DRUG NAME: Cabazitaxel

SYNONYM(S): XRP6258[1,2]; 183133-96-2[3]; TXD258; RPR116258A[2]

COMMON TRADE NAME(S): JEVTANA®

CLASSIFICATION: mitotic inhibitor

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cabazitaxel is a taxane derivative similar to docetaxel and paclitaxel. It is equipotent to docetaxel against docetaxel-sensitive tumours but is also active against docetaxel-resistant tumours. Cabazitaxel binds to tubulin, the protein component of microtubules, and simultaneously promotes assembly and inhibits disassembly of microtubules.[4,5] This leads to stabilization of microtubules which inhibits cell division (mitosis) and tumour proliferation. Cabazitaxel is cell cycle phase-specific for the M phase.[5]

PHARMACOKINETICS:

Distribution	time to peak concentration 1 h	
	cross blood brain barrier?	CNS penetration greater than other taxanes[6]
	volume of distribution	2640 L/m²
	plasma protein binding	89-92%
Metabolism	extensively in the liver via CYP 3A4/5 (80-90%) and CYP 2C8 (minor)[5,7]	
	active metabolite(s)	3 (unnamed)
	inactive metabolite(s)	4 (unnamed)
Excretion	minimally by the kidneys; 80% of administered dose was eliminated within 2 weeks	
	urine	4% (2% as unchanged drug)
	feces	76% (as metabolites)
	terminal half life	95 h
	clearance	26 L/h/m²
Elderly	no pharmacokinetic differences observed	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***Severe hypersensitivity reactions*** can occur. No information on cross-sensitivity with other taxanes is available at the time of writing. All patients should be premedicated prior to the initiation of the infusion.[4]

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Special populations: Elderly patients (age ≥ 65) have a 5% greater risk of developing the following toxicities compared to younger patients: neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection, dehydration, cardiac disorders.[4]

Carcinogenicity: no information found

Mutagenicity: Cabazitaxel is not mutagenic in Ames test and bacterial *in vitro* mutation test. Cabazitaxel is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: Testicular degeneration (seminal vesicle and seminiferous tubule atrophy in the testis) were observed in animal studies. Men are advised to conserve sperm prior to treatment with cabazitaxel if planning to father children in the future.[4]

Pregnancy: FDA Pregnancy Category D.[7] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Animal studies have shown cabazitaxel crosses the placental barrier leading to reproductive toxicity. Fetal deaths and decreased fetal weight associated with a delay in skeletal ossification were observed in animal studies. Cabazitaxel may be present in semen. Male patients should use reliable contraception during treatment and for six months after the last dose to prevent pregnancy or cabazitaxel exposure in their partners.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Animal data has shown excretion of cabazitaxel and its metabolites in maternal milk.[4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[8]. When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (97%, severe 11%)
	febrile neutropenia (8%)
	leucopenia (96%, severe 68%)
	neutropenia (94%, severe 82%); see paragraph following **Side Effects** table
	thrombocytopenia (47%, severe 4%)
cardiac	arrhythmias (severe 2%)
	atrial fibrillation (1%)
	tachycardia (2%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (12%, severe 2%)
	constipation (21%, severe 1%)
	diarrhea (47%, severe 6%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspepsia (7%)
	gastroesophageal reflux disease (3%)
	hemorrhoids (4%)
	nausea (34%, severe 2%)
	vomiting (23%, severe 2%)
general disorders and administration site conditions	*extravasation hazard:* none[10]
	asthenia (21%, severe 5%)
	fatigue (37%, severe 5%)
	mucosal inflammation (6%, severe <1%)
	pyrexia (12%, severe 1%)
immune system	***hypersensitivity reactions***[11]; see paragraph following **Side Effects** table
infections and infestations	urinary tract infection (7%, severe 1%)
investigations	ALT, elevated (severe <1%)
	AST, elevated (severe <1%)
	bilirubin, elevated (severe <1%)
metabolism and nutrition	anorexia (16%, severe <1%)
	dehydration (5%, severe 2%)
musculoskeletal and connective tissue	arthralgia (11%, severe 1%)
	back pain (16%, severe 4%)
	muscle spasms (7%)
nervous system	dizziness (8%)
	dysgeusia (11%)
	headache (8%)
	peripheral neuropathy (8%, severe <1%)
renal and urinary	dysuria (7%)
	hematuria (17%, severe 2%)
	renal failure (2%, severe 2%)
	urinary incontinence (2%)
respiratory, thoracic and mediastinal	cough (11%)
	dyspnea (12%, severe 1%)
skin and subcutaneous tissue	alopecia (10%)
vascular	hypotension (5%, severe <1%)

