosage of Cabazitaxel for Injection by one dose level.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of Cabazitaxel for Injection by one dose level.
Grade > 2 peripheral neuropathy	Delay treatment until improvement, then consider a dose reduction by one dose level.

Patients at a 20 mg/m^2 dose who require dose reduction should decrease dosage of Cabazitaxel for Injection to 15 mg/m^2 (see 8 ADVERSE REACTIONS).

Patients at a 25 mg/m^2 dose who require dose reduction should decrease dosage of Cabazitaxel for Injection to 20 mg/m^2. One additional dose reduction to 15 mg/m^2 may be considered (see 8 ADVERSE REACTIONS).

Pediatrics (<18 years of age): Limited data are available on the use of cabazitaxel in pediatric patients. The safety and the efficacy of cabazitaxel in children have not been established (see 1 INDICATIONS, 1.1 Pediatrics, 10 CLINICAL PHARMACOLOGY – Special Populations and Conditions).

Geriatrics (≥ 65 years of age): No specific dose adjustment for the use of Cabazitaxel for Injection in elderly patients is recommended (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

4.3 Reconstitution

Read this ENTIRE section carefully before mixing and diluting. Cabazitaxel for Injection requires dilution prior to administration. Follow the preparation instructions provided below.

Note: Cabazitaxel for Injection contains an overfill to compensate for liquid loss during preparation.

Inspect the Cabazitaxel for Injection vial. The Cabazitaxel for Injection is a clear colorless to pale yellow viscous solution.

Cabazitaxel for Injection should not be mixed with any other drugs.

Dilution
Withdraw the recommended dose from the Cabazitaxel for Injection solution containing 10 mg / mL using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of Cabazitaxel for Injection is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg / mL cabazitaxel is not exceeded. The concentration of the Cabazitaxel for Injection final infusion solution should be between 0.10 mg / mL and 0.26 mg / mL.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Fully prepared Cabazitaxel for Injection infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at room temperature (including the one-hour infusion), or for a total of 48 hours (including the one-hour infusion which should be administrated at room temperature) under the refrigerated conditions.

Discard any unused portion.

4.4 Administration

- The final Cabazitaxel for Injection solution should be administered intravenously as a

one-hour infusion at room temperature.

- 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 infusions sets for preparation and administration of Cabazitaxel for Injection infusion solution.

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the Cabazitaxel for Injection solution is not clear or appears to have precipitation, it should be discarded.

4.5 Missed Dose

This medicine needs to be given on a fixed schedule. Instruct the patient to call their doctor or nurse for instructions.

5 OVERDOSAGE

Signs and Symptoms
The anticipated complications of overdose would be exacerbation of adverse reactions as bone marrow suppression (manifested as neutropenia, anemia, thrombocytopenia, or pancytopenia) and gastrointestinal disorders.

Management
There is no known antidote to Cabazitaxel for Injection. 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.

6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength /Composition	Non-medicinal Ingredients
Intravenous infusion	Concentrated solution 10 mg /mL	Polysorbate 80, Polyethylene Glycol 300, Ethanol

Dosage Forms

Cabazitaxel for Injection is supplied as follows:

Cabazitaxel injection: 45 mg / 4.5 mL or 60 mg / 6 mL multi-dose vial; a clear colorless to pale yellow viscous solution.

Composition

Cabazitaxel for Injection 10 mg / mL Concentrated Solution
Each mL contains 10 mg cabazitaxel (anhydrous), 260 mg polysorbate 80, 4.5 mg citric acid anhydrous, 198 mg ethanol absolute, and 560 mg polyethylene glycol 300.

Cabazitaxel for Injection requires dilution prior to intravenous infusion. Cabazitaxel for Injection should be diluted in either 0.9% sodium chloride solution or 5% dextrose solution.

Note: The Cabazitaxel for Injection 45 mg / 4.5 mL concentrate multi-dose vials are filled with an 11% excess (corresponding to 50 mg cabazitaxel for a total fill volume of 5.0 mL). The Cabazitaxel for Injection 60 mg / 6 mL concentrate multi-dose vials are filled with a 10% excess (corresponding to 66 mg cabazitaxel for a total fill volume of 6.6 mL).

Table 3 – Nominal and actual fill volumes for Cabazitaxel for Injection concentrate vials

	Diluent vial	Concentrate vial
Nominal volume	4.5 mL (45 mg cabazitaxel) multi-dose vial	6 mL (60 mg cabazitaxel) multi-dose vial
Actual fill volume	5.0 mL (50 mg cabazitaxel) multi-dose vial	6.6 mL (66 mg cabazitaxel) multi-dose vial

The fill volumes of 5.0 and 6.6 mL for the 45 mg and 60 mg respectively are aligned with the USP <1151> recommendations for viscous liquids and ensure that there is a minimal extractable volume of 4.5 mL and 6.0 mL, respectively, containing 10 mg / mL cabazitaxel which corresponds to the labelled amount.

Packaging

Cabazitaxel for Injection (45 mg / 4.5 mL or 60 mg / 6 mL) is supplied as a multi-dose vial containing clear colorless to pale yellow viscous solution in a clear glass vial with a grey rubber closure, aluminum cap, and plastic flip-off cap.

The vial stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIOUS BOX.

Cardiovascular

There is pre-clinical evidence that cabazitaxel may prolong the QT interval (see 10 CLINICAL PHARMACOLOGY, 16 NON-CLINICAL TOXICOLOGY, Cardiovascular Safety Pharmacology). 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 cabazitaxel, most commonly tachycardia and atrial fibrillation. During the randomized TROPIC clinical trial, 4 fatal cases related to cardiac events were reported, although none was considered related to cabazitaxel by the investigator (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Study EFC6193 [TROPIC], Cardiac disorders and arrhythmias). During the randomized PROSELICA study, one death due to cardiac arrest occurred in the cabazitaxel 25 mg/m^2 arm.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. However, based on the safety profile, cabazitaxel may have moderate influence on the ability to drive and use machines as it may cause fatigue and dizziness. Patients should be advised not to drive or use machines if they experience these adverse reactions during treatment.

