Drug Monograph

A - Drug Name

cabazitaxel

COMMON TRADE NAME(S): Jevtana®

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B - Mechanism of Action and Pharmacokinetics

Cabazitaxel, a semi-synthetic taxane produced from yew needles, binds to tubulin, stabilizes microtubules, and inhibits mitosis. Cabazitaxel is active in docetaxel-sensitive as well as resistant tumours.

Distribution	Pharmacokinetics are dose proportional between 10 and 30mg/m^2	
	Cross blood brain barrier?	yes
	PPB	89 to 92%;(albumin and lipoproteins)
Metabolism	Cabazitaxel is extensively metabolized in the liver (≥95%), primarily by the CYP3A4 isoenzyme (80% to 90%)	
	Active metabolites	yes
	Inactive metabolites	yes
Elimination	The predominant route of cabazitaxel elimination is fecal excretion.	
	Feces	76%, as metabolites
	Urine	<4% (2% unchanged)

Half-life	95 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Prostate cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following table contains adverse effects reported in patients treated with cabazitaxel 20 mg/m^2 and prednisone in prostate cancer. It also includes severe or life-threatening adverse effects from both 20mg/m^2 and 25mg/m^2 treated groups.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (2%) (≥grade 3: 2%, including tachycardia, atrial/ventricular fibrillation, ↑ QTc)	I E
	Cardiotoxicity (<1%)	E
	Hypotension (5%) (reported at 25 mg/m2)	I
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (3%)	E
Gastrointestinal	Abdominal pain (6%)	E
	Anorexia, weight loss (13%)	E
	Constipation (18%)	E
	Diarrhea (31%) (1% severe)	E

	GI hemorrhage (rare)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Mucositis (5%)	E
	Nausea, vomiting (25%)	I
General	Edema (7%)	E
	Fatigue (25%)	E
Hematological	Myelosuppression ± infection, bleeding (42%) (severe) (including anemia)	E
Hepatobiliary	↑ LFTs (< 1% severe)	E
Hypersensitivity	Hypersensitivity (rare)	I E
Musculoskeletal	Musculoskeletal pain (11%)	E
Nervous System	Dizziness (4%)	E
	Dysgeusia (7%)	E
	Headache (5%)	E
	Peripheral neuropathy (7%)	E
Renal	Renal failure (2%)	E
Respiratory	Cough, dyspnea (6%)	E
	Pneumonitis , ARDS (rare)	E D
Urinary	Cystitis (rare; with previous radiation and docetaxel)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for cabazitaxel include myelosuppression, diarrhea, fatigue, nausea, vomiting, constipation, hematuria, musculoskeletal pain, anorexia, peripheral neuropathy and dysgeusia.

The major dose-limiting adverse effect of cabazitaxel is **myelosuppression** which may be severe and is dose-related (21% vs 6% severe neutropenia /febrile infective events for 25 vs 20mg/m^2 respectively). In most patients, neutropenia first occurred within the first 2 cycles of treatment. Anemia has been observed as well and may be severe.

Severe **hypersensitivity** reactions characterized by hypotension, bronchospasm or generalized rash/erythema may occur within a few minutes of cabazitaxel infusions. Patients should be observed closely for these reactions, especially during the 1st and 2nd infusions. Because of the significant

risk of hypersensitivity reactions, pre-medications are recommended prior to each treatment; emergency medications and resuscitation equipment must be readily available. Patients who experience severe hypersensitivity reactions should not be re-challenged.

Common **gastrointestinal symptoms** associated with cabazitaxel include diarrhea, nausea and/or vomiting. These symptoms may be treated with commonly used anti-diarrheal or anti-emetic medications and hydration as needed. If left untreated, renal failure may ensue.

Patients should be monitored closely for **cardiovascular effects**. Preclinical studies suggest a QTc effect; although no formal QT prolongation study has been conducted, cardiac arrhythmias have been reported in patients treated with cabazitaxel.

Interstitial pneumonitis/lung disease (ILD) and acute respiratory distress syndrome (ARDS) have been observed and may be fatal.

Cystitis due to radiation recall reaction has been observed in patients who previously received pelvic radiation and docetaxel-containing chemotherapy.

