WARNINGS: 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. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² (4, 5.1, 5.2).

Severe hypersensitivity reactions 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)

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)

Dosage 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)

In patients with hepatic impairment, 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, 5.6, 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)

PV fluid 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 (2.1)

Antiemetic prophylaxis (oral or intravenous) is recommended as needed. (2.1)

Dosage Modifications: See full prescribing information (2.2, 2.3, 2.4, 2.5)

ADVERSE REACTIONS
Most common all grades adverse reactions and laboratory abnormalities (≥10%) with JEVTANA 20 mg/m² or 25 mg/m² are neutropenia, anemia, diarrhea, nausea, fatigue, asthenia, vomiting, hematuria, constipation, decreased appetite, back pain, and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Avoid coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25%-JEVTANA dose reduction. (2.4, 7.1, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2023
1 INDICATIONS AND USAGE
JEVTANA® 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 JEVTANA 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 JEVTANA treatment.

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² [see Contraindications (4) and Warnings and Precautions (5.1, 5.2)].

Severe hypersensitivity: Severe hypersensitivity reactions may occur and may require premedication [e.g., ranitidine, hydrocortisone, diphenhydramine]. Severe hypersensitivity reactions may require discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive pretreatment with G-CSF, if available, 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)].

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue JEVTANA dosing for adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged grade ≥3 neutropenia (greater than 1 week) despite appropriate medication and treatment with granulocyte-colony stimulating factor (G-CSF)</td>
<td>Delay treatment until neutrophil count is &gt;1,500 cells/mm³, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.</td>
</tr>
<tr>
<td>Moderate neutropenia or neutrophinic infection</td>
<td>Delay treatment until improvement or resolution, and until neutrophil count is &gt;1,500 cells/mm³, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.</td>
</tr>
<tr>
<td>Grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement</td>
<td>Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.</td>
</tr>
<tr>
<td>Grade 2 peripheral neuropathy</td>
<td>Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.</td>
</tr>
<tr>
<td>Grade ≥3 peripheral neuropathy</td>
<td>Discontinue JEVTANA.</td>
</tr>
</tbody>
</table>

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 >1.5 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 (5.8) 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, and voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with these drugs. 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 hazardous anticancer drug. Follow applicable special handling and disposal procedures [see Reference (15)]. If JEVTANA first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water. Do not use PVC infusion containers or polyurethane infusion sets for preparation and administration of JEVTANA injection 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.

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 supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEVTANA.

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

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

The resulting initial diluted JEVTANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

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 infusible vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

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

As the final infusion solution is supersaturated, it may crystalize over time. Do not use it 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 JEVTANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

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

The final JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

3 DOSE 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/v) 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 (5.8)]

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.

TROPIC Trial (JEVTANA 25 mg/m²)

In the TROPIC trial with G-CSF administered only at the investigator's discretion, 5 patients (1.3%) died from neutropenic infection (sepsis or septic shock); 4 of these patients died in the first 30 days of treatment. One additional patient’s death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued treatment due to neutropenia, febrile neutropenia, infection, or sepsis. Grade 3–4 neutropenia occurred in 82% of patients treated with JEVTANA in the randomized trial [see Adverse Reactions (6.1)].
PROSELICA Trial (comparison of JEVTANA 20 mg/m² versus 25 mg/m²).

In the PROSELICA trial comparing two doses of JEVTANA, primary prophylaxis with G-CSF was not allowed, but could be administered after development of neutropenia at investigators discretion. Eight patients (1%) on the 20 mg/m² arm and 15 patients (3%) on the 25 mg/m² arm developed neutropenia; of those, 3 patients on the 20 mg/m² arm and 8 deaths on the 25 mg/m² arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events occurred and included febrile neutropenia (21.1% on 20 mg/m² arm and 9.2% on 25 mg/m² arm), neutropenic infection/sepsis (2.1% on 20 mg/m² arm and 14.4% on 25 mg/m² arm), and neutropenic deaths (0.3% on 20 mg/m² arm and 0.7% on 25 mg/m² arm).

Fever. Patients receiving JEVTANA 20 mg/m² were reported to have infectious adverse reactions. In PROSELICA, 3 were experienced by 160 patients (26%) 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)].

