

FULL PRESCRIBING INFORMATION

Cabazitaxel S.K. (cabazitaxel 60mg/1.5ml) concentrate and solvent for solution for I.V. infusion

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. Cabazitaxel S.K. is contraindicated in patients with neutrophil counts of $\leq 1,500$ cells/mm³. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features [see *Contraindications (4) and Warnings and Precautions (5.1, 5.2)*].

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the Cabazitaxel S.K. infusion and administration of appropriate therapy. Patients should receive premedication. Cabazitaxel S.K. is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see *Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions*].

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of **Cabazitaxel S.K.** is based on calculation of the Body Surface Area (BSA), and is 20 mg/m² administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout **Cabazitaxel S.K.** treatment.

A dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider [see *Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Clinical Studies (14)*].

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features.

Premedicate at least 30 minutes prior to each dose of **Cabazitaxel S.K.** with the following intravenous medications to reduce the risk and/or severity of hypersensitivity [see *Warnings and Precautions (5.3)*]:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),

- H₂ antagonist (ranitidine 50 mg or equivalent H₂ antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed [see *Warnings and Precautions (5.3)*].

Cabazitaxel S.K. injection single-dose vial requires **two** dilutions prior to administration [see *Dosage and Administration (2.5)*].

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue **Cabazitaxel S.K.** dosing for adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Cabazitaxel S.K.

Toxicity	Dosage Modification
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including granulocyte-colony stimulating factor (G-CSF)	Delay treatment until neutrophil count is $>1,500$ cells/mm ³ , then reduce dosage of Cabazitaxel S.K. by one dose level. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is $>1,500$ cells/mm ³ , then reduce dosage of Cabazitaxel S.K. by one dose level. Use G-CSF for secondary prophylaxis.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of Cabazitaxel S.K. by one dose level.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of Cabazitaxel S.K. by one dose level.
Grade ≥ 3 peripheral neuropathy	Discontinue Cabazitaxel S.K.

Patients at a 20 mg/m² dose who require dose reduction should decrease dosage of **Cabazitaxel S.K.** to 15 mg/m² [see *Adverse Reactions (6.1)*].

Patients at a 25 mg/m² dose who require dose reduction should decrease dosage of **Cabazitaxel S.K.** to 20 mg/m². One additional dose reduction to 15 mg/m² may be considered [see *Adverse Reactions (6.1)*].

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to $\leq 1.5 \times$ Upper Limit of Normal (ULN) or AST $>1.5 \times$ ULN): Administer **Cabazitaxel S.K.** at a dose of 20 mg/m².
- Moderate hepatic impairment (total bilirubin >1.5 to $\leq 3 \times$ ULN and AST = any): Administer **Cabazitaxel S.K.** at a dose of 15 mg/m² based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin $>3 \times$ ULN): **Cabazitaxel S.K.** is contraindicated in patients with severe hepatic impairment [see *Warning and Precautions (5.8) and Clinical Pharmacology (12.3)*].

2.4 Dose Modifications for Use with Strong CYP3A Inhibitors

Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole,

clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of **Cabazitaxel S.K.** with these drugs. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% **Cabazitaxel S.K.** dose reduction [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

2.5 Preparation and Administration

Cabazitaxel S.K. is a cytotoxic anticancer drug. Follow applicable special handling and disposal procedures. If **Cabazitaxel S.K.**, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water.

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of **Cabazitaxel S.K.** infusion solution.

Cabazitaxel S.K. should not be mixed with any other drugs.

Preparation

Read this **entire** section carefully before mixing and diluting. **Cabazitaxel S.K.** requires **two** dilutions prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to overdose [see *Overdosage (10)*].

Note: Both the **Cabazitaxel S.K.** injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire contents** of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL **Cabazitaxel S.K.**.

Inspect the **Cabazitaxel S.K.** injection and supplied diluent vials. The **Cabazitaxel S.K.** injection is a clear yellow to brownish-yellow viscous solution.

Step 1 – first dilution

Each vial of **Cabazitaxel S.K.** (cabazitaxel) 60 mg/1.5 mL must first be mixed with the **entire contents** of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of **Cabazitaxel S.K.**.

When transferring the diluent, direct the needle onto the inside wall of **Cabazitaxel S.K.** vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted **Cabazitaxel S.K.** solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 1 hour) to obtain the final infusion as detailed in Step 2.

Step 2 – second (final) dilution

Withdraw the recommended dose from the **Cabazitaxel S.K.** solution containing 10 mg/mL as prepared in Step 1 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 S.K.** is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL **Cabazitaxel S.K.** is not exceeded. The concentration of the **Cabazitaxel S.K.** 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 S.K.** infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

Discard any unused portion.

Administration

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the **Cabazitaxel S.K.** first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

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

The final **Cabazitaxel S.K.** infusion solution should be administered intravenously as a one-hour infusion at room temperature.