Renal disorders reported were associated with sepsis, severe dehydration due to diarrhea, vomiting and obstructive uropathy, and may be fatal.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients on LHRH agonists should continue on the agents.

Use with caution in patents with hemoglobin < 10 g/dL. Hemoglobin and hematocrit should be checked prior to treatment.

Pre-medications (prophylaxis for infusion reaction):

At least 30 minutes prior to each administration of cabazitaxel:

- A corticosteroid IV/PO (e.g. Dexamethasone 8 mg)
- An H1-receptor antagonist IV/PO (e.g. Diphenhydramine 25 mg)
- An H2-receptor antagonist IV/PO (e.g. Ranitidine 50 mg)

Other Supportive Care:

- The product monograph recommends that primary G-CSF prophylaxis be considered in patients at higher risk of complications from prolonged neutropenia (e.g. age > 65 years, poor performance or nutritional status, previous occurrence of febrile neutropenia, extensive prior radiation ports, or other serious comorbidities).
- Also refer to CCO GCSF recommendations.

Adults:

Q3weeks: cabazitaxel 20 mg/m^2 on day 1, as 1 hour IV infusion, with prednisone 10 mg po daily on days 1-21

(Cabazitaxel 25 mg/m^2 may be used in select patients at the physician's discretion)

Dosage with Toxicity:

Do not treat until ANC > 1.5 x 10^9/L and platelets are ≥ 100 x 10^9/L.

	Dose (mg/m^2)	Dose (mg/m^2)
Starting dose	25	20
First reduction	20	15
Second reduction	15	Discontinue

Adverse reactions / Counts (x 10^9/L)	Action	Dose for Next Cycle*
Neutropenia grade ≥3 for ≥ 7 days (despite supportive care)	Hold until ANC >1.5 and platelets ≥ 100, then	↓ 1 dose level
Febrile neutropenia or thrombocytopenic bleeding	Hold until ANC >1.5 and platelets ≥ 100, then	↓ 1 dose level
Diarrhea grade 2 persisting despite adequate supportive care	Hold until recovery to grade ≤1	↓ 1 dose level
Diarrhea or other organ/ non-hematologic toxicity grade 3	Hold until recovery to ≤ grade 2	↓ 1 dose level
Grade 3 peripheral neuropathy	Hold until recovery to ≤ grade 2	↓ 1 dose level

Grade 3 GI perforation/hemorrhage	Hold or Discontinue	↓ 1 dose level or Not applicable
Grade 4 organ, other non-hematologic toxicity	Discontinue	Not applicable
≥ grade 3 renal failure	Discontinue	Not applicable
New or worsening respiratory symptoms	Hold and investigate	Discontinue if confirmed pneumonitis/ILD or ARDS
Signs & symptoms suggesting cystitis	Hold and investigate	Consider discontinuing if confirmed cystitis
*Do not retreat until neutrophils > 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and other toxicity ≤ grade 2 (grade 1 for persistent diarrhea) **Discontinue if toxicity continues at reduced dose		

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, replace with a different taxane. Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital symptoms have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

Dosage with Hepatic Impairment:

Total Bilirubin		AST/ALT	Dose (mg/m^2)
< ULN	and	<1.5 x ULN	No change
>1 to ≤ 1.5 x ULN	or	>1.5 x ULN	20 (monitor carefully)
>1.5 to ≤ 3 x ULN	and	any	Maximum 15 (unknown efficacy; monitor carefully)
>3 x ULN	and	any	Contraindicated

Dosage with Renal Impairment:

No dosage adjustment is needed in patients with renal impairment not requiring hemodialysis.

Creatinine Clearance (ml/min)	Dosage modification
50 - 80	No adjustment.
15 - 50	No adjustment.
<15; end stage renal disease	Limited clinical data. Treat with caution and monitor patient carefully.