CARD Trial (JEVTANA 25 mg/m² + primary prophylaxis G-CSF). In the CARD trial where JEVTANA 25 mg/m² was administered with primary prophylaxis of G-CSF, 1 patient (0.8%) died from sepsis within the first 30 days of treatment. Grade 3–4 neutropenia-related adverse reactions were experienced in 33 patients (28%) and 38 patients (30%) on the 20 mg/m² arm and 25 mg/m² arm, respectively. Fewer patients receiving JEVTANA 20 mg/m² were reported to have infectious adverse reactions. In PROSELICA, 25 mg/m² arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events occurred and included febrile neutropenia (21.1% on 20 mg/m² arm and 9.2% on 25 mg/m² arm), neutropenic infection/sepsis (2.1% on 20 mg/m² arm and 14.4% on 25 mg/m² arm), and neutropenic deaths (0.3% on 20 mg/m² arm and 0.7% on 25 mg/m² arm).

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Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reactions</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></td>
<td>Grade 1–4</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain‡</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia§</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**General Disorders and Administration Site Conditions**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucosal Inflammation</td>
<td>6</td>
<td>&lt;1</td>
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<tr>
<td>Pain</td>
<td>5</td>
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</tbody>
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**Renal and Urinary Tract Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Dysuria</td>
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**Musculoskeletal and Connective Tissue Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Pain</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
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<tr>
<td>Muscle Spasms</td>
<td>7</td>
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**Metabolism and Nutrition Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dehydration</td>
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<td>2</td>
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**Nervous System Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy§</td>
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<tr>
<td>Dysgeusia</td>
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<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
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</tr>
<tr>
<td>Headache</td>
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**Respiratory, Thoracic and Mediastinal Disorders**

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<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
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**Skin and Subcutaneous Tissue Disorders**

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<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
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**Investigations**

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<th>Adverse Reactions</th>
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<tbody>
<tr>
<td>Weight Decreased</td>
<td>9</td>
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</table>

**Infections and Infestations**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract Infection¶</td>
<td>8</td>
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**Cardiac Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
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</tr>
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<tbody>
<tr>
<td>Arrhythmia¶</td>
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**Vascular Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>&lt;1</td>
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</table>

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Table 2: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in TROPIC (continued)

**Table 3: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in PROSELICA**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>JEVTANA 20 mg/m² every 3 weeks with prednisone 10 mg daily n=595</th>
<th>JEVTANA 25 mg/m² every 3 weeks with prednisone 10 mg daily n=598</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1–4</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Blood and Lymphatic System Disorders</td>
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</tr>
<tr>
<td>Anemia‡</td>
<td>99.8</td>
<td>10</td>
</tr>
<tr>
<td>Leukopenia‡</td>
<td>80</td>
<td>29</td>
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<tr>
<td>Neutropenia‡</td>
<td>67</td>
<td>42</td>
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<tr>
<td>Thrombocytopenia‡</td>
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<td>3</td>
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<tr>
<td>Febrile Neutropenia</td>
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**Gastrointestinal Disorders**

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<thead>
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<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>3</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Constipation</td>
<td>18</td>
<td>0.3</td>
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<tr>
<td>Vomiting</td>
<td>15</td>
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<td>Abdominal pain</td>
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<td>0.5</td>
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<td>Stomatitis</td>
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**General Disorders and Administration Site Conditions**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15</td>
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<tr>
<td>Edema peripheral</td>
<td>7</td>
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</tr>
<tr>
<td>Pyrexia</td>
<td>5</td>
<td>0.2</td>
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</table>

**Renal and Urinary Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Dysuria</td>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Musculoskeletal and Connective Tissue Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Metabolism and Nutrition Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Nervous System Disorders**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Grade 1–4</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyseusia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

---

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=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 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, diarrhea, 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 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 reactions occurred in 17% of patients in the 25 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.