3 DOSAGE FORMS AND STRENGTHS

Cabazitaxel S.K. (cabazitaxel) injection is supplied as a kit consisting of the following:

- Cabazitaxel injection: 60 mg/1.5 mL; a clear yellow to brownish-yellow viscous solution
- Diluent: 5.7 mL of 13% (w/w) ethanol in water; a clear colorless solution

4 CONTRAINDICATIONS

Cabazitaxel S.K. is contraindicated in patients with:

- neutrophil counts of $\leq 1,500/\text{mm}^3$ [*see Warnings and Precautions (5.1)*].
- History of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [*see Warnings and Precautions (5.3)*].
- severe hepatic impairment (total bilirubin $>3 \times \text{ULN}$) [*see Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Cabazitaxel S.K. is contraindicated in patients with neutrophils $\leq 1,500/\text{mm}^3$ [*see Contraindications (4)*]. Closely monitor patients with hemoglobin $<10 \text{ g/dL}$.

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

In a randomized trial (TROPIC) in previously treated patients with metastatic castration-resistant prostate cancer, five patients (1.3%) died from infection (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued **cabazitaxel** treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the **cabazitaxel** group was neutropenia (2%). Grade 3-4 neutropenia has been observed in 82% of patients treated with **cabazitaxel** in the randomized trial. In a randomized trial (PROSELICA) comparing two doses of **cabazitaxel** in previously treated metastatic castration-resistant prostate cancer, 8 patients (1%) on the 20 mg/m² arm and 15 patients (3%) on the 25 mg/m² arm died from infection; of these, 4 deaths on the 20 mg/m² arm and 8 deaths on the 25 mg/m² arm occurred within the first 30 days of treatment.

Fewer patients receiving **cabazitaxel** 20 mg/m² were reported to have infectious adverse reactions. Grade 1-4 infections were experienced by 160 patients (28%) on the 20 mg/m² arm and 227 patients (38%) on the 25 mg/m² arm. Grade 3-4 infections were experienced by 57 patients (10%) on the 20 mg/m² arm and 120 patients (20%) on the 25 mg/m² arm. Noninferiority for overall survival was demonstrated between these two arms [*see Adverse Reactions (6.1)*].

Based on guidelines for the use of G-CSF and the adverse reactions profile of **Cabazitaxel S.K.**, primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features (older patients, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

The effectiveness of primary prophylaxis with G-CSF in patients receiving **cabazitaxel** has not been studied. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients at increased risk for neutropenia complications.

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed [*see Dosage and Administration (2.2)*].

5.2 Increased Toxicities in Elderly Patients

In a randomized trial (TROPIC), 2% of patients (3/131) <65 years of age and 6% (15/240) ≥65 years of age died of causes other than disease progression within 30 days of the last **cabazitaxel** dose. Patients ≥65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia. The incidence of the following grade 3-4 adverse reactions were higher in patients ≥65 years of age compared to younger patients; neutropenia (87% vs 74%), and febrile neutropenia (8% vs 6%).

In a randomized clinical trial (PROSELICA) comparing two doses of **cabazitaxel**, deaths due to infection within 30 days of starting **cabazitaxel** occurred in 0.7% (4/580) patients on the 20 mg/m² arm and 1.3% (8/595) patients on the 25 mg/m² arm; all of these patients were >60 years of age.

In PROSELICA, on the 20 mg/m² arm, 3% (5/178) of patients <65 years of age and 2% (9/402) ≥65 years of age died of causes other than disease progression within 30 days of the last

cabazitaxel dose. On the 25 mg/m² arm, 2% (3/175) patients <65 years of age and 5% (20/420) ≥65 years of age died of causes other than disease progression within 30 days of the last **cabazitaxel** dose [see *Adverse Reactions (6)* and *Use in Specific Populations (8.5)*].

5.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of **cabazitaxel**, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm.

Premedicate all patients prior to the initiation of the infusion of **cabazitaxel** [see *Dosage and Administration (2.1)*]. Observe patients closely for hypersensitivity reactions, especially during the first and second infusions.

Severe hypersensitivity reactions require immediate discontinuation of the **cabazitaxel** infusion and appropriate therapy. **cabazitaxel** is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see *Contraindications (4)*].

5.4 Gastrointestinal Adverse Reactions

Nausea, vomiting and severe diarrhea, at times, may occur. Deaths related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Antiemetic prophylaxis is recommended. Treat patients with rehydration, antidiarrheal or antiemetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥ 3 diarrhea [see *Dosage and Administration (2.2)*].

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with **cabazitaxel** [see *Adverse Reactions (6.2)*]. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants, and patients with a prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.

Abdominal pain and tenderness, fever, persistent constipation, diarrhea, 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.

The incidence of gastrointestinal adverse reactions is greater in the patients who have received prior radiation. In PROSELICA, diarrhea was reported in 41% (297/732) of patients who had received prior radiation and in 27% (118/443) of patients without prior radiation. Of the patients who had previously received radiation, more patients on the 25 mg/m² arm reported diarrhea, compared to patients on the 20 mg/m² arm.

