HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JEVTANA safely and effectively. See full prescribing information for JEVTANA.

JEVTANA® (cabazitaxel) injection, for intravenous use

Initial U.S. Approval: 2010

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

See full prescribing information for complete boxed warning.

- Neutropenic deaths have been reported. Obtain frequent blood counts to monitor for neutropenia. JEVTANA 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 (4, 5.1, 5.2).
- Severe hypersensitivity can occur and may include generalized rash/erythema, hypotension and bronchospasm. Discontinue JEVTANA immediately if severe reactions occur and administer appropriate therapy (2.1, 5.2).
- Contraindicated if history of severe hypersensitivity reactions to cabazitaxel or to drugs formulated with polysorbate 80. (4)

RECENT MAJOR CHANGES

Boxed Warning 08/2017
Dosage and Administration (2.1, 2.2) 08/2017
Contraindications (4) 08/2017
Warnings and Precautions (5.1, 5.2) 08/2017
Warnings and Precautions (5.6) 09/2016

INDICATIONS AND USAGE

JEVTANA is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen. (1)

DOSE AND ADMINISTRATION

Recommended Dose: JEVTANA 20 mg/m² administered every three weeks as a one-hour intravenous infusion in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment. (2.1)

- A dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider. (2.1, 5.1, 5.2, 6.1, 14)
- JEVTANA requires two dilutions prior to administration. (2.5)
- Use the entire contents of the accompanying diluent to achieve a concentration of 10 mg/mL JEVTANA. (2.5)
- PVC equipment should not be used. (2.5)
- Premedication Regimen: Administer intravenously 30 minutes before each dose of JEVTANA:
  - Antihistamine (deschlorpheniramine 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) (2.1)
- Antiemetic prophylaxis (oral or intravenous) is recommended as needed. (2.1)

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*Sections or subsections omitted from the full prescribing information are not listed.
Patients at a 20 mg/m² dose who require dose reduction should decrease dosage of JEVTANA to 15 mg/m² [see Adverse Reactions (6.1)]. Patients at a 25 mg/m² dose who require dose reduction should decrease dosage of JEVTANA 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 x Upper Limit of Normal [ULN] or AST >1.5 x ULN): Administer JEVTANA at a dose of 20 mg/m².
- Moderate hepatic impairment (total bilirubin >1 to ≤3 x ULN and AST = any): Administer JEVTANA 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 x ULN): JEVTANA is contraindicated in patients with severe hepatic impairment [see Warning and Precautions (5.7) 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, erythromycin, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

2.5 Preparation and Administration

JEVTANA is a cytotoxic antineoplastic drug. Follow applicable special handling and disposal procedures [see References (15)]. If JEVTANA first diluted solution, or second (final) dilution for intravenous infusion should be used in close 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 JEVTANA infusion solution. JEVTANA should not be mixed with any other drugs.

Preparation

Read this entire section carefully before mixing and diluting. JEVTANA 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 JEVTANA 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 JEVTANA. Inspect the JEVTANA injection and supplied diluent vials. The JEVTANA injection is a clear yellow to brownish-yellow viscous solution.

Step 1 – First Dilution

Each vial of JEVTANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the entire contents of each vial of polysorbate 80 [see Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions (5.3)].

Step 2 – Second (Final) Dilution

Withdraw the recommended dose from the JEVTANA 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 JEVTANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusional solution should be between 0.10 mg/mL and 0.26 mg/mL. Remove the syringe and gently mix the final infusional solution by inverting the bag or bottle. As the final infusional solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Fully prepared JEVTANA 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 final dilution solution or (second) final infusional 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 JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

3. DOSAGE FORMS AND STRENGTHS

JEVTANA (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

JEVTANA 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 x ULN) [see Warnings and Precautions (5.7)]
- pregnancy (JEVTANA can cause fetal harm and potential loss of pregnancy) [see Use in Specific Populations (8.1)]

5. WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

JEVTANA 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 JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%). Grade 3–4 neutropenia has been observed in 22% of patients treated with JEVTANA in the randomized trial. In a randomized trial (PROSELICA) comparing two doses of JEVTANA 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 JEVTANA 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. Noninfectious for overall survival was demonstrated between these two arms [see Clinical Studies (14)].