Gastrointestinal

If patients experience diarrhea following administration of Cabazitaxel for Injection 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 4 DOSAGE AND ADMINISTRATION). During the randomized clinical trial, one fatal case was due to electrolyte imbalance (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Study EFC6193 [TROPIC], Gastrointestinal).

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.

Genitourinary

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 8 ADVERSE REACTIONS, 8.5 Post-Market Reactions). Appropriate measures should be initiated. Interruption or discontinuation of Cabazitaxel for Injection therapy may be necessary.

Hematologic

Bone marrow suppression

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

Anemia

Anemia has been observed in patients receiving cabazitaxel. Hemoglobin and hematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anemia or blood loss (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Caution is recommended in patients with hemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated.

Neutropenia

During the randomized TROPIC 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 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Study EFC6193 [TROPIC], 8.4 Abnormal Hematologic and Clinical Chemistry and Other Quantitative Data).

In the randomized PROSELICA trial, 125 (21.0%) patients in the cabazitaxel 25 mg/m^2 group and 37 (6.4%) patients in the cabazitaxel 20 mg/m^2 group experienced at least one treatment-emergent adverse event (TEAE) of febrile neutropenia, neutropenic infection, neutropenic sepsis or Grade 4 neutropenia. Grade 4 neutropenia, febrile neutropenia, neutropenic infection, and neutropenic sepsis were all reported in more cycles in the cabazitaxel 25 mg/m^2 group compared with the cabazitaxel 20 mg/m^2 group, irrespective of G-CSF use, and were reported in

fewer cycles for subjects who took G-CSF as prophylaxis compared with patients with no G-CSF use.

Neutropenia is the most common adverse reaction of cabazitaxel (see 8 ADVERSE REACTIONS).

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). Reduce dose in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see 4 DOSAGE AND ADMINISTRATION). Re-treat only when neutrophils recover to a level > 1500/mm^3 (see 2 CONTRAINDICATIONS).

Patients treated with Cabazitaxel for Injection 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. 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.

Immune

Hypersensitivity reactions

All patients should be premedicated prior to the initiation of the infusion of Cabazitaxel for Injection (see 4 DOSAGE AND ADMINISTRATION).

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of Cabazitaxel for Injection, 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 for Injection and appropriate therapy. Patients who have a history of severe hypersensitivity reactions should not be rechallenged with Cabazitaxel for Injection (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Monitoring of complete blood count (including differential and platelets) 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 7 WARNINGS AND PRECAUTIONS, Hematologic).

Renal function should be monitored during Cabazitaxel for Injection therapy. Serum creatinine should be measured at baseline and with each blood count. Cabazitaxel for Injection treatment should be discontinued in case of renal failure ≥ grade 3 (see 7 WARNINGS AND PRECAUTIONS, Renal, Monitoring and Laboratory Tests).

Liver function tests (including AST, ALT and total bilirubin) should be measured at baseline and before each cycle of Cabazitaxel for Injection (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic, Monitoring and Laboratory Tests).

Neurologic

Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel (see 8 ADVERSE REACTIONS).

Renal

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 was observed during the TROPIC randomized clinical trial; 1 fatal case of renal failure was observed in the PROSELICA trial in the cabazitaxel 20 mg/m^2 arm (see 8 ADVERSE REACTIONS, 8.2 Clinical Trials Adverse Drug Reactions). Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs.

Renal function should be monitored during Cabazitaxel for Injection therapy. Serum creatinine should be measured at baseline and with each blood count. Cabazitaxel for Injection treatment should be discontinued in case of renal failure ≥ grade 3 (see 7 WARNINGS and PRECAUTIONS, Monitoring and Laboratory tests).

Reproductive Health: Female and Male Potential

Due to potential exposure via seminal liquid, men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of Cabazitaxel for Injection. Men being treated with Cabazitaxel for Injection are advised to seek advice on conservation of sperm prior to treatment (see 7.1.1 Pregnant Women).

- **Fertility**

  The effect of Cabazitaxel for Injection on human fertility is unknown. Animal studies showed that cabazitaxel affected reproductive system in male rats and dogs (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions). If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of Cabazitaxel for Injection therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming Cabazitaxel for Injection treatment must be carefully evaluated.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of cabazitaxel in pregnant women. Cabazitaxel crosses the placenta barrier. 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 (see 16 NON-CLINICAL TOXICOLOGY). Cabazitaxel for Injection is not recommended during pregnancy.

7.1.2 Breast-feeding

Nursing Women:

Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk (see 16 NON-CLINICAL TOXICOLOGY). Cabazitaxel for Injection should not be used during breast-feeding.

7.1.3 Pediatrics (<18 years of age)

Limited data are available on the use of cabazitaxel in pediatric patients. The safety and the efficacy of cabazitaxel in children have not been established (see 10 CLINICAL PHARMACOLOGY – Special Populations and Conditions).

7.1.4 Geriatrics (≥ 65 years of age)

Elderly patients may be more likely to experience certain adverse reactions including neutropenia and febrile neutropenia (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions). However, no specific dose adjustment for the use of Cabazitaxel for Injection in elderly patients is recommended (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

7.1.5 Hepatic insufficiency

Cabazitaxel is extensively metabolized in 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 for injection dose reduced to 20 mg/m^2. Administration of Cabazitaxel for Injection to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety.
- In patients with moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3.0 x ULN), the maximum tolerated dose (MTD) was 15 mg/m^2. If the treatment is considered in patients with moderate hepatic impairment, the dose of cabazitaxel should not exceed 15 mg/m^2. However, limited efficacy data are available and the efficacy of cabazitaxel at this dose is unknown. Patients should be treated with caution and monitored carefully during treatment.
- Cabazitaxel for Injection is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN) (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).
- Hepatic impairment increases the risk of severe and life-threatening complications in patients receiving other drugs belonging to the same class as Cabazitaxel for Injection.