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PROSELICA Trial (comparison of two doses of JEVTANA)
months and 4.7% remained on treatment at 12 months. Among patients receiving JEVTANA, 35% remained on treatment at 6 months. In the PROSELICA trial, 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily, and primary prophylaxis with G-CSF was evaluated in a randomized, open-label study (CARD) in patients with metastatic castration-resistant prostate cancer who progressed after receiving prior docetaxel-containing regimens and abiraterone acetate and/or enzalutamide. This study compared JEVTANA 25 mg/m² (N=126) in combination with prednisone/prednisolone and primary prophylaxis G-CSF to either abiraterone acetate 10 mg daily every 2 weeks with prednisone or enzalutamide 10 mg daily for 3 weeks with prednisone 10 mg daily every 2 weeks. The safety of JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis G-CSF was evaluated in a randomized, open-label study (CARD) in patients with metastatic castration-resistant prostate cancer who progressed after receiving prior docetaxel-containing regimens and abiraterone acetate or enzalutamide [see Clinical Studies 14.3]. This study compared JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis with G-CSF to either abiraterone acetate 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily. Among patients receiving JEVTANA, 35% remained on treatment at 6 months and 4.7% remained on treatment at 12 months. Treatment discontinuations due to adverse drug reactions occurred in 20% of patients who received JEVTANA 25 mg/m², 10% of patients who received JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis G-CSF, and 10% of patients who received abiraterone acetate 10 mg daily every 2 weeks with prednisone or enzalutamide 10 mg daily for 3 weeks with prednisone. Serious adverse reactions occurred in 38% of patients receiving JEVTANA. Serious adverse reactions in ≥10% of patients included fatigue, diarrhea, myalgia, pain abdomen, dyspepsia, decreased appetite, nausea, severe abdominal pain, constipation, hematuria, and urinary tract infection. Fatal adverse reactions in JEVTANA-treated patients were septic shock, urinary tract infection (UTI), and aspiration (0.8% each).

The most common (≥10%) adverse reactions were fatigue, diarrhea, musculoskeletal pain, nausea, infections, peripheral neuropathy, hematoma, constipation, abdominal pain, decreased appetite, vomiting, dysgeusia, edema peripheral and lower urinary tract symptoms, and thrombocytopenia. The most common (≥10%) hematologic abnormalities were anemia, lymphopenia, neutropenia, and thrombocytopenia. The most common (≥10%) adverse reactions leading to interruption of JEVTANA were fatigue (7%), and hypersensitivity reaction (3.2%). The most frequent adverse reactions leading to reduction of JEVTANA were neutropenia and thrombocytopenia.

Table 3: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in PROSELICA (continued)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>JEVTANA 20 mg/m² every 3 weeks with prednisone 10 mg daily (n=380)</th>
<th>JEVTANA 25 mg/m² every 3 weeks with prednisone 10 mg daily (n=395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–4 %</td>
<td>Grade 3–4 %</td>
<td>Grade 1–4 %</td>
</tr>
</tbody>
</table>

Infections and Infestations

- Urinary tract infection
- Neutropenic infection

Respiratory, Thoracic and Mediastinal Disorders

- Dyspnea
- Cough

Investigations

- Weight decreased

Skin and Subcutaneous Tissue Disorders

- Alopecia

Injury, Poisoning and Procedural Complications

- Wrong technique in drug usage process

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>JEVTANA 25 mg/m² + prednisone/prednisolone + G-CSF (N=126)</th>
<th>Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–4 %</td>
<td>Grade 3–4 %</td>
<td>Grade 1–4 %</td>
</tr>
</tbody>
</table>

Blood and Lymphatic System Disorders

- Anemia
- Lymphopenia
- Neutropenia
- Thrombocytopenia

General Disorders and Administration Site Conditions

- Fatigue

Table 4: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in CARD Trial (continued)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>JEVTANA 25 mg/m² + prednisone/prednisolone + G-CSF (N=126)</th>
<th>Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–4 %</td>
<td>Grade 3–4 %</td>
<td>Grade 1–4 %</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders

- Diarrhea
- Nausea
- Constipation
- Abdominal pain
- Vomiting
- Stomatitis
- Dyspepsia

Musculoskeletal and Connective Tissue Disorders

- Musculoskeletal pain
- Pain in extremity
- Bone fracture

Metabolism and Nutrition Disorders

- Decreased appetite
- Hypokalemia

Vascular Disorders

- Hypertension

Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)

