CABAZITAXEL EVER PHARMA 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. CABAZITAXEL EVER PHARMA is contraindicated in patients with neutrophil counts of ≤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 EVER PHARMA infusion and administration of appropriate therapy. Patients should receive premedication. CABAZITAXEL EVER PHARMA 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 (5.3)]*.

1 INDICATIONS AND USAGE

CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA 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),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist).

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

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue CABAZITAXEL EVER PHRMA dosing for adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with CABAZITAXEL EVER PHARMA

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/mm³, then reduce dosage of CABAZITAXEL EVER PHARMA 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/mm³, then reduce dosage of CABAZITAXEL EVER PHARMA 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 EVER PHARMA by one dose level.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of CABAZITAXEL EVER PHARMA by one dose level.
Grade ≥3 peripheral neuropathy	Discontinue CABAZITAXEL EVER PHARMA

Patients at a 20 mg/m² dose who require dose reduction should decrease dosage of CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 ≤1.5 × Upper Limit of Normal (ULN) or AST >1.5 x ULN): Administer CABAZITAXEL EVER PHARMA at a dose of 20 mg/m².
- Moderate hepatic impairment (total bilirubin >1.5 to ≤3 × ULN and AST = any): Administer CABAZITAXEL EVER PHARMA 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 × ULN): CABAZITAXEL EVER PHARMA 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 EVER PHARMA with these drugs. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% CABAZITAXEL EVER PHARMA dose reduction *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

2.5 Preparation and Administration

CABAZITAXEL EVER PHARMA should only be prepared and administered by personnel trained in handling cytotoxic agents. Pregnant staff should not handle the product.
As for any other antineoplastic agent, caution should be exercised when handling and preparing CABAZITAXEL EVER PHARMA solutions, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures. If CABAZITAXEL EVER PHARMA, 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.

Read this ENTIRE section carefully. CABAZITAXEL EVER PHARMA requires ONE dilution prior to administration. Follow the preparation instructions provided below.
The following dilution process must be carried out in an aseptic manner for preparing the solution for infusion.
More than one vial of the concentrate may be necessary to administer the prescribed dose.

Dilution for infusion

Step 1: Aseptically withdraw the required amount of concentrate (10 mg/ml of cabazitaxel), with a graduated syringe fitted with a needle. As an example, a dose of 60 mg CABAZITAXEL EVER PHARMA would require 6 ml of the concentrate.
CABAZITAXEL EVER PHARMA 10 mg/ml concentrate for solution for infusion contains an overfill. This overfill ensures that there is extractable volume of 6 ml containing 10 mg/ml cabazitaxel.
Step 2: Inject in a sterile PVC-free container of either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. The concentration of the infusion solution should be between 0.10 mg/ml and 0.26 mg/ml.
Step 3: Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion.
Step 4: As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. As the infusion solution is supersaturated, it may crystallize over time. In this case, the solution must not be used and should be discarded.
The infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned below.

3 DOSAGE FORMS AND STRENGTHS

CABAZITAXEL EVER PHARMA 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION.

- Cabazitaxel injection: 60 mg/6ml, clearly slightly yellow oily solution
  Excipient with known effect
  Each vial of 6ml of concentrate contains 1,185mg of ethanol (19.75% w/v)

4 CONTRAINDICATIONS

CABAZITAXEL EVER PHARMA is contraindicated in patients with:

- neutrophil counts of ≤ 1,500/mm³ *[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 × ULN) *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

CABAZITAXEL EVER PHARMA is contraindicated in patients with neutrophils ≤1,500/mm³ *[see Contraindications (4)]*. Closely monitor patients with hemoglobin <10 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 EVER PHARMA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the CABAZITAXEL EVER PHARMA group was neutropenia (2%). Grade 3-4 neutropenia has been observed in 82% of patients treated with CABAZITAXEL EVER PHARMA in the randomized trial. In a randomized trial (PROSELICA) comparing two doses of CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA, 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 EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA, deaths due to infection within 30 days of starting CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA, 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 EVER PHARMA *[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 EVER PHARMA infusion and appropriate therapy. CABAZITAXEL EVER PHARMA 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 EVER PHARMA *[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 EVER PHARMA 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 EVER PHARMA, 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 EVER PHARMA 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 EVER PHARMA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on CABAZITAXEL EVER PHARMA. Interrupt or discontinue CABAZITAXEL EVER PHARMA 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 EVER PHARMA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving CABAZITAXEL EVET PHARMA. Consider discontinuation. The benefit of resuming CABAZITAXEL EVER PHARMA treatment must be carefully evaluated.