Based on guidelines for the use of G-CSF and the adverse reactions profile of JEVTANA, 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 JEVTANA has not been studied. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients at increased risk for neutropenia complications.
In a randomized clinical trial (PROSELICA) comparing two doses of JEVTANA, deaths due to infection (8% vs 6%).

Patients 65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. Patients Administration (2.1)] [see Adverse

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

5.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Premedicate all patients prior to the initiation of the infusion of JEVTANA [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 JEVTANA infusion and appropriate therapy. JEVTANA 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, antiarrhythmic or antiemetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade 3 diarrhea [see Dosage and Administration (2.1)].

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with JEVTANA [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. JEVTANA treatment delay or discontinuation may be necessary.

5.5 Renal Failure

In the randomized clinical trial (TROPIC), renal failure of any grade occurred in 4% of the patients being treated with JEVTANA, 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 Respiratory Disorders

Intestinal pneumatosis/pneumonitis, intestinal 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 JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

5.7 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) [see 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 (2.9) and Use in Specific Populations (8.7)]. Administration of JEVTANA to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

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)]
• Use 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)]
• Respiratory Disorders [see Warnings and Precautions (5.6)]
• Use in Patients with Hepatic Impairment [see Warnings and Precautions (5.7)]

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 (JEVTANA + prednisone compared to mitoxantrone)

The safety of JEVTANA 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%) JEVTANA-treated patients and 3 (1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-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 JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1–4 adverse reactions were: diarrhea, leukenia, neutropenia, thrombocytopenia, diarrea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hema- turia, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

Table 2: Incidence of Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone in TROPIC

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JEVTANA 25 mg/m² every 3 weeks with prednisone 10 mg daily n=371</th>
<th>Mitoxantrone 12 mg/m² every 3 weeks with prednisone 10 mg daily n=371</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–4 n (%)</td>
<td>Grade 3–4 n (%)</td>
<td>Grade 1–4 n (%)</td>
</tr>
<tr>
<td>Any Adverse Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>347 (94%) 303 (82%)</td>
<td>325 (87%) 215 (58%)</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>176 (48%) 15 (4%)</td>
<td>160 (43%) 6 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>173 (47%) 23 (6%)</td>
<td>39 (11%) 1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (34%) 7 (2%)</td>
<td>85 (23%) 1 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>83 (22%) 6 (2%)</td>
<td>38 (10%) 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>76 (20%) 4 (1%)</td>
<td>57 (15%) 2 (1%)</td>
</tr>
<tr>
<td>Abdominal Pain§</td>
<td>64 (17%) 7 (2%)</td>
<td>23 (6%) 0</td>
</tr>
<tr>
<td>Dyspepsia§</td>
<td>36 (10%) 0</td>
<td>9 (2%) 0</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>136 (37%) 18 (5%)</td>
<td>102 (27%) 11 (3%)</td>
</tr>
<tr>
<td>Aesthesia</td>
<td>76 (20%) 17 (5%)</td>
<td>46 (12%) 9 (2%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 (12%) 4 (1%)</td>
<td>23 (6%) 1 (1%)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>34 (9%) 2 (1%)</td>
<td>34 (9%) 2 (1%)</td>
</tr>
<tr>
<td>Muscular Inflammation</td>
<td>22 (6%) 1 (1%)</td>
<td>10 (3%) 0</td>
</tr>
<tr>
<td>Pain</td>
<td>20 (5%) 4 (1%)</td>
<td>18 (5%) 7 (2%)</td>
</tr>
<tr>
<td>Infections and Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection†</td>
<td>29 (8%) 6 (2%)</td>
<td>12 (3%) 4 (1%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>32 (9%) 0</td>
<td>28 (8%) 1 (1%)</td>
</tr>
</tbody>
</table>
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 JEVTANA 25 mg/m² or 20 mg/m². Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m² group and 20% of patients in the 25 mg/m² group received a median of 3 weeks with prednisone 10 mg daily.