- Cancer pain

Cardiac disorders

- Respiratory, Thoracic and Mediastinal Disorders

- Pneumonia
- Dyspnea

Skin and Subcutaneous Tissue Disorders

- Alopecia

Injury, Poisoning and Procedural Complications

- Weight decreased
**Table 4: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in Card Trial (Continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JEVETANA 25 mg/m² + prednisone/predonisolone or G-CSF (N=126)</th>
<th>Aribatrone + prednisone/ predonisolone or Enzalutamide (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Aribatrone + prednisone/ predonisolone or Enzalutamide (N=124)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>3.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Grade 3-4 (%)</td>
<td>4.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Grade from NCI CTC version 4.0.*
†Based on laboratory values % calculated using the number of patients with at least one event(n) over the number of patients assessed for each parameter during the on-treatment period.
‡Includes asthenia, fatigue, lethargy, malaise.
§Includes lymphoedema, edema peripheral, peripheral swelling.
¶Includes diabetes, diabetes insipidus, secondary, encephalopathy, gout, edema, peripheral edema, cholecystitis, hemorrhagic, gastroparesis.
∥Includes abdominal pain, abdominal pain lower, abdominal pain upper, flank pain, gastrointestinal pain.
\| Includes cold, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain.
*Includes femoral neck fracture, pathological fracture, rib fracture, spinal compression fracture, sternal fracture, thoracic vertebral fracture.
*Includes bacteremia, bacteriuria, cellulitis, device related sepsis, Enterobacter species, escherichia coli, fever, hypothermia, hantavirus, influenza, iritis, leukocytosis, meningitis, pneumonia, sepsis, septic shock, subcutaneous abscess, upper respiratory tract infection, urosepsis, urinary tract infection, wound infection.
**Includes neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy.
†Includes lower urinary tract symptoms, urinary incontinence, urinary retention, dysuria.
‖Includes acute kidney injury, blood creatinine increased, renal failure, renal impairment.
‡Includes aortic valve incompetence, aortic valve stenosis, atrial fibration, atrial flutter, atrioventricular block complete, atrioventricular block second degree, bradycardia, sinus bradycardia, tachycardia, cardiac arrest, conduction disturbance, angina pectoris.
§Includes lower respiratory tract infection, lung infection, lung infiltration, pneumonia.
¶Includes hypertension, hypertensive crisis.

**Psychiatric Disorders**

**Hematuria** (3.2%), pulmonary embolism (1.6%), and neutropenic infection (0.8%).

In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and fetal deaths. In the TROPIC study, of the 371 patients with prostate cancer treated with JEVETANA every 15 days for 24 weeks of a single intravenous administration of cabazitaxel to latching rats at a dose of 0.08 mg/kg (approximately 0.02 times the Cmax in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 95% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

**8. Females and Males of Reproductive Potential**

**Conception**

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 last dose of JEVETANA [see Use in Specific Populations (8.1)].

**Interruption**

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

**8.5 Geriatric Use**

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVETANA every 15 days for 24 weeks of a single intravenous administration of cabazitaxel to latching rats at a dose of 0.08 mg/kg (approximately 0.02 times the Cmax in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 95% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

**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 (CLcr 30 ≤ CLcr <15.0 mL/min/1.73 m²) should have the dose of 20 mg/m² decreased to 15 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 administration of a reduced dose tolerated dose in patients with moderate hepatic impairment [CLcr between 10 ≤ CLcr ≤ 30 mL/min/1.73 m² and AST > ULN or ALT > ULN] was 15 mg/m² (approximately 0.06 times the Cmax in patients at the recommended human dose). The safety and efficacy of JEVETANA have been established in females. There is no information available on the presence of cabazitaxel in human milk, the effects of the drug or its active metabolites in infants, or their effects on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats [see Data].