7.1.6 Renal insufficiency

Cabazitaxel for Injection is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting end-stage renal failure (CL_{CR} <15 mL/min/1.73m^2), by their condition and the limited amount of available data should be treated with caution and monitored carefully during treatment (see also 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

The Grade ≥ 3 adverse reactions reported in ≥ 5% of the patients in the phase III TROPIC study including 371 patients in the cabazitaxel group treated with cabazitaxel 25 mg/m^2 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 7 WARNINGS AND PRECAUTIONS and Study EFC6193 [TROPIC] below).

The Grade ≥ 3 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m^2 versus 20 mg/m^2 arms in the phase III PROSELICA study were leukopenia, neutropenia, and febrile neutropenia. The most common adverse reactions leading to treatment discontinuation were neutropenia/neutropenic infection/neutropenic sepsis, fatigue and hematuria on the 25

mg/m^2 arm, and fatigue and neutropenia/neutropenic infection/neutropenic sepsis on the 20 mg/m^2 arm. (see 7 WARNINGS AND PRECAUTIONS and Study EFC11785 [PROSELICA] below).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Study EFC6193 (TROPIC)

The safety of cabazitaxel 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), who were randomized to receive either cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2. Patients received a median duration of 6 cycles of cabazitaxel 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 4**).

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

Discontinuation of treatment due to adverse reactions occurred in 68 patients (18.3%) in the cabazitaxel group and 31 patients (8.4%) in the mitoxantrone group. The most common adverse reactions leading to treatment discontinuation in the cabazitaxel 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%) cabazitaxel-treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in cabazitaxel-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 cabazitaxel.

Table 4 provides the incidence of all adverse reactions and hematologic abnormalities occurring at higher rate (at least 2% higher) in patients receiving cabazitaxel 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 4 - Incidence of reported adverse reactions and hematologic abnormalities in patients receiving cabazitaxel in combination with prednisone (or prednisolone) and patients receiving mitoxantrone in combination with prednisone (or prednisolone) (at least 2% higher incidence rate in the cabazitaxel group compared to mitoxantrone) [TROPIC study]

Body System / Preferred term	Cabazitaxel at 25 mg/m² every 3 weeks in combination with prednisone 10 mg daily (or prednisolone) n=371		Mitoxantrone at 12 mg/m² 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 (%)
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%)
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 cabazitaxel of which 6 patients (1.6%) had grade ≥3 cardiac arrhythmias. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were grade ≥3. The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%). One patient in the cabazitaxel group died from cardiac failure. Fatal ventricular fibrillation was reported in 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel-treated patients.

Study EFC 11785 (PROSELICA)

EFC11785 was a non-inferiority, multicenter, multinational, randomized, open label phase III

study in patients with metastatic castration resistant prostate cancer, previously treated with a docetaxel containing regimen, who were randomized to receive either cabazitaxel 25 mg/m^2 (n=602) or 20 mg/m2 (n=598) dose in combination with prednisone or prednisolone.

EFC11785 study demonstrated a better safety profile for the cabazitaxel 20 mg/m^2 dose. The safety profile of cabazitaxel 25 mg/m^2 observed in this study was qualitatively and quantitatively similar to that observed in the study EFC6193 (TROPIC study).

The patients in the 20 mg/m^2 group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m^2 group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m^2 group, 128 patients (21.5%) had a dose reduced from 25 to 20 mg/m^2, 19 patients (3.2%) had a dose reduced from 20 to 15 mg/m^2 and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m^2. In the 20 mg/m2 group, 58 patients (10.0%) had a dose reduced from 20 to 15 mg/m^2 and 9 patients (1.6%) had a dose reduced from 15 to 12 mg/m^2.

Treatment discontinuations due to adverse drug reactions occurred in 16% of patients in the 20 mg/m^2 group and 20% of patients in the 25 mg/m^2 group. The most common adverse reactions leading to treatment discontinuation were neutropenia/neutropenic infection/neutropenic sepsis, fatigue and hematuria on the 25 mg/m^2 arm, and fatigue and neutropenia/neutropenic infection/neutropenic sepsis on the 20 mg/m^2 arm.

Grade 1-4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m^2 versus 20 mg/m^2 arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, diarrhea, nausea, hematuria and asthenia.

Grade 3-4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m^2 versus 20 mg/m2 arms were leukopenia, neutropenia, and febrile neutropenia.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m^2 and 32 (5.4%) patients in the 25 mg/m^2 arm. Deaths within 30 days of last study drug dose due to adverse events were reported in 3.2% on the 25 mg/m^2 arm and in 2.1% on the 20 mg/m^2 arm. The most common fatal adverse reactions in cabazitaxel-treated patients were related to infections, and these occurred more commonly on the 25 mg/m^2 arm (n=15) than on the 20 mg/m^2 arm (n=8). Other fatal adverse reactions within 30 days of last study drug dose in cabazitaxel-treated patients included cerebral hemorrhage, respiratory failure, paralytic ileus, diarrhea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, and cardiorenal syndrome.

Table 5 - Incidence of Adverse Reactions* in ≥5% of Patients Receiving cabazitaxel 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone in PROSELICA Study

Primary System Organ Class / Preferred term	Cabazitaxel 20 mg/m² every 3 weeks with prednisone 10 mg daily n=580		Cabazitaxel 25 mg/m² every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	12 (2%)	12 (2%)	55 (9%)	55 (9%)
Neutropenia†	18 (3%)	14 (2%)	65 (11%)	57 (10%)
Infections and Infestations				
Urinary tract infection‡	43 (7%)	12 (2%)	66 (11%)	14 (2%)
Neutropenic infection§	15 (3%)	13 (2%)	42 (7%)	36 (6%)
Metabolism and Nutrition Disorders				
Decreased appetite	76 (13%)	4 (0.7%)	110 (19%)	7 (1%)
Nervous System Disorders				
Dysgeusia	41 (7%)	0	63 (11%)	0
Peripheral sensory neuropathy	38 (7%)	0	63 (11%)	4 (0.7%)
Dizziness	24 (4%)	0	32 (5%)	0
Headache	29 (5%)	1 (0.2%)	24 (4%)	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	30 (5%)	5 (0.9%)	46 (8%)	4 (0.7%)
Cough	34 (6%)	0	35 (6%)	0
Gastrointestinal Disorders				
Diarrhea	178 (31%)	8 (1%)	237 (40%)	24 (4%)
Nausea	142 (25%)	4 (0.7%)	191 (32%)	7 (1%)
Vomiting	84 (15%)	7 (1.2%)	108 (18 %)	8 (1%)
Constipation	102 (18%)	2 (0.3%)	107 (18%)	4 (0.7%)
Abdominal pain	34 (6%)	3 (0.5%)	52 (9%)	7 (1%)
Stomatitis	27 (5%)	0	30 (5%)	2 (0.3%)
Skin and Subcutaneous Tissue Disorders				
Alopecia	15 (3%)	0	36 (6.1%)	0
Musculoskeletal and Connective Tissue Disorders				