### Table 2: Incidence of Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone in TROPIC (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1–4 n (%)</th>
<th>Grade 3–4 n (%)</th>
<th>Grade 1–4 n (%)</th>
<th>Grade 3–4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>59 (16%)</td>
<td>3 (&lt;1%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>18 (5%)</td>
<td>8 (2%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Back Pain</td>
<td>60 (16%)</td>
<td>14 (4%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>39 (11%)</td>
<td>4 (1%)</td>
<td>31 (8%)</td>
</tr>
<tr>
<td></td>
<td>Muscle Spasms</td>
<td>27 (7%)</td>
<td>0</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Peripheral Neuropathy</td>
<td>50 (13%)</td>
<td>3 (&lt;1%)</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td></td>
<td>Dysesthesia</td>
<td>41 (11%)</td>
<td>0</td>
<td>15 (4%)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>30 (8%)</td>
<td>0</td>
<td>21 (6%)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>28 (8%)</td>
<td>0</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Renal and Urinary Tract Disorders</td>
<td>Hematuria</td>
<td>62 (17%)</td>
<td>7 (2%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td></td>
<td>Dysuria</td>
<td>25 (7%)</td>
<td>0</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Gynecomastia</td>
<td>43 (12%)</td>
<td>4 (1%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>40 (11%)</td>
<td>0</td>
<td>22 (6%)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Alopecia</td>
<td>37 (10%)</td>
<td>0</td>
<td>18 (5%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Hypertension</td>
<td>20 (5%)</td>
<td>2 (&lt;1%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Median Duration of Treatment</td>
<td>6 cycles</td>
<td>4 cycles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Graded using NCI CTCAE version 3
†Based on laboratory values, JEVTANA: 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.
\*Graded from NCI CTCAE version 4.03.

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

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 JEVTANA 25 mg/m² (n=559) 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 JEVTANA-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 JEVTANA-treated patients included cerebral hemorrhage, respiratory failure, paralytic ileus, diarrohea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, diverticular perforation, and cardioenal syndrome.

Grade 1–4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leucopenia, 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 leucopenia, neutropenia, and febrile neutropenia.