**Antimalarial drug**

A milk excretion study, radioactivity related to cabazitaxel was detected in the stools of the nursing female rats within 2 hours of a single intravenous administration of cabazitaxel to latching rats at a dose of 0.08 mg/kg (approximately 0.02 times the Cmax in patients at the recommended human dose). Of the dose delivered to the mother was calculated to be delivered in the maternal milk.
Cabazitaxel is a white or almost white powder with a molecular formula of C_{37}H_{49}NO_{14}C_{2}H_{2}O and a molecular weight of 894.01 (for the acetone solvate)/835.93 (for the sodium chloride solution or 5% dextrose solution). The solubility of cabazitaxel is 0.1 mg/mL in water and 1.56 g polysorbate 80 (citric acid monohydrate is used to adjust the pH of the polysorbate 80 between 3.3 to 3.8).

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

DILUTION 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 solution 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 polymerization into microtubules.

**12.2 Pharmacodynamics**

**Cardiac Electrophysiology**

The effect of cabazitaxel following a single dose of 25 mg/m² administered by intravenous infusion on QTc interval was evaluated in 94 patients with solid tumors. No large changes of the QTc interval were observed when compared to baseline.

**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 ng/mL (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 (Vdss) 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 bound to human albumin (82%), and lipoproteins (88% for HDL, 70% for LDL, and 58% for VLDL). In vivo, cabazitaxel has a half-life of 1.1 days, with half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

**Metabolism**

Cabazitaxel is extensively metabolized in the liver (>95%), mainly by the CYP3A4/5 isoenzyme, to C4-epoxide, and to a lesser extent by CYP2C8. Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic model with α1, β1, 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 excluding 14 patients with moderate renal impairment (30 mL/min < CrCl ≤ 50 mL/min) and 59 patients with mild renal impairment (50 mL/min < CrCl ≤ 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, CrCl > 90 mL/min/1.73 m²), severe (n=9, CrCl <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, CrCl < 15 mL/min/1.73 m²).

**Hepatic Impairment**

Cabazitaxel is extensively metabolized in the liver.

A dedicated comparative pharmacokinetic study in 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× 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 cabazitaxel exposure was observed when compared to patients with mild hepatic impairment (Cr 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 (5.6) and Use in Specific Populations (6.7)].

**Drug Interactions**

A drug interaction study of JEVTANA in 23 patients with advanced cancers has shown that ritonavir-based administration of ketoconazole (400 mg once daily) increased CYP3A4 activity, increased the exposure to cabazitaxel (5 mg/m² intravenous) by 25%.

A drug interaction study of JEVTANA in 13 patients with advanced cancers has shown that repeated administration of ranitidine (400 mg once 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 isoenzymes (1A2, 2C9 and 3A4) in vivo.

**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 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 assay, though induction of structural aberrations was not 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 fertility studies in male rats, 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 prostate 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 once three weeks for up to 9 months, degeneration of seminal vesicle and seminiferous tubule atrophy in the testes were observed in rats at a dose of 1 mg/kg (approximately 0.2 times the AUC in patients at the recommended human dose), with minimal testicular tubular atrophy (orchitis). The AUC at the 10 mg/kg level (approximately 3 times the AUC at the clinically recommended human dose) was observed in treated mice at a dose of 0.5 mg/kg (approximately 0.1 times the AUC at the recommended human dose).

**14 CLINICAL STUDY**

**14.1 TROPIC Trial (JEVTANA + prednisone compared to mitoxantrone)**

The efficacy and safety of JEVTANA in combination with prednisone were evaluated in a randomized, double-blind, international, phase III, placebo-controlled, 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 JEVTANA 25 mg/m² intravenously every 3 weeks for a maximum of 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× ULN, total bilirubin ≤1.5× ULN, and AST/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, anemia pectoris, and/or oxygenation 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, 6.0% 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>Overall Survival</th>
<th>Mitoxantrone + Prednisone n=377</th>
<th>JEVTANA + Prednisone n=377</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths (%)</td>
<td>234 (61.9%)</td>
<td>279 (74.0%)</td>
</tr>
<tr>
<td>Median survival (months) (95% CI)</td>
<td>15.1 (14.1–16.3)</td>
<td>12.7 (11.6–13.7)</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.