Back pain	64 (11%)	5 (0.9%)	83 (14%)	7 (1%)
Bone pain	46 (8%)	10 (2%)	50 (8%)	13 (2 %)
Arthralgia	49 (8%)	3 (0.5%)	41 (7%)	5 (0.8%)
Pain in extremity	30 (5%)	1 (0.2%)	41 (7%)	3 (0.5%)
Renal and Urinary Disorders				
Hematuria	82 (14%)	11 (2%)	124 (21%)	25 (4%)
Dysuria	31 (5%)	2 (0.3%)	24 (4%)	0
General Disorders and Administration Site Conditions				
Fatigue	143 (25%)	15 (3%)	161 (27%)	22 (4%)
Asthenia	89 (15%)	11 (2%)	117 (20%)	12 (2%)
Edema peripheral	39 (7%)	1 (0.2%)	53 (9%)	1 (0.2%)
Pyrexia	27 (5%)	1 (0.2%)	38 (6 %)	1 (0.2%)
Investigations				
Weight decreased	24 (4%)	1 (0.2%)	44 (7%)	0
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	2 (0.3%)	0	32 (5%)	0

* Grade from NCI CTCAE version 4.03.
† Based on adverse event reporting.
‡ Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.
§ Includes neutropenic sepsis.

Of the 595 patients treated with cabazitaxel 25 mg/m^2 in the prostate cancer EFC11785 study, 420 patients were 65 years or over. The adverse reactions (all grades) reported at rates of at least 5% higher in patients 65 years of age or greater compared to younger patients were diarrhea (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 dyspnea (9.5% vs. 3.4%).

Of the 580 patients treated with cabazitaxel 20 mg/m^2, 402 patients were 65 years or over. The adverse reactions (all grades) reported at rates of at least 5% higher in patients 65 years of age or greater compared to younger patients were diarrhea (34.3% vs. 22.5%), fatigue (27.6% vs. 18.0%), decreased appetite (15.4% vs. 7.9%), back pain (12.9% vs. 6.7%), and dysgeusia (8.7% vs. 3.4%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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 4 DOSAGE AND ADMINISTRATION).

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.

Table 6- Incidence of Hematologic Laboratory Abnormalities in Patients Receiving cabazitaxel 20 mg/m² or 25 mg/m² in Combination with Prednisone in PROSELICA Study

	Cabazitaxel 20 mg/m² every 3 weeks with prednisone 10 mg daily n=577	Cabazitaxel 25 mg/m² every 3 weeks with prednisone 10 mg daily n=590

	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Laboratory Abnormality				
Neutropenia	384 (67%)	241 (42%)	522 (89%)	432 (73%)
Anemia	576 (99.8%)	57 (10%)	588 (99.7%)	81 (14%)
Leukopenia	461 (80%)	167 (29%)	560 (95%)	351 (60%)
Thrombocytopenia	202 (35%)	15 (3%)	251 (43%)	25 (4%)

8.5 Post-Market Adverse Reactions

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 7 WARNINGS AND PRECAUTIONS – Respiratory).

Renal and urinary disorders: Cystitis due to radiation recall phenomenon (see 7 WARNINGS AND PRECAUTIONS –Renal).

Vascular disorders: cases of venous thromboembolic events including pulmonary embolism have been reported.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Cabazitaxel 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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

In vitro studies have shown that cabazitaxel is mainly metabolized through CYP3A. The metabolism of cabazitaxel 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 9.4 Drug-Drug Interactions).

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, Cabazitaxel for Injection 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 cabazitaxel on drugs that are substrates of CYP1A, CYP2C9, and CYP3A.

In vitro cabazitaxel did not inhibit the multidrug resistance proteins 1 and 2 (MRP1 and MRP2) or the organic cation transporter (OCT1). Cabazitaxel 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.

9.4 Drug-Drug Interactions

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

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%.

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

cabazitaxel on warfarin is expected *in vivo*.

Vaccinations

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

Cabazitaxel for Injection is an antineoplastic agent that acts by disrupting the microtubular network in cells.

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

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.

10.2 Pharmacodynamics

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

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

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.

10.3 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 cabazitaxel ranging from 10 to 30 mg/m^2 weekly or every 3 weeks.

Table 7 - Summary of cabazitaxel'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 cabazitaxel 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 cabazitaxel at 25 mg/m^2 in patients with metastatic prostate cancer (n=67), the mean C_{max} was 226 ng/mL (coefficient of variation, CV 107%) and was reached at the end of the 1-hour infusion (T_{max}). The mean AUC was 991 ng.h/mL (CV: 34%).

No major deviation to the dose proportionality was observed from 10 to 30 mg/m² in patients with advanced solid 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 cabazitaxel to human serum proteins was 89 to 92% and was not saturable up to 50 000 ng/mL, which covers the maximum concentration observed in clinical studies. Cabazitaxel is mainly bound to human serum albumin (82.1%) and lipoproteins (87.9% for HDL, 69.8% for LDL, and 55.8% for VLDL). The *in vitro* blood-to-plasma concentration ratios in human blood ranged from 0.90 to 0.99 indicating that cabazitaxel was equally distributed between blood and plasma.