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1–4 n (%)</th>
<th>Grade 3–4 n (%)</th>
<th>Grade 1–4 n (%)</th>
<th>Grade 3–4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Febrile Neutropenia</td>
<td>12 (2%)</td>
<td>12 (2%)</td>
<td>55 (9%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia²</td>
<td>18 (3%)</td>
<td>14 (2%)</td>
<td>65 (11%)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Urinary tract infection³</td>
<td>43 (7%)</td>
<td>12 (2%)</td>
<td>66 (11%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenic infection⁴</td>
<td>15 (3%)</td>
<td>13 (2%)</td>
<td>42 (7%)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased appetite</td>
<td>76 (13%)</td>
<td>4 (0.7%)</td>
<td>110 (19%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dysesthesia</td>
<td>41 (7%)</td>
<td>0</td>
<td>63 (11%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral sensory neuropathy</td>
<td>38 (7%)</td>
<td>0</td>
<td>63 (11%)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>24 (4%)</td>
<td>0</td>
<td>32 (5%)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>29 (6%)</td>
<td>1 (0.2%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Dyspnea</td>
<td>33 (5%)</td>
<td>5 (0.9%)</td>
<td>46 (8%)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>34 (6%)</td>
<td>0</td>
<td>35 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhoea</td>
<td>178 (31%)</td>
<td>8 (1%)</td>
<td>237 (40%)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>142 (25%)</td>
<td>4 (0.7%)</td>
<td>191 (32%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>84 (15%)</td>
<td>7 (1.2%)</td>
<td>108 (18 %)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>102 (18%)</td>
<td>2 (0.3%)</td>
<td>107 (18%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>34 (6%)</td>
<td>3 (0.5%)</td>
<td>52 (9%)</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>27 (5%)</td>
<td>0</td>
<td>30 (5%)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Alopecia</td>
<td>15 (3%)</td>
<td>0</td>
<td>36 (6.1%)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Back pain</td>
<td>64 (11%)</td>
<td>5 (0.9%)</td>
<td>83 (14%)</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>46 (8%)</td>
<td>10 (2%)</td>
<td>50 (8%)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>49 (8%)</td>
<td>3 (0.5%)</td>
<td>41 (7%)</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity</td>
<td>30 (5%)</td>
<td>1 (0.2%)</td>
<td>41 (7%)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Hematuria</td>
<td>82 (14%)</td>
<td>11 (2%)</td>
<td>124 (21%)</td>
</tr>
<tr>
<td></td>
<td>Dysuria</td>
<td>31 (5%)</td>
<td>2 (0.3%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>143 (25%)</td>
<td>15 (3%)</td>
<td>161 (27%)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>89 (15%)</td>
<td>11 (2%)</td>
<td>117 (20%)</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>39 (7%)</td>
<td>1 (0.2%)</td>
<td>53 (9%)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>27 (5%)</td>
<td>1 (0.2%)</td>
<td>38 (6 %)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>24 (4%)</td>
<td>1 (0.2%)</td>
<td>44 (7%)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Wrong technique in drug usage process</td>
<td>2 (0.3%)</td>
<td>0</td>
<td>32 (5%)</td>
</tr>
</tbody>
</table>

*Graded 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 ureosepsis.
§Includes neutropenic sepsis.
Cabazitaxel is primarily metabolized through CYP3A. The following adverse reactions have been identified from clinical trials and/or postmarketing

6.2 Postmarketing Experience

Hematuria

The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

6.3 Hematuria

In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade 2 or higher hematuria was 6% in JEVTANA-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 JEVTANA arm.

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

6.4 Adverse Reactions by Body Weight

There were no clinically meaningful differences in incidence of adverse reactions between patients with normal or reduced renal function or patients with mild hepatic impairment.

The incidences of grade 3–4 neutropenia were higher in patients who were 65 years of age or greater compared to younger patients (54% vs 41%), and in patients with severe hepatic impairment (30% vs 19%).

6.5 Pregnancy

In an embryo-fetal 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 postimplantation loss of at least 2 mg/kg/day and an increase in partial resorptions at ≥0.1 mg/kg/day (approximately 0.06 and 0.02 times the 

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 JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction (see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

JEVTANA is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. JEVTANA is not indicated for use in female patients. There are no human data on the use of cabazitaxel injection in pregnant women. 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 postimplantation loss of at least 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 

8.2 Lactation

Risk Summary

JEVTANA is not indicated for use in female patients. 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 

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 JEVTANA (see Use in Specific Populations (8.1)).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>JEVTANA 20 mg/m2 every 3 weeks with prednisone 10 mg daily n=577</th>
<th>JEVTANA 25 mg/m2 every 3 weeks with prednisone 10 mg daily n=590</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Grade 1–4 n (%)</td>
<td>Grade 1–4 n (%)</td>
</tr>
<tr>
<td></td>
<td>384 (67%)</td>
<td>241 (42%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3–4 n (%)</td>
<td>522 (89%)</td>
</tr>
<tr>
<td></td>
<td>432 (73%)</td>
<td>388 (69.7%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>576 (99.8%)</td>
<td>57 (10%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>461 (80%)</td>
<td>167 (29%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>202 (35%)</td>
<td>15 (3%)</td>
</tr>
</tbody>
</table>

Incidence

The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

8.4 Pediatric Use

The safety and effectiveness of JEVTANA in pediatric patients have not been established.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVTANA 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 (60% vs 44%), anemia (20% vs 16%), nausea and vomiting (39% vs 29%), diarrhea (34% vs 25%), infection (20% vs 14%), dyspnea (10% vs 5%), and rash (10% vs 5%).