5.5 Renal Failure

In the randomized clinical trial (TROPIC), renal failure of any grade occurred in 4% of the patients being treated with **cabazitaxel**, including four cases with fatal outcome. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy [see *Adverse Reactions (6.1)*]. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.6 Urinary Disorders Including Cystitis

Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with **cabazitaxel** in patients who previously received pelvic radiation [*see Adverse Reactions (6.2)*]. In PROSELICA, cystitis and radiation cystitis were reported in 1.2% and 1.5% of patients who received prior radiation, respectively. Hematuria was reported in 19.4% of patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur late in treatment with **cabazitaxel**. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on **cabazitaxel**. Interrupt or discontinue **cabazitaxel** in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

5.7 Respiratory Disorders

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome [*see Adverse Reactions (6.2)*]. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection.

Interrupt **cabazitaxel** if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving **cabazitaxel**. Consider discontinuation. The benefit of resuming **cabazitaxel** treatment must be carefully evaluated.

5.8 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

cabazitaxel is contraindicated in patients with severe hepatic impairment (total bilirubin $>3 \times$ ULN) [*see Contraindications (4)*]. Dose should be reduced for patients with mild (total bilirubin >1 to $\leq 1.5 \times$ ULN or AST $>1.5 \times$ ULN) and moderate (total bilirubin >1.5 to $\leq 3.0 \times$ ULN and any AST) hepatic impairment, based on tolerability data in these patients [*see Dosage and Administration (2.3) and Use in Specific Populations (8.7)*]. Administration of **cabazitaxel** to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

5.9 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies and its mechanism of action, **cabazitaxel** can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose (approximately 0.06 times the C_{max} in patients at the recommended human dose). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of **Cabazitaxel S.K.** [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression [see Warnings and Precautions (5.1)].
- Increased Toxicities in Elderly Patients [see Warnings and Precautions (5.2)].
- Hypersensitivity Reactions [see Warnings and Precautions (5.3)].
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.4)].
- Renal Failure [see Warnings and Precautions (5.5)].
- Urinary Disorders Including Cystitis [see Warnings and Precautions (5.6)].
- Respiratory Disorders [see Warnings and Precautions (5.7)].
- Use in Patients with Hepatic Impairment [see Warnings and Precautions (5.8)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

TROPIC Trial (cabazitaxel + prednisone compared to mitoxantrone)

The safety of **cabazitaxel** in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROPIC trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) **cabazitaxel** -treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in **cabazitaxel** -treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of **cabazitaxel** . Other fatal adverse reactions in **cabazitaxel** -treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common ($\geq 10\%$) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common ($\geq 5\%$) grade 3-4 adverse reactions in patients who received **cabazitaxel** were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received **cabazitaxel** and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the **cabazitaxel** group were neutropenia and renal failure. Dose reductions were reported in 12% of **cabazitaxel** -treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of **cabazitaxel** -treated patients and 15% of mitoxantrone-treated patients.

Table 2: Incidence of Adverse Reactions* and Hematologic Abnormalities in $\geq 5\%$ of Patients Receiving cabazitaxel in Combination with Prednisone or Mitoxantrone in Combination with Prednisone in TROPIC

	cabazitaxel 25 mg/m² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m² every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4

	n (%)	n (%)	n (%)	n (%)
Any Adverse Reaction				
Blood and Lymphatic System Disorders				
Neutropenia [†]	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile Neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia [†]	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia [†]	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia [†]	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac Disorders				
Arrhythmia [‡]	18 (5%)	4 (1%)	6 (2%)	1 (<1%)
Gastrointestinal Disorders				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (<1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (<1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (<1%)
Abdominal Pain [§]	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia [¶]	36 (10%)	0	9 (2%)	0
General Disorders and Administration Site Conditions				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (<1%)
Peripheral Edema	34 (9%)	2 (<1%)	34 (9%)	2 (<1%)
Mucosal Inflammation	22 (6%)	1 (<1%)	10 (3%)	1 (<1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections and Infestations				
Urinary Tract Infection [#]	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Investigations				
Weight Decreased	32 (9%)	0	28 (8%)	1 (<1%)
Metabolism and Nutrition Disorders				
Anorexia	59 (16%)	3 (<1%)	39 (11%)	3 (<1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (<1%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle Spasms	27 (7%)	0	10 (3%)	0
Nervous System Disorders				

Peripheral Neuropathy ^p	50 (13%)	3 (<1%)	12 (3%)	3 (<1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (<1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and Urinary Tract Disorders				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (<1%)
Dysuria	25 (7%)	0	5 (1%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (<1%)
Cough	40 (11%)	0	22 (6%)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular Disorders				
Hypotension	20 (5%)	2 (<1 %)	9 (2%)	1 (<1%)
Median Duration of Treatment	6 cycles		4 cycles	

* Graded using NCI CTCAE version 3

† Based on laboratory values, **cabazitaxel** : n =369, mitoxantrone: n = 370.

‡ Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

§ Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

¶ Includes gastroesophageal reflux disease and reflux gastritis.

Includes urinary tract infection enterococcal and urinary tract infection fungal.

^p Includes peripheral motor neuropathy and peripheral sensory neuropathy.

PROSELICA Trial (comparison of two doses of **cabazitaxel**)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA), 1175 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were treated with either **cabazitaxel** 25 mg/m² (n=595) or the 20 mg/m² (n=580) dose.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m² and 32 (5.4%) patients in the 25 mg/m² arm. The most common fatal adverse reactions in **cabazitaxel** -treated patients were related to infections, and these occurred more commonly on the 25 mg/m² arm (n=15) than on the 20 mg/m² arm (n=8). Other fatal adverse reactions 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, diverticular perforation, and cardiorenal syndrome.