Metabolism:
Cabazitaxel is extensively metabolized in the liver (≥ 95%), mainly by the CYP3A isoenzyme (80 to 90%). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued from O-demethylation), with the main one accounting for 5% of parent exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and feces.

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

Elimination:
After a 1-hour IV infusion [^{14}C]-cabazitaxel at 25 mg/m² in patients, approximately 80% of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the feces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel 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 cabazitaxel 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.

Cabazitaxel had a high plasma clearance of 48.5 L/h (26.4 L/h/m² for a patient with a median BSA of 1.84 m²).

Special Populations and Conditions

- **Pediatrics:** Limited data are available on the use of cabazitaxel in pediatric patients. Cabazitaxel was evaluated in an open label, multi-center Phase 1/2 study conducted in a total of 39 pediatric patients (aged between 4 to18 years for the phase 1 part of the study and between 3 to 16 years for the phase 2 part of the study). The phase 2 part did not demonstrate efficacy of cabazitaxel as single agent in pediatric population with recurrent or refractory diffuse intrinsic pontine glioma (DIPG) and high grade glioma (HGG).

- **Geriatrics:** In the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients ≤ 65 years (n=100) and older (n=70; 57 patients from 65 to 75 years and 13 patients above 75 years) (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

  Of the 371 patients treated with cabazitaxel in the prostate cancer study, 240 patients were 65 years or over including 70 patients older than 75 years. The following adverse reactions reported at rates ≥ 5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40.4% 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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 8.2 Clinical Trial Adverse Reactions, 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

  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 cabazitaxel dose.

- **Hepatic Insufficiency:** Cabazitaxel is eliminated primarily via hepatic metabolism.

  A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to ≤ 1.5 x ULN or AST >1.5 x ULN) or moderate (total bilirubin >1.5 to ≤3.0 x ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated cabazitaxel dose (MTD) was 20 and 15 mg/m^2, respectively.

  In 3 patients with severe hepatic impairment (total bilirubin > 3 x ULN), a 39% decrease

in clearance was observed when compared to patients with mild hepatic impairment, indicating some effect of severe hepatic impairment on cabazitaxel pharmacokinetics. The MTD of cabazitaxel in patients with severe hepatic impairment was not established.

Based on safety and tolerability data, cabazitaxel dose should be reduced in patients with mild and moderate hepatic impairment. Cabazitaxel is contraindicated in patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, and 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations).

- **Renal Insufficiency:** Cabazitaxel is minimally excreted via the kidney (2.3% of the dose). A population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (30 mL/min ≤ CL_{CR} <50 mL/min) and 59 patients with mild renal impairment (50 mL/min ≤ CL_{CR} ≤80 mL/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. This was confirmed by a dedicated comparative pharmacokinetic study in solid cancer patients with normal renal function (8 patients; CL_{CR} > 80 mL/min/1.73m^2), moderate (8 patients; 30 mL/min/1.73m^2 ≤ CL_{CR} <50 mL/min/1.73m^2) and severe (9 patients; CL_{CR} < 30 mL/min/1.73m^2) renal impairment, who received several cycles of cabazitaxel in single IV infusion up to 25 mg/m^2 (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 4 DOSAGE AND ADMINISTRATION, 4.1 Dosage Considerations). Limited data is available in patients with end-stage renal disease (CL_{CR} <15 mL/min/1.73m^2); therefore, these patients should be treated with caution and monitored carefully during treatment with Cabazitaxel for Injection.

  No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting end stage renal failure(CL_{CR} <15 mL/min/1.73m^2), by their condition and the limited amount of available data; should be treated with caution and monitored carefully during treatment (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

11 STORAGE, STABILITY AND DISPOSAL

Before dilution
Stability of the solution in the vial after the removal of the first dose:

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 - 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions. The solution has been shown to be chemically stable for 28 days if pierced by a needle or for 10 days if a spike is used for solution withdrawal. The solution can be stored either at room temperature or at 2-8 °C.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Solutions which are discoloured or which contain particulate matter should not be administered.

Do not use if solution is coloured or if it contains a precipitate. The vials should not be used for more than 28 days after the container has been opened for the first time. There is a greater risk of microbial contamination with multidose vials than with single dose vials. Single-dose vials should therefore be used whenever possible. If a multidose vial is used, appropriate control procedures to prevent contamination should be employed, including the following: • use of single-use sterile injecting equipment; • use of a sterile needle and syringe for each insertion into the vial; • rule out the introduction of contaminated material or fluid into a multidose vial.

After dilution:
Stability of the solution in the infusion bag / bottle:

After 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.

12 SPECIAL HANDLING INSTRUCTIONS

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

If Cabazitaxel for Injection 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.

Cabazitaxel for Injection 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

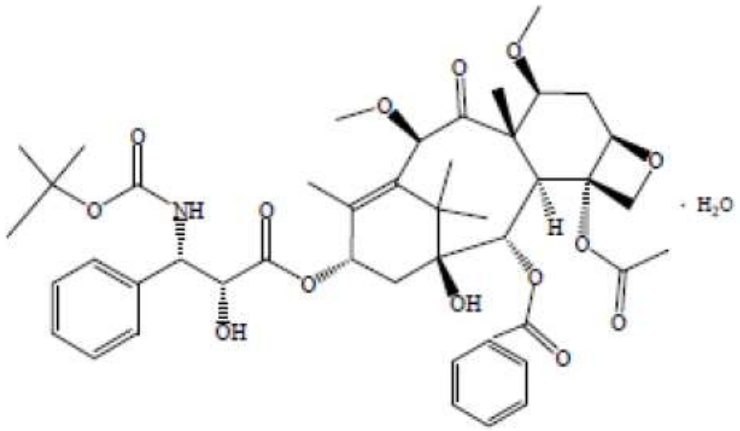
Proper name: Cabazitaxel

Chemical name:

(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetyloxy-9-(((2R,3S)-3-((tert-butoxycarbonyl) amino)-2-hydroxy-3-phenylpropanoyl)oxy)-11 hydroxy-4,6-dimethoxy 4a,8,13,13-tetramethyl-5-oxo 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11 methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate, monohydrate.