In the PROSELIKA 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 diarreha (43% vs 33%), fatigue (20% vs 16%), anemia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 5%).

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 (12.4)).

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin >1.0 to ≤1.5 x ULN or AST >1.5 x ULN) should have JEVTANA dose reduced by 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 (12.4)). The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3.0 x ULN and AST = any) was 15 mg/m2. However, the efficacy at this dose level was unknown. JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 x ULN) (see Contraindications (4)).

10. OVERDOSAGE

There is no known antidote for JEVTANA 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

JEVTANA (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 (2x,5x,7x,10x,13x)-4-acetoxy-13-(125R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyloxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20- dihydro-5β,11β,12α,13α,14α,17α-hexahydro-2H-cyclopenta[a]phenanthrene-3-carboxylic acid.

Cabazitaxel has the following structural formula:

\[ \text{Cabazitaxel} \]

\[ \text{C}_{45} \text{H}_{57} \text{O}_{12} \]

Cabcabazitaxel is a white to almost-white powder with a molecular formula of C_{45}H_{57}O_{12} and a molecular weight of 884.01 (for the acetoxy solvate) / 835.93 (for the solvent free). It is lipophilic, practically insoluble in water and soluble in alcohol.
JEVTANA (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 (1.56 g polysorbate 80).

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

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

JEVTANA requires two dilutions prior to intravenous infusion. JEVTANA injection should be diluted only with the supplied DILUENT for JEVTANA, 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 64 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 Cmax in patients with metastatic prostate cancer was 226 mg/L (CV 107%) and was reached at the end of the one-hour infusion (Tmax). 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 (Vd) was 4.66 L (2.64 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 isoenzyme (80% to 90%), and to a lesser extent by CYP2D6. Cabazitaxel is the main circulating moiety in human plasma. Seven metabolites were detected in plasma (including the 3 active metabolites issued from CYP metabolism), 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 (i.v.)-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 (>95% 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 ranging from 10 to 30 mg/m² at steady state.

In vivo, 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, in the in vivo risk of cabazitaxel inhibiting MRP2, OCT1, P-gp, BCRP, OATP1B1 or OATP1B3 is low at the dose of 25 mg/m² in vivo, 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 clastogenicity in the in vitro 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 toxicity 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 toxicity studies with intravenous cabazitaxel administration three weeks for up to 8 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 epididymal 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 (JEVTANA + prednisone compared to mitoxantrone)

The efficacy and safety of JEVTANA 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, NCT01417079). A total of 755 patients were randomized to receive either JEVTANA 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 with rising PSA levels or appearance of new lesions, and ECOG (Eastern Cooperative Oncology Group) performance status 0–2. Patients treated in the JEVTANA + Prednisone arm were allowed to continue with previous concomitant anti-androgens, if this was part of the patients’ routine. The patients had to have previously failed at least three lines of systemic therapy for metastatic CRPC. All patients were required to be treatment-naive to docetaxel and there were no geographic restrictions. Patients were randomized on a 2:1 ratio (JEVTANA:mitoxantrone) to receive each treatment arm. The median age was 68 years (range 46–92) and the racial distribution for all groups was ≥80% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others in the JEVTANA group. Efficacy results for the JEVTANA arm versus the control arm are summarized in Table 5 and Figure 1.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>JEVTANA + Prednisone</th>
<th>Mitoxantrone + Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>n=378</td>
<td>n=377</td>
</tr>
<tr>
<td>Number of deaths (%)</td>
<td>234 (61.9%)</td>
<td>279 (74%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>15.1 (14.1–16.3)</td>
<td>12.7 (11.6–13.7)</td>
</tr>
<tr>
<td>Hazard Ratio* (95% CI)</td>
<td>0.70 (0.59–0.83)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Hazard ratio estimated using Cox model, a hazard ratio of less than 1 favors JEVTANA
Hazard ratio is estimated using a Cox Proportional Hazards regression model. A hazard ratio CI=confidence interval.