Grade 1-4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, nausea, diarrhea, asthenia, and hematuria.

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

Treatment discontinuations due to adverse drug reactions occurred in 17% of patients in the 20 mg/m² group and 20% of patients in the 25 mg/m² group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m² group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m² group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m² group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m², 19 patients (3%) had a dose reduced from 20 to 15 mg/m² and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m². In the 20 mg/m² group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m², and 9 patients (2%) had a dose reduced from 15 to 12 mg/m².

Table 3: Incidence of Adverse Reactions* in ≥5% of Patients Receiving cabazitaxel 20 mg/m² or 25 mg/m² in Combination with Prednisone in PROSELICA

	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	
Primary System Organ Class Preferred Term	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%)

	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	
Primary System Organ Class Preferred Term	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
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.

Table 4: Incidence of Hematologic Laboratory Abnormalities in Patients Receiving cabazitaxel 20 mg/m² or 25 mg/m² in Combination with Prednisone in Study PROSELICA

Laboratory Abnormality	cabazitaxel 20 mg/m ² every 3 weeks with prednisone 10 mg daily n=577		cabazitaxel 25 mg/m ² 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 (%)
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%)

Hematuria:

In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in **cabazitaxel**-treated patients. The incidence of grade ≥ 2 hematuria was 6% in **cabazitaxel**-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well balanced between arms and do not account for the increased rate of hematuria on the **cabazitaxel** arm.

In study PROSELICA, hematuria of all grades was observed in 18% of patients overall.

Hepatic Laboratory Abnormalities:

The incidences of grade 3-4 increased AST, increased ALT, and increased bilirubin were each $\leq 1\%$.

6.2 Postmarketing Experience

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

Gastrointestinal: Gastritis, intestinal obstruction.

Respiratory: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome.

Renal and urinary disorders: Radiation recall hemorrhagic cystitis.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il/>

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Cabazitaxel is primarily metabolized through CYP3A [see *Clinical Pharmacology (12.3)*]. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of **Cabazitaxel S.K.** with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% **Cabazitaxel S.K.** dose reduction [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of **Cabazitaxel S.K.** have not been established in females. There are no human data on the use of **cabazitaxel** in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose [see *Data*].

Data

Animal data

In an early embryonic developmental toxicity study in rats, cabazitaxel was administered intravenously for 15 days prior to mating through Day 6 of pregnancy, which resulted in an increase in pre-implantation loss at 0.2 mg/kg/day and an increase in early resorptions at ≥ 0.1 mg/kg/day (approximately 0.06 and 0.02 times the C_{max} in patients at the recommended human dose, respectively).

In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased postimplantation loss, embryoletality, and fetal deaths when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the C_{max} in patients at the recommended human dose). Decreased mean fetal birthweight associated with delays in skeletal ossification was observed at doses ≥ 0.08 mg/kg. Cabazitaxel crossed the placenta barrier within 24 hours of a single intravenous administration of 0.08 mg/kg to pregnant rats at gestational day 17. A dose of 0.08 mg/kg in rats resulted in a C_{max} approximately 0.02 times that observed in patients at the recommended human dose. Administration of cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

8.2 Lactation

Risk Summary

The safety and efficacy of **Cabazitaxel S.K.** have not been established in females.

There is no information available on the presence of cabazitaxel in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats [see *Data*].

Data

Animal data

In a milk excretion study, radioactivity related to cabazitaxel was detected in the stomachs of nursing pups within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the C_{max} in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of **Cabazitaxel S.K.** [see *Use in Specific Populations (8.1)*].

Infertility

Males

Based on animal toxicology studies, **cabazitaxel** may impair human fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of **Cabazitaxel S.K.** in pediatric patients have not been established. **cabazitaxel** was evaluated in 39 pediatric patients (ages 3 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m² intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid pre-medication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearances by body surface area were comparable to those in adults.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with **cabazitaxel** every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients [see *Warnings and Precautions (5.2)*]. The incidence of grade 3-4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. The following

grade 1-4 adverse reactions were reported at rates $\geq 5\%$ higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (97% vs 89%), asthenia (24% vs 15%), pyrexia (15% vs 8%), dizziness (10% vs 5%), urinary tract infection (10% vs 3%), and dehydration (7% vs 2%), respectively.

In the PROSELICA study, the grade 1-4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were diarrhea (43% vs 33%), fatigue (30% vs 19%), asthenia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 3%).

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients <65 years (n=100) and older (n=70).

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance CLCR <15 mL/min/1.73 m²), should be monitored carefully during treatment [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin >1 to $\leq 1.5 \times$ ULN or AST >1.5 \times ULN) should have **cabazitaxel** dose of 20 mg/m². Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety [see *Clinical Pharmacology (12.3)*]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to $\leq 3.0 \times$ ULN and AST= any) was 15 mg/m², however, the efficacy at this dose level was unknown.