Molecular formula and molecular mass: $C_{45}H_{57}NO_{14} \cdot H_2O$, molecular weight 853.95

Structural formula:



Physicochemical properties:

- White to off-white powder
- Freely soluble in dichloromethane, soluble in absolute ethanol, insoluble in water

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study EFC6193 (TROPIC)

Study demographics and trial design

The efficacy and safety of cabazitaxel 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).

Table 8 - Summary of patient demographics for EFC6193 in patients with castration resistant metastatic prostate cancer

Study #	Studydesign	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	cabazitaxel 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 cabazitaxel arm 377 in the mitoxantrone arm	68 years (range 46-92) in the cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 9 – 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%)

	MTX+PRED (N=377)	CBZ+PRED (N=378)
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 cabazitaxel group and 4 in the mitoxantrone group.

The median relative dose intensity was 96.12% in the cabazitaxel 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 cabazitaxel 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 cabazitaxel group than in the comparator group (29.4% vs. 13.5%).

Study EFC11785 (PROSELICA)

In a non-inferiority, multicenter, multinational, randomized, open label phase III study (EFC11785 study), 1200 patients with metastatic castration resistant prostate cancer, previously treated with a docetaxel containing regimen, were randomized to receive either cabazitaxel 25 mg/m^2 (n=602) or 20 mg/m^2 (n=598) dose IV every 3 weeks for a maximum of 10 cycles. Patients in both arms also received daily prednisone or prednisolone. Overall survival (OS) in the Intent-to-Treat (ITT) population was the primary efficacy end-point. Non-inferiority was defined as cabazitaxel 20 mg/m^2 preserving at least 50% of the overall survival benefit of cabazitaxel 25 mg/m^2 relative to mitoxantrone demonstrated in the TROPIC study.

14.2 Study results

Overall survival was significantly longer in the cabazitaxel arm with cabazitaxel-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 10** and **Figure 1**). At 12 months and 18 months, overall survival was 64% and 39% in the cabazitaxel arm and 53% and 28% in the mitoxantrone arm.

Table 10 - Efficacy of cabazitaxel in the treatment of patients with castration resistant metastatic prostate cancer (EFC6193 study) (Intent-to–treat analysis) – Primary Endpoint

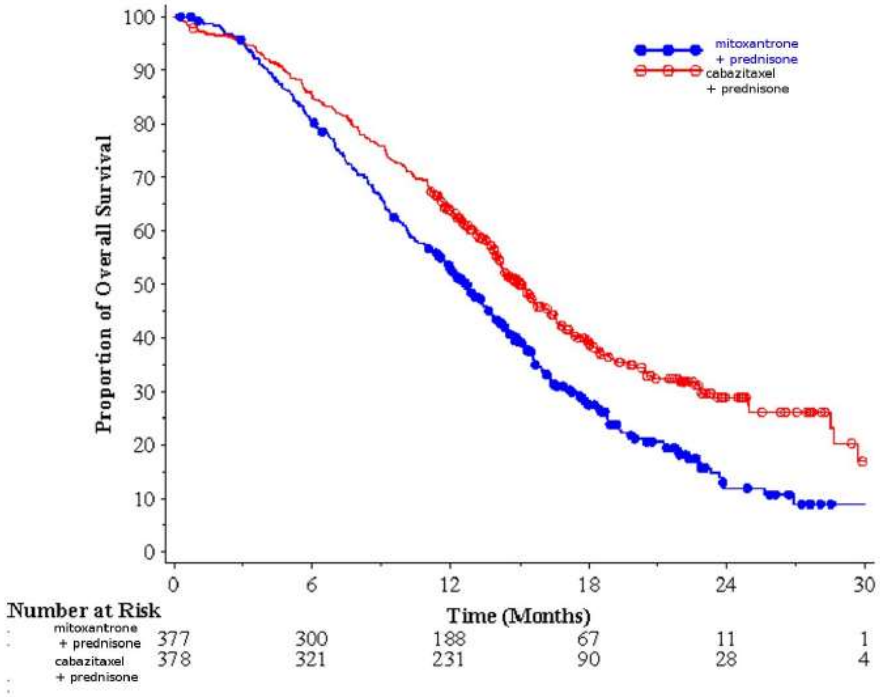
	cabazitaxel + prednisone* n=378	mitoxantrone + prednisone* n=377
Overall Survival		
Number of patients with deaths (%)	234 (61.9 %)	279 (74%)
Median survival (months) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio (HR)1 (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

[1]HR estimated using Cox model; a hazard ratio of less than 1 favors cabazitaxel

* prednisone or prednisolone

A sub-group of 59 patients received prior cumulative dose of docetaxel <225mg/m^2 (29 patients in the cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel 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 cabazitaxel arm. There was a median PSA progression free interval of 6.4 months (95% CI: 5.1-7.3) for patients in the cabazitaxel 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 cabazitaxel (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.

Study Results (EFC11785 PROSELICA study)

The study met its primary objective of demonstrating the non-inferiority of cabazitaxel 20 mg/m^2 in comparison with 25 mg/m^2 (see **Table 11**). The observed hazard ratio of the cabazitaxel 20 mg/m^2 group compared with the cabazitaxel 25 mg/m^2 group was 1.024. The 1-sided 98.89% upper bound of the confidence interval (UCI) was 1.184, below the 1.214 non-inferiority margin.

A significantly higher percentage of patients showed a PSA response in the 25 mg/m^2 group (42.9%) compared to the 20 mg/m^2 group (29.5%). A significantly higher risk of PSA progression in patients with the 20 mg/m^2 dose with respect to the 25 mg/m^2 dose was observed (HR 1.195 ; 95% CI: 1.025 to 1.393).

There was no significant difference with regards to other secondary endpoints (PFS, tumor and pain response, tumor and pain progression, and five subcategories of FACT-P).