14.2 PROSELICA Trial (comparison of two doses of JEVTANA)

The efficacy and safety of JEVTANA were evaluated in a noninferiority, multicenter, randomized, open-label study (PROSELICA, NCT01308580). A total of 1200 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen were randomized to receive either JEVTANA 25 mg/m\(^2\) (n=600) or 20 mg/m\(^2\) (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 JEVTANA 25 mg/m\(^2\) 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 JEVTANA 25 mg/m\(^2\) group. The study demonstrated noninferiority in overall survival (OS) of JEVTANA 20 mg/m\(^2\) in comparison with JEVTANA 25 mg/m\(^2\) 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/m\(^2\) and 15.9 months on JEVTANA 25 mg/m\(^2\), the observed hazard ratio (HR) of OS was 1.024 (97.78% CI: 0.886, 1.224). Among the subgroup analyses intended for assessing the heterogeneity, no notable difference in OS was observed in the JEVTANA 25 mg/m\(^2\) arm compared to the JEVTANA 20 mg/m\(^2\) arm in subgroups based on the stratification factors of ECOG performance status 0–2, time from abiraterone acetate or enzalutamide to disease progression, and receipt of abiraterone acetate or enzalutamide before or after docetaxel containing regimen.

The major efficacy outcome measure was radiographic progression free-survival (rPFS) as defined by Prostate Cancer Working Group-2 (PCWG2) assessed by study investigators. Other efficacy outcome measures included overall survival and objective response rate. Demographics and baseline disease characteristics were balanced between treatment arms. The overall median age was 70 years (range 45 to 88), 95% of patients had an ECOG PS of 0 to 1 and median Gleason score was 8. A majority of the patients (61%) had their prior treatment with abiraterone acetate or enzalutamide after docetaxel. There were 36% of patients on the cabazitaxel arm with visceral disease (liver 8%, lung 8%, other 20%) and 57% with bone-only disease. Race and ethnicity data were not collected. Approximately 92% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF compared to abiraterone acetate or enzalutamide and had progressed within 12 months of initiating either abiraterone or enzalutamide. A total of 255 patients were randomized to receive either JEVTANA 25 mg/m\(^2\) every 3 week plus prednisone/prednisolone 10 mg daily (n=129), abiraterone 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily depending on prior therapy received (n=126). Primary prophylactic G-CSF was administered at each cycle for patients in the JEVTANA arm. This study included patients over 18 years of age with ECOG performance status 0–2. Patients who had to have neutrophils >1,500 cells/mm\(^3\), platelets >100,000 cells/mm\(^3\), hemoglobin >10 g/dL, creatinine <1.5 × upper limit of normal (ULN), total bilirubin <1 × ULN, AST <1.5 × ULN, 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. Randomization was stratified by ECOG performance status (0 or 1 vs 2), time from abiraterone acetate or enzalutamide to disease progression, and receipt of abiraterone acetate or enzalutamide before or after docetaxel containing regimen.

The efficacy and safety of JEVTANA were evaluated in a multinational, randomized, active-controlled, open-label study (CARD: NCT02485691) in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen and had progressed within 12 months of initiating either abiraterone or enzalutamide. The study demonstrated noninferiority in overall survival (OS) of JEVTANA compared to abiraterone acetate plus prednisone/prednisolone or enzalutamide. The major efficacy outcome measure was radiographic progression free-survival (rPFS) as defined by Prostate Cancer Working Group-2 (PCWG2) assessed by study investigators. Other efficacy outcome measures included overall survival and objective response rate. Demographics and baseline disease characteristics were balanced between treatment arms. The overall median age was 70 years (range 45 to 88), 95% of patients had an ECOG PS of 0 to 1 and median Gleason score was 8. A majority of the patients (61%) had their prior treatment with abiraterone acetate or enzalutamide after docetaxel. There were 36% of patients on the cabazitaxel arm with visceral disease (liver 8%, lung 8%, other 20%) and 57% with bone-only disease. Race and ethnicity data were not collected. Approximately 92% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy during the first 3 cycles and, overall, 90% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy at each cycle. Efficacy results from the CARD trial are summarized in Table 7 and Figure 3.