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Hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Hypersensitivity reactions may occur within minutes of the initiation of a cabazitaxel infusion. Patients should be closely observed for reactions, especially during the first and second infusions. Premedication with antihistamine, corticosteroid and H2 antagonist is recommended prior to each treatment to reduce the incidence and severity of reactions. For severe hypersensitivity reactions, cabazitaxel treatment should be stopped immediately. Patients with a severe reaction should not be rechallenged with cabazitaxel.[4]

Neutropenia is the most common side effect leading to drug discontinuation in clinical trials. Fatalities have been reported from neutropenic complications. Patients at greatest risk are those of age greater than 65, poor performance status, previous episodes of febrile neutropenia, poor nutritional status or other serious comorbidities.[4,7] Dose modifications may be required. Prophylaxis with G-CSF may limit the incidence and severity of neutropenia.[4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
disulfiram[12]	development of acute and severe alcohol intolerance reactions	inhibition of aldehyde dehydrogenase by disulfiram, leading to development of toxic metabolites of ethanol (found in the supplied diluent)	avoid disulfiram concurrently with cabazitaxel administration
metronidazole and derivatives[12]	possible development of acute alcohol intolerance reactions; the risk for most patients appears slight	inhibition of aldehyde dehydrogenase by metronidazole, leading to development of toxic metabolites of ethanol (found in the supplied diluent)	avoid metronidazole or its derivatives concurrently with cabazitaxel administration
vaccines, live[4,12]	increased risk of serious infection and diminished therapeutic effect of vaccine	decreased immune response allows live vaccine to produce infection	avoid vaccination with live vaccines during treatment

Cabazitaxel is a **substrate** of CYP 3A. Inhibitors of CYP 3A may increase cabazitaxel plasma concentrations.[4,7] Co-administration with strong CYP 3A inhibitors should be avoided. Use caution with concomitant use of moderate CYP 3A inhibitors.[7,12] Inducers of CYP 3A may decrease cabazitaxel plasma concentrations.[4,7] Co-administration with strong CYP 3A inducers should be avoided.[7,12]

Cabazitaxel is an **inhibitor** of P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP). Plasma concentrations of the substrates of P-gp and BCRP may increase when given with cabazitaxel; however, this is unlikely to occur at a dose of 25 mg/m² *in vivo*.[4]

SUPPLY AND STORAGE:

***Injection*:**
Sandoz Canada Inc. supplies cabazitaxel as a ready-to-use solution in 45 mg and 60 mg multi-dose vials in a concentration of 10 mg/mL. Vials contain ethanol absolute (in a concentration of 198 mg/mL). Store at room temperature.[13]

sanofi-aventis Canada Inc. supplies cabazitaxel as a 60 mg/1.5 mL vial of concentrated solution that requires further dilution with a supplied diluent to achieve a reconstituted concentration of 10 mg/mL. The supplied diluent contains 13% (w/w) of 95% ethanol[14] (approximately 0.56 g ethanol in 4.5 mL).[15] Store at room temperature.[14]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

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SOLUTION PREPARATION AND COMPATIBILITY:

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Additional information:
- Use 0.22 micron in-line filter.[4]
- Prepare solutions in non-DEHP containers and administer using non-DEHP administration sets.[4]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion[13,14,16]	***over 1 hour*** (use non-DEHP administration sets)
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: 3 weeks[13,14,16]:	***25 mg/m^2 IV for one dose on day 1*** (total dose per cycle 25 mg/m^2)
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required[4]	
Dosage in hepatic failure:	no information found	
Dosage in dialysis:	no information found	
Children:	no information found	

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