Table 11 - Overall survival in EFC11785 study comparing cabazitaxel 20 mg/m^2 arm versus cabazitaxel 25 mg/m^2 (Intent-to-treat analysis) – Efficacy primary endpoint

	CBZ20 + PRED n=598	**CBZ25 + PRED n=602**
Overall Survival		
Number of deaths, n (%)	497 (83.1%)	501 (83.2%)
Median survival	13.4	14.5
(95% CI) (months)	(12.19 to 14.88)	(13.47 to 15.28)
Hazard Ratio[a]		
Versus CBZ25+PRED	1.024	-
1-sided 98.89% UCI[b]	1.184	-
1-sided 95% LCI	0.922	-

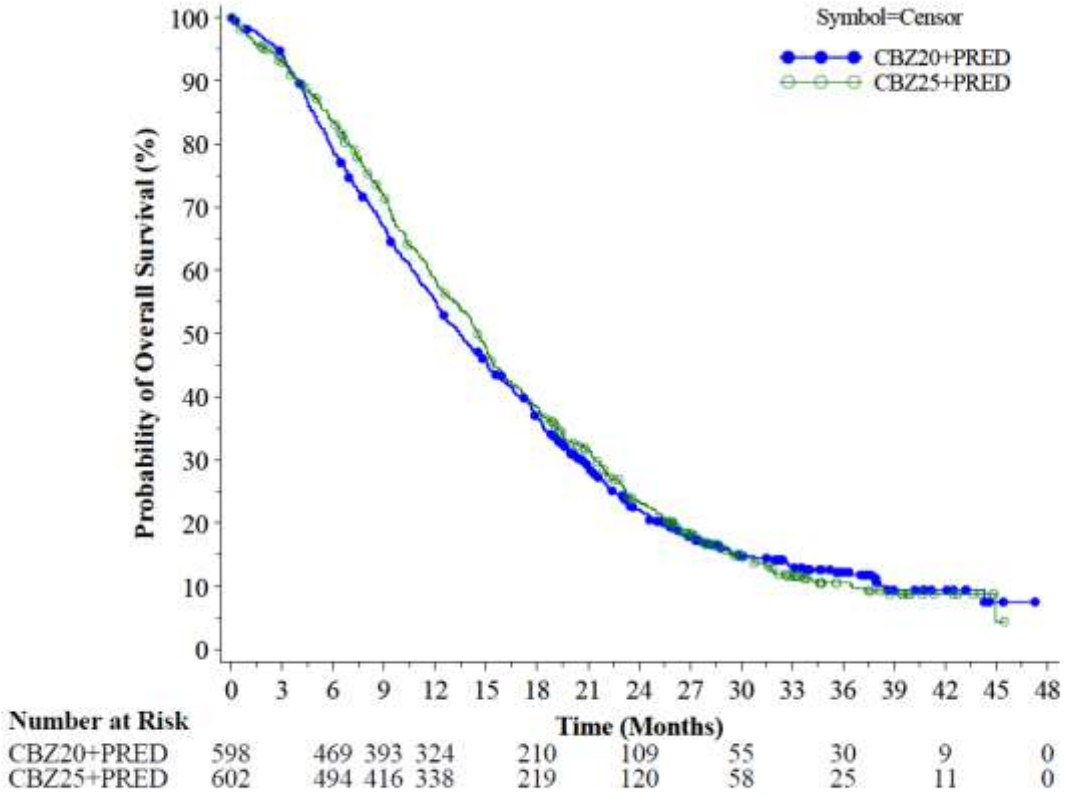
CBZ20=cabazitaxel 20 mg/m^2, CBZ25=cabazitaxel 25 mg/m^2, PRED=prednisone/prednisolone

CI=confidence interval, LCI = lower bound of the confidence interval, UCI = upper bound of the confidence interval

a Hazard ratio is estimated using a Cox Proportional Hazards regression model. A hazard ratio < 1 indicates a lower risk of cabazitaxel 20 mg/m^2 with respect to 25 mg/m^2.

b Non-inferiority margin: 1.214

Figure 2 - Kaplan-Meier Overall Survival curves (intention-to treat population) in the PROSELICA trial



CBZ20=Cabazitaxel 20 mg/m^2, CBZ25=Cabazitaxel 25 mg/m^2, PRED=Prednisone/Prednisolone

EFC11785 study demonstrated a better safety profile for the cabazitaxel 20 mg/m^2 dose. The safety profile of cabazitaxel 25 mg/m^2 observed in this study was qualitatively and quantitatively similar to that observed in the study EFC6193 [see ADVERSE REACTIONS, Clinical Trials Adverse Drug Reactions, 2. Study EFC11785 (PROSELICA)].

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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 [^{14}C]-cabazitaxel to lactating rats, a small amount of radioactivity was excreted into milk (between 0.23% and 1.5% of the dose).

General Toxicology:

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.

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.

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.

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.

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

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**.**

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

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.

Reproductive and Developmental Toxicology: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrJEVTANA®, cabazitaxel for injection, 40 mg / mL (60 mg/1.5 mL) submission control # 257684, Product Monograph, Sanofi-Aventis Canada Inc. JUL 29, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Cabazitaxel for Injection
(45 mg / 4.5 mL & 60 mg / 6 mL)

Read this carefully before you start taking **Cabazitaxel for Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Cabazitaxel for Injection.**

Serious Warnings and Precautions

Cabazitaxel for Injection should only be administered by a qualified healthcare professional experienced in the use of anticancer treatments.

Possible serious side effects with the use of Cabazitaxel for Injection 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

What the medication is used for?

Cabazitaxel for Injection is used with prednisone or prednisolone to treat prostate cancer in adults who have been previously treated with docetaxel and who have:

- Prostate cancer that has spread to other parts of the body (metastasized)
- Prostate cancer that no longer responds to hormone treatment

How does it work?

Every cell in your body contains a supporting structure. If this structure is damaged, the cell cannot grow or divide.

Cabazitaxel for Injection makes the structure in cells unnaturally stiff, so the cancer cells then can no longer grow or divide.