Cabazitaxel S.K. is contraindicated in patients with severe hepatic impairment (total bilirubin >3 \times ULN) [see *Contraindications (4)*].

10 OVERDOSAGE

There is no known antidote for **Cabazitaxel S.K.** overdose. Overdose has resulted from improper preparation [see *Dosage and Administration (2.5)*]. Read the entire section *Dosage and Administration (2)* carefully before mixing or diluting. Complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcome.

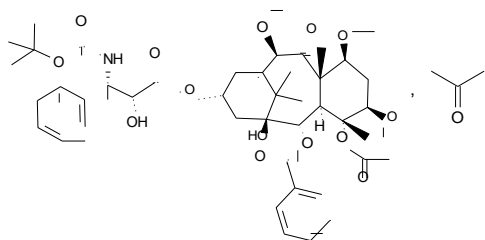
In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

11 DESCRIPTION

Cabazitaxel S.K. (cabazitaxel) injection is an antineoplastic agent belonging to the taxane class that is for intravenous use. It is prepared by semi-synthesis with a precursor extracted from yew needles.

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

Cabazitaxel has the following structural formula:



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

Cabazitaxel S.K. (cabazitaxel) injection 60 mg/1.5 mL is a sterile, non-pyrogenic, clear yellow to brownish-yellow viscous solution and is available in single-dose vials containing 60 mg cabazitaxel (anhydrous and solvent free) and 1.56 g polysorbate 80 (citric acid monohydrate is used to adjust the pH of the polysorbate 80 between 3.3 to 3.8).

Each mL contains 40 mg cabazitaxel (anhydrous) and 1.04 g polysorbate 80.

DILUENT for **Cabazitaxel S.K.** is a clear, colorless, sterile, and non-pyrogenic solution containing 13% (w/w) ethanol in water for injection, approximately 5.7 mL.

Cabazitaxel S.K. requires two dilutions prior to intravenous infusion. **Cabazitaxel S.K.** injection should be diluted only with the supplied DILUENT for **Cabazitaxel S.K.**, followed by dilution in either 0.9% sodium chloride solution or 5% dextrose solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of cabazitaxel following a single dose of 25 mg/m² administered by intravenous infusion on QTc interval was evaluated in 94 patients with solid tumors. 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.

12.3 Pharmacokinetics

A population pharmacokinetic analysis was conducted in 170 patients with solid tumors at doses ranging from 10 to 30 mg/m² weekly or every three weeks.

Absorption

Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m² every three weeks, the mean C_{max} in patients with metastatic prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the one-hour infusion (T_{max}). The mean AUC in patients with metastatic prostate cancer was 991 ng·h/mL (CV 34%).

No major deviation from the dose proportionality was observed from 10 to 30 mg/m² in patients with advanced solid tumors.

Distribution

The volume of distribution (V_{ss}) was 4,864 L (2,643 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 trials. Cabazitaxel is mainly bound to human serum albumin (82%) and lipoproteins (88% for HDL, 70% for LDL, and 56% for VLDL). The *in vitro* blood-to-plasma concentration ratio 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 CYP3A4/5 isoenzyme (80% to 90%), and to a lesser extent by CYP2C8. Cabazitaxel is the main circulating moiety in human plasma. Seven metabolites were detected in plasma (including the 3 active metabolites issued from O-demethylation), with the main one accounting for 5% of cabazitaxel exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and feces.

Elimination

After a one-hour intravenous infusion [¹⁴C]-cabazitaxel 25 mg/m², 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 3.7% of the dose (2.3% as unchanged drug in urine).

Based on the population pharmacokinetic analysis, cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%; 26.4 L/h/m² for a patient with a median BSA of 1.84 m²) in patients with metastatic prostate cancer. Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic model with α -, β -, and γ -half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Renal Impairment

Cabazitaxel is minimally excreted via the kidney. A population pharmacokinetic analysis carried out in 170 patients including 14 patients with moderate renal impairment (30 mL/min \leq CL_{CR} <50 mL/min) and 59 patients with mild renal impairment (50 mL/min \leq 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 patients with solid tumors with normal renal function (n=8, CL_{CR} >80 mL/min/1.73 m²), or moderate (n=8, 30 mL/min/1.73 m² \leq CL_{CR} <50 mL/min/1.73 m²) and severe (n=9, CL_{CR} <30 mL/min/1.73 m²) renal impairment, who received several cycles of cabazitaxel in single IV infusion up to 25 mg/m². Limited pharmacokinetic data were available in patients with end-stage renal disease (n=2, CL_{CR} <15 mL/min/1.73 m²).

Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to $\leq 1.5 \times$ ULN or AST $>1.5 \times$ ULN) or moderate (total bilirubin >1.5 to $\leq 3.0 \times$ ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated dose (MTD) of cabazitaxel was 20 and 15 mg/m², respectively.

In 3 patients with severe hepatic impairment (total bilirubin $>3 \times$ ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment (ratio=0.61, 90% CI: 0.36-1.05), 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 maintained at 20 mg/m² in patients with mild hepatic impairment and reduced to 15 mg/m² in patients with moderate hepatic impairment [see *Warnings and Precautions (5.8) and Use in Specific Populations (8.7)*]. Cabazitaxel is contraindicated in patients with severe hepatic impairment [see *Contraindications (4) and Use in Specific Populations (8.7)*].