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 88.7% Caucasian, 6.9% Asian, 2.3% Black, and 2.8% Others in the JEVTANA 20 mg/m² group. The median age was 69 years (range 45–88) and the racial distribution for all groups was 86.7% Caucasian, 6.6% Asian, 1.8% Black, and 2.6% Others in the JEVTANA 25 mg/m² group. The study demonstrated noninferiority in overall survival (OS) of JEVTANA 25 mg/m² in comparison with JEVTANA 20 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 JEVTANA 20 mg/m² and 15.9 months on JEVTANA 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 JEVTANA 25 mg/m² arm compared to the JEVTANA 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 JEVTANA 20 mg/m² versus JEVTANA 25 mg/m² (intent-to-treatment analysis)

<table>
<thead>
<tr>
<th></th>
<th>CBZ20+PRED n=598</th>
<th>CBZ25+PRED n=602</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>497 (83.1 %)</td>
<td>501 (83.2 %)</td>
</tr>
<tr>
<td>Median survival (95% CI) (months)</td>
<td>13.4 (12.2 to 14.9)</td>
<td>14.5 (13.5 to 15.3)</td>
</tr>
<tr>
<td>Hazard Ratio (97.78% CI)</td>
<td>1.024 (0.886, 1.184)</td>
<td></td>
</tr>
</tbody>
</table>

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

The study demonstrated noninferiority in overall survival (OS) of JEVTANA 20 mg/m² (n=602) or 20 mg/m² (n=598) dose. Overall survival (OS) was the major efficacy outcome. The study demonstrated noninferiority in overall survival (OS) of JEVTANA 20 mg/m² compared to the JEVTANA 20 mg/m² group. 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 2.8% Others in the JEVTANA 20 mg/m² group. The median age was 69 years (range 45–88) and the racial distribution for all groups was 86.7% Caucasian, 6.6% Asian, 1.8% Black, and 2.6% Others in the JEVTANA 25 mg/m² group. The study demonstrated noninferiority in overall survival (OS) of JEVTANA 25 mg/m² in comparison with JEVTANA 20 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 JEVTANA 20 mg/m² and 15.9 months on JEVTANA 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 JEVTANA 25 mg/m² arm compared to the JEVTANA 20 mg/m² arm in subgroups based on the stratification factors of ECOG performance status score, measurability of disease, or region.

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<td>501 (83.2 %)</td>
</tr>
<tr>
<td>Median survival (95% CI) (months)</td>
<td>13.4 (12.2 to 14.9)</td>
<td>14.5 (13.5 to 15.3)</td>
</tr>
<tr>
<td>Hazard Ratio (97.78% CI)</td>
<td>1.024 (0.886, 1.184)</td>
<td></td>
</tr>
</tbody>
</table>

JEVTANA is a cytotoxic anticancer drug. Follow applicable special handling and disposable procedures [see References (15)].

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

<table>
<thead>
<tr>
<th></th>
<th>CBZ20+PRED n=598</th>
<th>CBZ25+PRED n=602</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>497 (83.1 %)</td>
<td>501 (83.2 %)</td>
</tr>
<tr>
<td>Median survival (95% CI) (months)</td>
<td>13.4 (12.2 to 14.9)</td>
<td>14.5 (13.5 to 15.3)</td>
</tr>
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<td>Hazard Ratio (97.78% CI)</td>
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<td></td>
</tr>
</tbody>
</table>

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

*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.**

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What is the most important information I should know about JEVTANA?
JEVTANA may cause serious side effects including:
Low white blood cells. Low white blood cells can cause you to get serious infections, and may lead to death. Men who are 65 years or older may be more likely to have these problems. Your healthcare provider:
- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your healthcare provider decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

Tell your healthcare provider right away if you have any of these symptoms of infection during treatment with JEVTANA:
- fever. Take your temperature often during treatment with JEVTANA.
- cough. burning on urination
- muscle aches

Also, tell your healthcare provider if you have any diarrhea during the time that your white blood cell count is low. Your healthcare provider may prescribe treatment for you as needed.