Dosage in the elderly:

No specific dose adjustment recommended in elderly patients, but they are more at risk for severe toxicity, including myelosuppression, infection and cardiac effects.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- Use non-PVC equipment for preparation and administration, as cabazitaxel contains polysorbate 80 that increases the rate of di-(2-ethylhexyl) phtalate extraction (DEHP) from polyvinyl chloride (PVC). Also do not use polyurethane equipment.
- Use a 0.22 micron in-line filter.
- Cabazitaxel products have different dilution instructions; refer to the respective product monograph to ensure that the appropriate instructions are followed.
- The concentrate-diluent solution should be further diluted immediately with either 5% dextrose or 0.9% sodium chloride solution.
- The final concentration of the infusion solution should be 0.1mg/mL-0.26mg/mL. Infuse IV over 1 hour at room temperature.
- Gently rotate the IV bag prior to administering to ensure proper mixing.
- Do not mix with other drugs. Crystallized infusion solutions should not be used.
- Store the unopened vials at room temperature (15°C- 30°C). Do not refrigerate.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who have hypersensitivities to this drug or any of its components, including other drugs formulated with polysorbate 80
- Patients with neutrophil counts of ≤1.5 x 10^9/L
- Patients with severe hepatic impairment (total bilirubin > 3 x ULN)
- Concomitant use of yellow fever vaccines

Other Warnings/Precautions:

- Avoid use of live vaccines in patients receiving cabazitaxel. Inactivated vaccines may be administered; however, response may be diminished.
- Exercise caution in patients with anemia and those most at risk of developing gastrointestinal complications: patients with neutropenia, with a prior history of pelvic radiotherapy, GI disease (e.g. ulceration, bleeding), the elderly, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants.
- Patients should exercise caution when driving or operating a vehicle or potentially dangerous machinery as fatigue and dizziness have been reported.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Genotoxicity: Probable
  (observed in drugs with same pharmacological activity)
- Crosses placental barrier: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Unknown
- Abortifacient effects: Yes
  Cabazitaxel may cause harm to a developing fetus or lead to loss of pregnancy. Adequate contraception should be used by both sexes during treatment and for **6 months** after the last dose.
- Excretion into breast milk: Yes
  Cabazitaxel and its metabolites were excreted in milk in animal studies.
- Fertility effects: Probable
  Effects on male fertility documented in animals. Men are advised to seek advice on conservation of sperm prior to treatment.

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H - Interactions

Drug interactions with therapeutic doses of cabazitaxel and co-administration of CYP3A4 substrates are not expected. There is no potential risk of inhibitory effects on substrates of other CYP enzymes (1A2, 2B6, 2C9, 2C8, 2C19, 2E1, and 2D6) and no potential risk of induction on substrates of CYP1A, CYP2C9, and CYP3A.

Cabazitaxel does not inhibit MRP, OCT1, P-gp, OATP1B3 and BCRP at clinically relevant doses. Interactions with food and herbals have not been established. Prednisone/prednisolone 10mg daily dosing did not affect cabazitaxel pharmacokinetics.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ cabazitaxel concentration and/or efficacy (up to 17% ↓ AUC)	↑ metabolism of cabazitaxel	Caution; co-administration with strong inducers should be avoided.

CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ cabazitaxel concentration and/or toxicity (up to 25% ↑ AUC)	↓ metabolism of cabazitaxel	Caution; co-administration with strong inhibitors should be avoided. (Note: aprepitant had no effect on cabazitaxel AUC)
OATP1B1 substrates (e.g. atorvastatin, glyburide, SN-38, rifampin, valsartan)	↑ OATP1B1 substrates concentration and/or toxicity	Cabazitaxel may inhibit OATP1B1 at clinically relevant doses. Limited data suggest that interaction risk may be limited to during the infusion and for 20 minutes afterwards.	Avoid, or separate cabazitaxel infusion and OATP1B1 substrate administration

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, weekly during cycle 1, before each cycle, and as clinically indicated (also in patients with symptoms of anemia)
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Clinical toxicity assessment for infusion reactions, GI effects, infection, hypersensitivity, bleeding, anemia, respiratory effects, peripheral neuropathy and thromboembolism	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events)

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Cabazitaxel - Metastatic Castration Resistant Prostate Cancer

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K - References

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [Internet]. U.S Food and Drug Administration; [updated 2011 July 28].

Prescribing Information: Jevtana™ (Cabazitaxel). Sanofi-aventis Inc (US), June 2010.

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Villaneueva C, Bazan F, Kim S et al. Cabazitaxel: A novel microtubule inhibitor. Drugs. 2011; 71(10): 1251-8.

February 2023 Updated Adverse effects, Dosage with hepatic impairment, Dosage with renal impairment, and Special Precautions sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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