Table 6: Overall Survival in PROSELICA for JEVTANA 20 mg/m\(^2\) versus JEVTANA 25 mg/m\(^2\) (intent-to-treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>CB220+PRED n=598</th>
<th>CB225+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>

14.3 CARD Trial (JEVTANA 25 mg/m\(^2\) + prednisone/prednisolone + primary prophylaxis with G-CSF compared to abiraterone acetate + prednisone/prednisolone or enzalutamide)

The efficacy and safety of JEVTANA were evaluated in a multinational, randomized, active-controlled, open-label study (CARD: NCT02485691) in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen and had progressed within 12 months of initiating either abiraterone or enzalutamide. The study demonstrated noninferiority in overall survival (OS) of JEVTANA compared to abiraterone acetate plus prednisone/prednisolone or enzalutamide. The major efficacy outcome measure was radiographic progression free-survival (rPFS) as defined by Prostate Cancer Working Group-2 (PCWG2) assessed by study investigators. Other efficacy outcome measures included overall survival and objective response rate. Demographics and baseline disease characteristics were balanced between treatment arms. The overall median age was 70 years (range 45 to 88), 95% of patients had an ECOG PS of 0 to 1 and median Gleason score was 8. A majority of the patients (61%) had their prior treatment with abiraterone acetate or enzalutamide after docetaxel. There were 36% of patients on the cabazitaxel arm with visceral disease (liver 8%, lung 8%, other 20%) and 57% with bone-only disease. Race and ethnicity data were not collected. Approximately 92% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy during the first 3 cycles and, overall, 90% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy at each cycle. Efficacy results from the CARD trial are summarized in Table 7 and Figure 3.

Table 7: Efficacy of JEVTANA in CARD Trial in the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (intent-to-treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>JEVTANA + prednisone/prednisolone + G-CSF n=129</th>
<th>Abiraterone + prednisone/prednisolone or Enzalutamide n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic Progression Free Survival (rPFS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>95 (73.6%)</td>
<td>101 (82.2%)</td>
</tr>
<tr>
<td>Median rPFS (months) (95% CI)</td>
<td>8.0 (5.7 to 9.2)</td>
<td>3.7 (2.8 to 5.1)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.54 (0.40 to 0.73)</td>
<td></td>
</tr>
<tr>
<td>p-value(^1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Overall Survival (OS)(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI) (months)</td>
<td>13.6 [11.5; 17.5]</td>
<td>11.0 [9.2; 12.8]</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.64 [0.46; 0.89]</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0078</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Investigator assessed.
\(^\dagger\)Stratified log-rank test, significance threshold = 0.05.
\(^\ddagger\)Overall survival was statistically significant.
In terms of therapy sequence prior to randomization, rPFS was consistent across the subgroups of patients who received abiraterone acetate/ezetimibe prior to docetaxel (HR=0.61, 95% CI: 0.39, 0.79) and those who received abiraterone acetate/ezetimibe after docetaxel (HR=0.45, 95% CI: 0.27, 0.75). Objective tumor response rate assessed by study investigators was 36.5% (95% CI: 26.6 to 46.4) for JEVTANA arm versus 11.5% (95% CI: 2.9 to 20.2) for abiraterone acetate plus prednisone/prednisolone or ezetimibe arm, p=0.004.

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
JEVTANA is supplied as a kit, NDC 0024-5824-11, that contains the following:
- One single-dose vial of JEVTANA (cabazitaxel) injection: a clear yellow to brownish-yellow viscous solution of 60 mg/1.5 mL in a clear glass vial with a grey rubber closure, aluminum cap, and light green plastic flip-off cap (JEVTANA vial NDC 0024-5823-15).
- One single-dose vial of Diluent for JEVTANA: a clear colorless solution of 13% (w/w) ethanol in water for injection in a clear glass vial with a grey rubber closure, gold-color aluminum cap, and colorless plastic flip-off cap (diluent vial NDC 0024-5822-01).

16.2 Storage
JEVTANA injection and Diluent for JEVTANA: Store at 25°C (77°F); excursions permitted between 15°C–30°C (59°F–86°F).
Do not refrigerate.

16.3 Handling and Disposal
JEVTANA is a hazardous antinecancer drug. Follow applicable special handling and disposal procedures (see References (15)).

17. PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions
Educate patients about the risk of potential hypersensitivity associated with JEVTANA. Confirm patients do not have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80. Instruct patients to immediately report signs of a hypersensitivity reaction (see Contraindications (4) and Warnings and Precautions (5.3)).