Drug Interactions

A drug interaction study of **cabazitaxel** in 23 patients with advanced cancers has shown that repeated administration of ketoconazole (400 mg orally once daily), a strong CYP3A inhibitor, increased the exposure to cabazitaxel (5 mg/m² intravenous) by 25%.

A drug interaction study of **cabazitaxel** in 13 patients with advanced cancers has shown that repeated administration of aprepitant (125 or 80 mg once daily), a moderate CYP3A inhibitor, did not modify the exposure to cabazitaxel (15 mg/m² intravenous).

A drug interaction study of **cabazitaxel** in 21 patients with advanced cancers has shown that repeated administration of rifampin (600 mg once daily), a strong CYP3A inducer, decreased the exposure to cabazitaxel (15 mg/m² intravenous) by 17%.

A drug interaction study of **cabazitaxel** in 11 patients with advanced cancers has shown that cabazitaxel (25 mg/m² administered as a single 1-hour infusion) did not modify the exposure to midazolam, a probe substrate of CYP3A.

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

Based on *in vitro* studies, the potential for cabazitaxel to inhibit drugs that are substrates of other CYP isoenzymes (1A2, -2B6, -2C9, -2C8, -2C19, -2E1, -2D6, and CYP3A4/5) is low. In addition, cabazitaxel did not induce CYP isozymes (-1A, -2C9 and -3A) *in vitro*.

In vitro, cabazitaxel did not inhibit the multidrug-resistance protein 1 (MRP1), 2 (MRP2) or organic cation transporter (OCT1). *In vitro*, cabazitaxel inhibited P-gp, BCRP, and organic anion transporting polypeptides (OATP1B1, OATP1B3). However, the *in vivo* risk of cabazitaxel inhibiting MRPs, OCT1, P-gp, BCRP, OATP1B1 or OATP1B3 is low at the dose of 25 mg/m².

In vitro, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, BCRP, OCT1, OATP1B1 or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Cabazitaxel was positive for clastogenesis in the *in vivo* micronucleus test, inducing an increase of micronuclei in rats at doses ≥ 0.5 mg/kg. Cabazitaxel increased numerical aberrations with or without metabolic activation in an *in vitro* test in human lymphocytes though no induction of structural aberrations was observed. Cabazitaxel did not induce mutations in the bacterial reverse mutation (Ames) test. The positive *in vivo* genotoxicity findings are consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization).

In a fertility study performed in female rats at cabazitaxel doses of 0.05, 0.1, or 0.2 mg/kg/day there was no effect of administration of the drug on mating behavior or the ability to become pregnant. In repeat-dose toxicology studies in rats with intravenous cabazitaxel administration once every three weeks for up to 6 months, atrophy of the uterus was observed at the 5 mg/kg dose level (approximately the AUC in patients with cancer at the recommended human dose) along with necrosis of the corpora lutea at doses ≥ 1 mg/kg (approximately 0.2 times the AUC at the clinically recommended human dose).

In a fertility study in male rats, cabazitaxel did not affect mating performances or fertility at doses of 0.05, 0.1, or 0.2 mg/kg/day. In repeat-dose toxicology studies with intravenous cabazitaxel administration once every three weeks for up to 9 months, degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats at a dose of 1 mg/kg (approximately 0.2 times the AUC in patients at the recommended human dose), and minimal testicular degeneration (minimal epithelial single cell necrosis in epididymis) was observed in dogs treated at a dose of 0.5 mg/kg (approximately 0.1 times the AUC in patients at the recommended human dose).

14 CLINICAL STUDIES

14.1 TROPIC Trial (cabazitaxel + prednisone compared to mitoxantrone)

The efficacy and safety of **cabazitaxel** in combination with prednisone were evaluated in a randomized, open-label, international, multi-center study in patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen (TROPIC, NCT00417079).

A total of 755 patients were randomized to receive either **cabazitaxel** 25 mg/m² intravenously every 3 weeks for a maximum of 10 cycles with prednisone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m² intravenously every 3 weeks for 10 cycles with prednisone 10 mg orally daily (n=377) for a maximum of 10 cycles.

This study included patients over 18 years of age with hormone-refractory metastatic prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. Patients had to have neutrophils $>1,500$ cells/mm³, platelets $> 100,000$ cells/mm³, hemoglobin > 10 g/dL, creatinine $<1.5 \times$ upper limit of normal (ULN), total bilirubin $<1 \times$ ULN, AST $<1.5 \times$ ULN, and ALT $<1.5 \times$ ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

Demographics, including age, race, and ECOG performance status (0-2) were balanced between the treatment arms. The median age was 68 years (range 46-92) and the racial distribution for all groups was 83.9% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others in the **cabazitaxel** group.