5.8 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.
CABAZITAXEL EVER PHARMA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) *[see Contraindications (4)]*. Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) and moderate (total bilirubin >1.5 to ≤3.0 × 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 EVER PHARMA 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 EVER PHARMA 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 Cmax in patients at the recommended human dose). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of CABAZITAXEL EVER PHARMA *[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 EVER PHARMA + prednisone compared to mitoxantrone)
The safety of CABAZITAXEL EVER PHARMA 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 EVER PHARMA treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in CABAZITAXEL EVER PHARMA -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 EVER PHARMA. Other fatal adverse reactions in CABAZITAXEL EVER PHARMA -treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.
The most common (≥5%) grade 3-4 adverse reactions in patients who received CABAZITAXEL EVER PHARMA 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 EVER PHARMA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the CABAZITAXEL EVER PHARMA group were neutropenia and renal failure. Dose reductions were reported in 12% of CABAZITAXEL EVER PHARMA -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 ≥ 5% of Patients Receiving CABAZITAXEL EVER PHARMA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone in TROPIC

	CABAZITAXEL EVER PHARMA 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 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 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 Neuropathyᵇ	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 EVER PHARMA: 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.
ᵇ Includes peripheral motor neuropathy and peripheral sensory neuropathy.

PROSELICA Trial (comparison of two doses of CABAZITAXEL EVER PHARMA)
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 EVER PHARMA 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 EVER PHARMA -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 EVER PHARMA 20 mg/m² or 25 mg/m² in Combination with Prednisone in PROSELICA

	CABAZITAXEL EVER PHARMA 20 mg/m² every 3 weeks with prednisone 10 mg daily n=580		CABAZITAXEL EVER PHARMA 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%)
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 EVER PHARMA 20 mg/m² or 25 mg/m² in Combination with Prednisone in Study PROSELICA

Laboratory Abnormality	CABAZITAXEL EVER PHARMA 20 mg/m² every 3 weeks with prednisone 10 mg daily n=577		CABAZITAXEL EVER PHARMA 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 (%)
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 EVER PHARMA -treated patients. The incidence of grade ≥2 hematuria was 6% in CABAZITAXEL EVER PHARMA -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 EVER PHARMA 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 ≤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 EVER PHARMA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% CABAZITAXEL EVER PHARMA 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 EVER PHARMA have not been established in females. There are no human data on the use of CABAZITAXEL EVER PHARMA 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, embryolethality, and fetal deaths when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the Cmax 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 EVER PHARMA 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 4 months after the final dose of CABAZITAXEL EVER PHARMA *[see Use in Specific Populations (8.1)]*.

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

8.4 Pediatric Use

The safety and effectiveness of CABAZITAXEL EVER PHARMA in pediatric patients have not been established.

CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 ≥ 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 ≤1.5 × ULN or AST >1.5 × ULN) should have CABAZITAXEL EVER PHARMA 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 ≤3.0 × ULN and AST= any) was 15 mg/m², however, the efficacy at this dose level was unknown. CABAZITAXEL EVER PHARMA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) *[see Contraindications (4)]*.

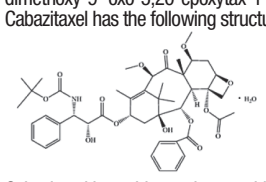
9 OVERDOSAGE

There is no known antidote for CABAZITAXEL EVER PHARMA 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.

10 DESCRIPTION

CABAZITAXEL EVER PHARMA 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 (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9- oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one (1:1).
Cabazitaxel 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 EVER PHARMA injection 60 mg/6 mL is a sterile, non-pyrogenic, clear slightly yellow oily solution and is available in single-dose vial.

11 CLINICAL PHARMACOLOGY

11.1 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.

11.2 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.