Severe allergic reactions. Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your healthcare provider should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your healthcare provider or nurse right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA:
- rash or itching
- skin redness
- feeling dizzy or faint
- breathing problems
- chest or throat tightness
- swelling of your face

Severe stomach and intestine (gastrointestinal) problems. JEVTANA can cause severe stomach and intestine problems, which may lead to death. You may need to go to a hospital for treatment.

Tell your healthcare provider if:
- you have vomiting or diarrhea
- your symptoms get worse or do not get better
- JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine. This can lead to death. Tell your healthcare provider if you get any of these symptoms:
  - severe stomach-area (abdomen) pain
  - blood in your stool, or changes in the color of your stool

Kidney failure. Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider if you develop these signs or symptoms:
- swelling of your face or body
- decrease in the amount of urine that your body makes each day
- blood in your urine

Lung or breathing problems. Lung or breathing problems may happen with JEVTANA and may lead to death. Men who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough or fever.

Before receiving JEVTANA, tell your healthcare provider about all your medical conditions, including if you:
- had allergic reactions in the past
- are over the age of 65
- have kidney or liver problems
- have lung problems
- are a male with a female partner who is able to become pregnant. Males should use effective birth control (contraception) during treatment with JEVTANA and for 3 months after your final dose of JEVTANA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your healthcare provider first. Your healthcare provider will tell you if it is safe to take the new medicine with JEVTANA.

How will I receive JEVTANA?
- JEVTANA will be given to you by an intravenous (IV) infusion into your vein.
- Your treatment will take about 1 hour.
- JEVTANA is usually given every 3 weeks. Your healthcare provider will decide how often you will receive JEVTANA.
- Your healthcare provider will also prescribe another medicine called prednisone for you to take by mouth every day during treatment with JEVTANA. Your healthcare provider will tell you how and when to take your prednisone.

It is important that you take prednisone exactly as prescribed by your healthcare provider. If you forget to take your prednisone, or do not take it on schedule, make sure to tell your healthcare provider or nurse. Before each infusion of JEVTANA, you may receive other medicines to prevent or treat side effects.
What are the possible side effects of JEVTANA?

JEVTANA may cause serious side effects including:

- See “What is the most important information I should know about JEVTANA?”

Common side effects of JEVTANA include:

- Low red blood cell count (anemia). Low red blood cell count is common with JEVTANA, but can sometimes also be serious. Your healthcare provider will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- Low blood platelet count. Low platelet count is common with JEVTANA, but can sometimes also be serious. Tell your healthcare provider if you have any unusual bruising or bleeding.

Diarrhea
- Low red blood cell count (anemia)
- Nausea
- Vomiting
- Constipation
- Weakness
- Stomach (abdominal) pain
- Blood in your urine. Tell your healthcare provider or nurse if you see blood in your urine.
- Back pain
- Decreased appetite
- Shortness of breath
- Hair loss
- Cough

JEVTANA may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of JEVTANA. For more information, ask your healthcare provider or pharmacist.

Tell your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of JEVTANA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about JEVTANA that is written for health professionals.

What are the ingredients in JEVTANA?

Active ingredient: cabazitaxel

Inactive ingredient: polysorbate 80

Manufactured by: sanofi-aventis U.S. LLC, Bridgewater, NJ 08807

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For more information, go to www.sanofi-aventis.us or call 1-800-633-1610.

This Patient Information has been approved by the U.S. Food and Drug Administration

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