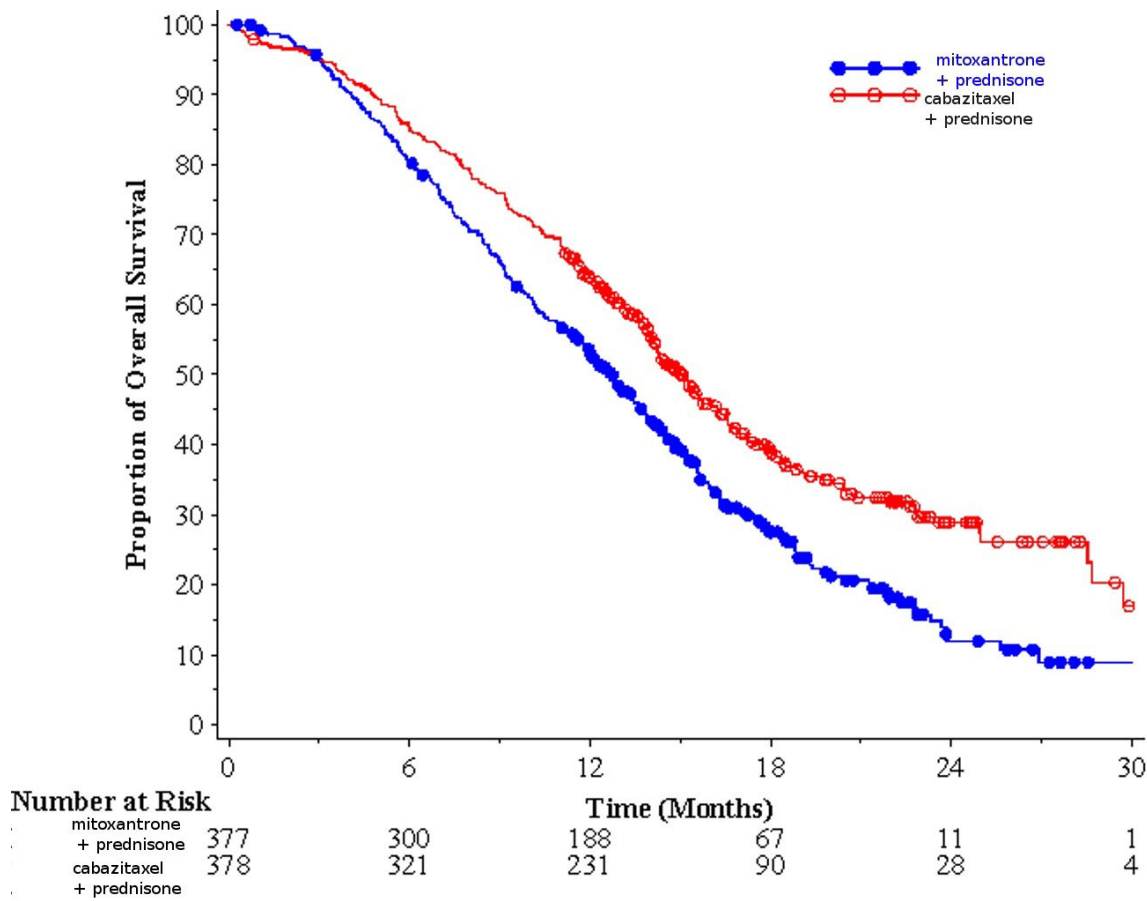
Efficacy results for the **cabazitaxel** arm versus the control arm are summarized in Table 5 and Figure 1.

Table 5: Efficacy of cabazitaxel in TROPIC in the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (intent-to-treat analysis)

	cabazitaxel + Prednisone n=378	Mitoxantrone + Prednisone n=377
Overall Survival		
Number of deaths (%)	234 (61.9 %)	279 (74.0%)
Median survival (month) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio* (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

*Hazard ratio estimated using Cox model; a hazard ratio of less than 1 favors **cabazitaxel**

Figure 1: Kaplan-Meier Overall Survival Curves (TROPIC)



Investigator-assessed tumor response of 14.4% (95%CI: 9.6-19.3) was higher for patients in the **cabazitaxel** arm compared to 4.4% (95%CI: 1.6-7.2) for patients in the mitoxantrone arm, p=0.0005.

14.2 PROSELICA Trial (comparison of two doses of cabazitaxel)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA, NCT01308580), 1200 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were randomized to receive either **cabazitaxel** 25 mg/m² (n=602) or 20 mg/m² (n=598) dose. Overall survival (OS) was the major efficacy outcome.

Demographics, including age, race, and ECOG performance status (0-2) were balanced between the treatment arms. The median age was 68 years (range 45-89) and the racial distribution for all groups was 87% Caucasian, 6.9% Asian, 2.3% Black, and 3.8% Others in the **cabazitaxel** 20 mg/m² group. The median age was 69 years (range 45-88) and the racial distribution for all groups was 88.7% Caucasian, 6.6% Asian, 1.8% Black, and 2.8% Others in the **cabazitaxel** 25 mg/m² group.