What are the ingredients in Cabazitaxel for Injection?

Medicinal ingredients: Cabazitaxel (anhydrous)

Non-medicinal ingredients are: Polysorbate 80, citric acid anhydrous, ethanol absolute and polyethylene glycol 300.

Cabazitaxel for Injection comes in the following dosage forms:
Cabazitaxel for Injection is a concentrated solution for injection and is available in a multidose vial. Each multidose vial contains 60 mg / 6 mL or 45 mg / 4.5 mL cabazitaxel.

Do not use Cabazitaxel for injection if:

- You have a history of severe allergic reactionsto:
  - Cabazitaxel, or
  - Othermedicines containing polysorbate 80, or
  - any of other ingredients in the formulation
- your white blood cell count is too low.
- you have a severe liver disease.
- you have recently received or you are about to receive the yellow fever vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cabazitaxel for Injection. Talk about any health conditions or problems you may have, including if you:

- you have a decreased ability to produce blood cells
- have anemia (low number of red blood cells)
- have or had gastrointestinal problems
- have stomach pain, fever, persistent constipation which may be a sign of gastrointestinal problems
- have severe or persistent diarrhea, nausea or vomiting which may result in dehydration.
- have a history of diseases of digestive tract
- have a fever. A fever is the earliest sign of infection which may be caused by reduced white blood cell count.
- have any allergies. Antiallergic medicines will be given to you to reduce the risk of an allergic reaction, as Cabazitaxel for Injection, may also cause serious allergic reactions (hypersensitivity).
- have previously received pelvic radiotherapy
- have liver or kidney problems.
- have inflammation of the bladder.
- have a heart problem or an irregular heart rate
- new or worsening lung problems
- are over the age of 65
- you are pregnant or planning on becoming pregnant
- you are breast-feeding or planning on breast-feeding. Cabazitaxel for Injection should not be used while breast-feeding
- are going to have any vaccines. Cabazitaxel for Injection 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.

Other Warnings you should know about:

Contraception for Men: Cabazitaxel for Injection 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 Cabazitaxel for Injection and for 6 months after your last dose of Cabazitaxel for Injection. You should talk to your doctor about preserving your sperm prior to receiving Cabazitaxel for Injection.

Driving and Using Machinery: Cabazitaxel for Injection may cause fatigue or dizziness. If you experience these symptoms, do not drive or use any tools or machines.
Laboratory Test: Your doctor will perform blood tests on a weekly basis and before each treatment cycle.

Problems with your Nervous System: Cabazitaxel can causeweakness, numbness and pain, usually in the hands and feet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Cabazitaxel for Injection:

- medicines used to treat infections, such as: ketoconazole, itraconazole, rifampicin, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir, voriconazole
- medicines used to treat seizures, such as: carbamazepine, phenytoin, phenobarbital.
- live vaccines

How to take Cabazitaxel for Injection?

- Cabazitaxel for Injection will be given to you as an infusion into the vein (intravenous infusion) by a healthcare professional every 3 weeks.

- The infusion will take about 1 hour.

- Your healthcare professional may also give you other medicines by injection, into the vein, to reduce your risk of experiencing an allergic reaction.

- During treatment with Cabazitaxel for Injection you will also need to take 10 mg of prednisone or prednisolone orally every day.

Usual dose:

Your healthcare professional will decide the dose of Cabazitaxel for Injection you should receive based on your height and weight.

Overdose:

If you think you, or a person you are caring for, have been given too much Cabazitaxel for Injection, contact a health care professional, 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.

What are possible side effects from using Cabazitaxel for Injection?

These are not all the possible side effects you may have when taking Cabazitaxel. If you experience any side effects not listed here, tell your healthcare professional.

- diarrhea, nausea, vomiting, constipation, abdominal pain
- decreased appetite
- change in the sense of taste
- blood in the urine (hematuria)
- hair loss
- tiredness
- muscle pain, muscle spasms, or joint pain or joint stiffness
- back pain
- weakness
- cough
- shortness of breath
- acid reflux (Gastroesophageal Reflux Disease)
- low blood pressure
- headache
- dizziness
- dehydration
- urinary tract infection

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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		✓	
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Persistent vomiting or diarrhea; abdominal pain, abdominal tenderness, persistent constipation, dark stool or blood in stool.		✓	
Gatrointestinal (GI) bleeding (bleeding anywhere along the GI tract between mouth and anus): blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness;			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Gastrointestinal perforation (a hole in the wall of your stomach or bowels): severe abdominal pain and tenderness, nausea, vomiting, chills or fever			✓
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.		✓	
Acute Kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain.			✓
Extreme weakness or fatigue		✓	
Peripheral neuropathy (damage to nerves outside the brain and spinal cord) with symptoms such as: numbness, tingling, burning or decreased sensation in the hands and feet		✓	
Radiation cystitis (inflammation of the bladder in patients that have received radiotherapy) with symptoms such as: persistent urge to		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
urinate; a burning sensation or pain when urinating; passing frequent, small amounts of urine; blood in the urine (hematuria).			
UNCOMMON			
Allergic reactions such as trouble breathing, tightness in the throat, rash, hives, swelling of the lips or tongue or low blood pressure		✓	
UNKNOWN FREQUENCY			
Respiratory problems with symptoms such as: difficulty breathing, shortness of breath, cough, fatigue.			✓
Vein thrombosis: blood clot formed in one or more of the veins in your body (usually in the legs or lungs), with symptoms such as: leg pain or swelling; shortness of breath, chest pain, cough; sweating, rapid or irregular heartbeat, dizziness.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

The unopened vials should be stored at room temperature between 15°C to 30°C. Do not refrigerate.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 - 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. The solution has been shown to be chemically stable for 28 days if pierced by a needle or for 10 days if a spike is used for solution withdrawal. The solution can be stored either at room temperature or at 2-8 °C.

If you want more information about Cabazitaxel for Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by callingat: 1-800-361-3062

This leaflet was prepared by Sandoz Canada Inc.

Last revised: February 14, 2023