Bone Marrow Suppression
Inform patients that JEVTANA decreases blood count such as white blood cells, platelets and red blood cells. Thus, it is important that periodic assessment of their blood count be performed to detect the development of neutropenia, thrombocytopenia, anemia, and/or pancytopenia (see Contraindications (4) and Warnings and Precautions (5.1)). Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever to their healthcare provider.

Increased Toxicities in Elderly Patients
Inform elderly patients that certain side effects may be more frequent or severe (see Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.5)).

Importance of Predisone
Explain that it is important to take the oral predisone as prescribed. Instruct patients to report if they were not compliant with oral corticosteroid regimen (see Dosage and Administration (2.1)).

Infections, Dehydration, Renal Failure
Explain to patients that severe and fatal infections, dehydration, and renal failure have been associated with cabazitaxel exposure. Patients should immediately report fever, significant vomiting or diarrhea, decreased urinary output, and hematruia to their healthcare provider (see Warnings and Precautions (5.1, 5.3)).

Urinary Disorders Including Cystitis
Inform patients that hematuria may occur during treatment with JEVTANA. Inform patients that previously received pelvic radiation that cystitis and radiation cystitis may occur during treatment with JEVTANA. Advise patients to report any occurrence of hematuria, or any signs and symptoms of cystitis or radiation cystitis, to their healthcare provider (see Warnings and Precautions (5.6)).

Respiratory Disorders
Explain to patients that severe and fatal interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have occurred with JEVTANA. Instruct patients to immediately report new or worsening pulmonary symptoms to their healthcare provider (see Warnings and Precautions (5.7)).

Drug Interactions
Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to their healthcare provider (see Drug Interactions (7.1)).

Embryo-Fetal Toxicity
Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of JEVTANA (see Use in Specific Populations (8.3)).
• Severe stomach and intestine (gastrointestinal) problems.
  o JEVTANA can cause severe vomiting and diarrhea, which may lead to death. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA.

You may need to go to a hospital for treatment. Your healthcare provider will prescribe medicines to prevent or treat vomiting and diarrhea, as needed, with JEVTANA.

Tell your healthcare provider right away if you develop vomiting or diarrhea or if your symptoms get worse or do not get better.

o JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine, which may lead to death.

Tell your healthcare provider if you develop any of these symptoms:
- severe stomach-area (abdomen) pain
- constipation
- fever
- 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

• Inflammation of the bladder and blood in the urine. Blood in the urine is common with JEVTANA, but it can also sometimes be severe. Some people who have had pelvic radiation in the past may develop inflammation of the bladder and blood in the urine that is severe enough that they need to be hospitalized for medical treatment or surgery. Your healthcare provider will check you for these problems during treatment with JEVTANA. Your healthcare provider may stop your treatment with JEVTANA for a short time, or permanently, if you develop inflammation of the bladder and bleeding that is severe. Tell your healthcare provider if you have blood in your urine, burning or pain during urination, or frequent or urgent need to urinate.

• 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.

What is JEVTANA?
JEVTANA is a prescription medicine used with the steroid medicine prednisone. JEVTANA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body, and that has worsened (progressed) after treatment with other medicines that included docetaxel.

It is not known if JEVTANA is safe and effective in females or children.

Who should not receive JEVTANA?
Do not receive JEVTANA if:
- your white blood cell (neutrophil count) is too low
- you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80. Ask your healthcare provider if you are not sure.
- you have severe liver problems

Before receiving JEVTANA, tell your healthcare provider about all your medical conditions, including if you:
- are over the age of 65
- had allergic reactions in the past
- have kidney or liver problems
- have lung problems
- are pregnant or plan to become pregnant. JEVTANA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- 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 4 months after the last 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.

Tell your healthcare provider if you have any unusual bruising or bleeding.

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:

The most 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
  - nausea
  - tiredness
  - weakness
  - vomiting
  - constipation
  - decreased appetite
  - back pain
  - stomach (abdominal) pain
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 of the possible side effects of JEVTANA. For more information, ask your healthcare provider or pharmacist.

Call 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 ingredients: polysorbate 80, citric acid monohydrate

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.

Revised: July 2023

CAB-FPLR-SL-JUL23 Rx Only