11.3 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 Cmax 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 (Vss) 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 [^{14}C]-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 ≤CLCR <50 mL/min) and 59 patients with mild renal impairment (50 mL/min ≤ CLCR <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, CLCR >80 mL/min/1.73 m²), or moderate (n=8, 30 mL/min/1.73 m² ≤ CLCR <50 mL/min/1.73 m²) and severe (n=9, CLCR <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, CLCR <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 ≤1.5 × ULN or AST >1.5 × ULN) or moderate (total bilirubin >1.5 to ≤3.0 × 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 × 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 EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA 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 EVER PHARMA 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, BRCP, 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.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of cabazitaxel.
Cabazitaxel was positive for genotoxicity by an aneugenic mechanism 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).

13 CLINICAL STUDIES

13.1 TROPIC Trial (CABAZITAXEL EVER PHARMA + prednisone compared to mitoxantrone)

The efficacy and safety of CABAZITAXEL EVER PHARMA 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 EVER PHARMA 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 × upper limit of normal (ULN), total bilirubin <1 × ULN, AST <1.5 × ULN, and ALT <1.5 × ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

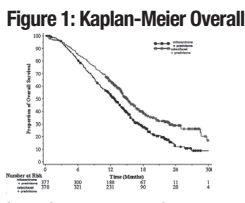
Demographics, including age, race, and ECOG performance status (0-2) were balanced between the treatment arms. The median age was 68 years (range 46-92) and the racial distribution for all groups was 83.9% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others in the CABAZITAXEL EVER PHARMA group.
Efficacy results for the CABAZITAXEL EVER PHARMA arm versus the control arm are summarized in Table 5 and Figure 1.

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

	CABAZITAXEL EVER PHARMA + 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 EVER PHARMA

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 EVER PHARMA arm compared to 4.4% (95%CI: 1.6-7.2) for patients in the mitoxantrone arm, p=0.0005.

13.2 PROSELICA Trial (comparison of two doses of CABAZITAXEL EVER PHARMA)

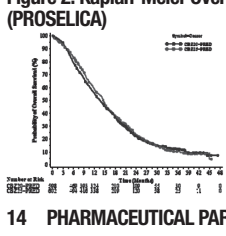
In a noninferiority, multicenter, randomized, open-label study (PROSELICA, NCT01308580), 1200 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were randomized to receive either CABAZITAXEL EVER PHARMA 25 mg/m² (n=602) or 20 mg/m² (n=598) 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 EVER PHARMA 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 EVER PHARMA 25 mg/m² group.
The study demonstrated noninferiority in overall survival (OS) of CABAZITAXEL EVER PHARMA 20 mg/m² in comparison with CABAZITAXEL EVER PHARMA 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 EVER PHARMA 20 mg/m² and 15.9 months on CABAZITAXEL EVER PHARMA 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 EVER PHARMA 25 mg/m² arm compared to the CABAZITAXEL EVER PHARMA 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 EVER PHARMA 20 mg/m² versus CABAZITAXEL EVER PHARMA 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)



14 PHARMACEUTICAL PARTICULARS

14.1 List of excipients

Macrogol 300, Polysorbate 80 super refined, Ethanol (anhydrous), Citric Acid (anhydrous)

14.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 7.1.
PVC Infusion container or polyethylene infusion sets should not be used for the preparation and administration of the infusion solution.

14.3 Shelf life

Unopened vial
3 years
The expiry date of the product is indicated on the packaging materials.
Multi dose vial: Chemical, physical and microbiological stability of the solution after first opening has been demonstrated for 28 days below 25°C (for multi dose use)

After dilution:
Chemical and physical stability of the diluted infusion (Infusion Solution Stability) has been demonstrated for 48 hours below 25°C (for multi- dose use) and for 14 days at refrigerated conditions.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

14.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. It is recommended to keep at R.T. Do not freeze.

14.5 Nature and contents of containers

One pack contains one vial of Cabazitaxel Ever Pharma 60mg/6ml concentrate for solution for Infusion. Clear, glass vial closed with a grey bromobutyl rubber stopper sealed with an aluminum cap.

15 MANUFACTURER

EVER Valinject GmbH, Oberburgau 3, 4866 Unterach am Attersee, Austria

16 LICENSE AND IMPORTER HOLDER

Pharmalogic Ltd., 14 Imber St., Petah-Tikva 49511
Revised in November 2023 according to MOH guidelines

EVER VALINJECT