The study demonstrated noninferiority in overall survival (OS) of **cabazitaxel** 20 mg/m² in comparison with **cabazitaxel** 25 mg/m² in an intent-to-treat population (see Table 6 and Figure 2). Based on the per-protocol population, the estimated median OS was 15.1 months on **cabazitaxel** 20 mg/m² and 15.9 months on **cabazitaxel** 25 mg/m², the observed hazard ratio (HR) of OS was 1.042 (97.78% CI: 0.886, 1.224). Among the subgroup analyses intended for assessing the heterogeneity, no notable difference in OS was observed on the **cabazitaxel** 25 mg/m² arm compared to the **cabazitaxel** 20 mg/m² arm in subgroups based on the stratification factors of ECOG performance status score, measurability of disease, or region.

Table 6: Overall Survival in PROSELICA for cabazitaxel 20 mg/m² versus cabazitaxel 25 mg/m² (intent-to-treat analysis)

	CBZ20+PRED n=598	CBZ25+PRED n=602
Overall Survival		
Number of deaths, n (%)	497 (83.1 %)	501 (83.2%)
Median survival (95% CI) (months)	13.4 (12.2 to 14.9)	14.5 (13.5 to 15.3)
Hazard Ratio* (97.78% CI [†])	1.024 (0.886, 1.184)	

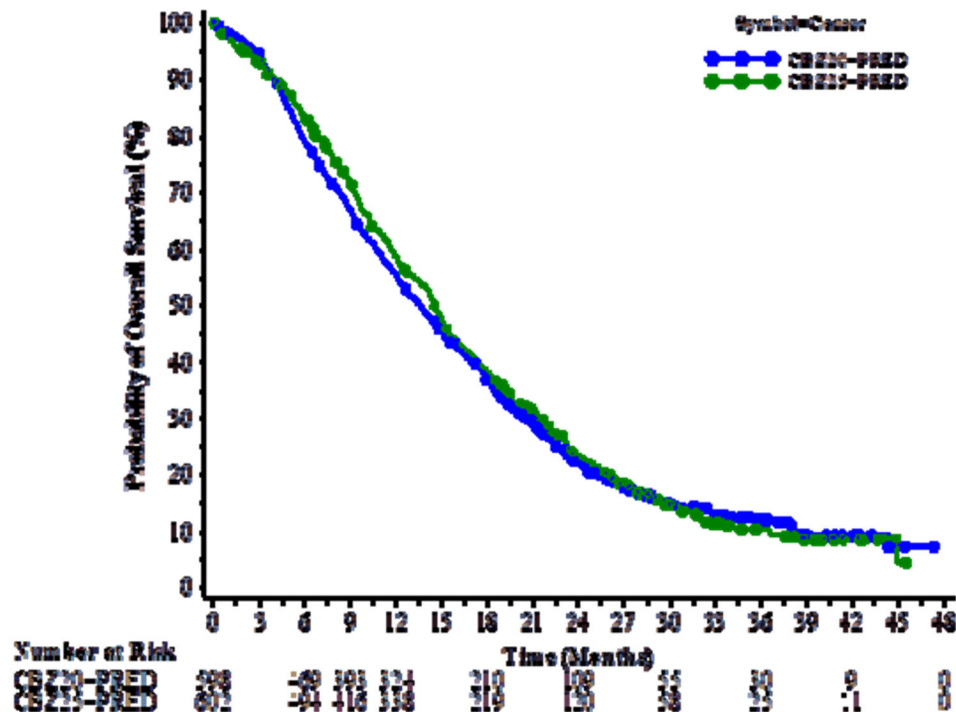
* Hazard ratio is estimated using a Cox Proportional Hazards regression model. A hazard ratio <1 indicates a lower risk of death for Cabazitaxel 20 mg/m² with respect to 25 mg/m².

† Adjusted for interim OS analyses. The noninferiority margin is 1.214.

CBZ20=Cabazitaxel 20 mg/m², CBZ25=Cabazitaxel 25 mg/m², PRED=Prednisone/Prednisolone.

CI=confidence interval.

Figure 2: Kaplan-Meier Overall Survival Curves (intent-to-treat population) (PROSELICA)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Cabazitaxel S.K. is supplied as a kit consisting of the following:

- One single dose vial of **Cabazitaxel S.K.** (cabazitaxel) injection: a clear yellow to brownish-yellow viscous solution of 60 mg/1.5 mL in a clear glass vial with a grey rubber closure, aluminum cap and light green plastic flip-off cap
- One single dose vial of Diluent for **Cabazitaxel S.K.**: a clear colorless solution of 13% (w/w) ethanol in water for injection in a clear glass vial with a grey chlorobutyl rubber stopper sealed with aluminum seal with light green plastic (Polypropylene homopolymer) button.

Both items are in a blister pack in one carton. Storage

Cabazitaxel S.K. injection and Diluent for **Cabazitaxel S.K.**:

Store below 30°C.

Do not refrigerate.

16.2 Handling and Disposal

Cabazitaxel S.K. is a cytotoxic anticancer drug. Follow applicable special handling and disposable procedures.

17. MARKETING AUTHORISATION HOLDER

K.S. KIM INTERNATIONAL (SK- PHARMA) LTD., ISRAEL

94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139

18. MANUFACTURER

DR. REDDY'S LABORATORIES LIMITED, INDIA

8-2-337, ROAD NO. 3, BANJARA HILLS, HYDERABAD– 500034 TELANGANA, INDIA

Revised in June 2022 according to MoH guidelines.

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