DRUG NAME: Polatuzumab vedotin

SYNONYM(S):

COMMON TRADE NAME(S): POLIVY®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Polatuzumab vedotin is an antibody-drug conjugate. It is composed of a humanized immunoglobulin G1 monoclonal antibody specific for human CD79b and the anti-mitotic agent monomethyl auristatin E (MMAE) covalently attached by a cleavable linker. Upon binding to CD79b on the B-cell surface, polatuzumab vedotin is internalized and the linker is cleaved by lysosomal proteases, thus enabling intracellular delivery of MMAE. The released MMAE inhibits cell division and induces apoptosis.[1,2] Polatuzumab vedotin is cell cycle phase-specific, inducing cell cycle arrest in the G2/M phase.[3]

PHARMACOKINETICS:

Distribution	blood to plasma ratio is 0.79 to 0.98; small volume of distribution	
	cross blood brain barrier?	no information found
	volume of distribution	3.15 L (antibody-conjugated MMAE)
	plasma protein binding	71-77% (MMAE)
Metabolism	expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily eliminated by non-specific linear clearance pathway	
	urine	minor
	feces	major
	terminal half life	unconjugated MMAE: ~4 days (after first dose)
	clearance	0.9 L/day (antibody-conjugated MMAE)
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1-3] unless specified otherwise.

USES:

Primary uses:

*Lymphoma, non-Hodgkin's[1]

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***infusion-related reactions*** have been reported; premedication with antihistamine and antipyretic is recommended for all patients prior to each dose of polatuzumab vedotin[1,2]
- ***opportunistic infections*** have been reported; consider appropriate prophylaxis for *Pneumocystis jirovecii* pneumonia and herpesvirus throughout treatment[2]
- risk of ***hepatotoxicity*** may be increased in patients with preexisting liver disease, elevated baseline liver enzymes, and/or concomitant hepatotoxic medication[1,2]
- patients with high tumour burden and rapidly proliferative tumours may be at increased risk for ***tumour lysis syndrome***[1,2]
- ***myelosuppression*** can be severe; consider prophylactic granulocyte colony stimulating factor (GCSF) administration as needed[1,2]
- patients with pre-existing ***peripheral neuropathy*** may experience worsening of this condition[1]

Special populations:
- ***patients aged 65 years or older*** may experience more grade 3 or 4 adverse events and/or discontinue treatment more frequently compared to younger patients[1,2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Polatuzumab vedotin is aneugenic in mammalian *in vivo* chromosome test. [1,2]

Fertility: In animal studies, dose-dependent degeneration of the testicular seminiferous tubule with abnormal epididymal lumen contents were observed in male subjects. These findings were non-reversible and correlated with decreased testes weight and gross findings of small and/or soft testes at exposures lower than those seen following human clinical exposure.[1,2]

Pregnancy: In animal studies using MMAE, external fetal malformations (e.g., protruding tongue, malrotated limbs, gastroschisis, and agnathia) were observed at exposures lower than those seen following human clinical exposure.[1,2] Female patients of reproductive potential should use effective contraception during treatment and for at least nine months after the last dose. Male patients with female partners of reproductive potential should use effective contraception during treatment and for at least six months after the last dose.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least three months after the last dose.[1]

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.[4,5] **Incidence data in the Side Effect table is based solely on combination therapy with bendamustine and rituximab/obinutuzumab unless otherwise indicated.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (28-47%, severe 14-24%)
	febrile neutropenia (severe 11-13%)
	leukopenia (11-12%, severe 7-8%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
(see paragraph following **Side Effects** table)	lymphopenia (11-13%, severe 11-13%)
	neutropenia (44-49%, severe 39-42%)
	pancytopenia (7%, severe 4%)
	thrombocytopenia (31-49%, severe 23-40%)
cardiac	tachycardia (9%, severe 2%)
eye	blurred vision (1%)
gastrointestinal	*emetogenic potential:* low[6]
	abdominal pain (11%, severe 2-4%)
	constipation (18%)
	diarrhea (38-45%, severe 4-8%)
	dyspepsia (7%)
	gastrointestinal reflux disease (7%)
	nausea (33%)
	stomatitis (7%)
	vomiting (18-27%, severe 2-3%)
general disorders and administration site conditions	*extravasation hazard:* none[7]
	asthenia (11%)
	chills (11%)
	fatigue (40%, severe 4-5%)
	pyrexia (30-33%, severe 2-3%)
hepatobiliary	***hepatic toxicity*** (20%, severe 4%)
infections and infestations (see paragraph following **Side Effects** table)	***cytomegalovirus infection*** (1-2%)
	herpesvirus infection (7-12%, severe 2%)
	infection (53%, severe 29%); fatal events reported
	lower respiratory tract infection (10%)
	opportunistic infection (9%)
	pneumonia (13-22%, severe 7-16%); fatal events reported
	sepsis (4-7%, severe 4-6%)
	upper respiratory tract infection (9-16%)
injury, poisoning, and procedural complications	***infusion-related reaction*** (7-33%, severe 2-7%); see paragraph following **Side Effects** table
investigations	ALT increase (7-38%)
	amylase increase (24%)
	AST increase (7-36%)
	creatinine increase (9-87%, severe 4%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	lipase increase (4-36%, severe 2-9%)
	weight loss (10-16%, severe 2%)
metabolism and nutrition	appetite decrease (27-29%, severe 2%)
	dehydration (9%)
	hypoalbuminemia (13%, severe 2%)
	hypocalcemia (11-44%, severe 2-9%)
	hypokalemia (16-24%, severe 6-11%)
	hypophosphatemia (9-33%, severe 4-7%)
	tumour lysis syndrome (severe 4-8%)[8]
musculoskeletal and connective tissue	arthralgia (7%)
nervous system	dizziness (10-13%)
	dysgeusia (7%)
	headache (9%, severe 2%)
	hypoesthesia (7%)
	neuropathy, peripheral (20-40%, severe 2%); see paragraph following **Side Effects** table
	progressive multifocal leukoencephalopathy (<1%); see paragraph following **Side Effects** table
psychiatric	anxiety (7%)
	insomnia (9%)
respiratory, thoracic and mediastinal	cough (16%)
	dyspnea (7-19%)
	pneumonitis (2-4%)
	productive cough (9%)
skin and subcutaneous tissue	pruritus (13%)
	rash (7%)
vascular	hypotension (9%, severe 4%)

Adapted from standard reference[1-3] unless specified otherwise.

Serious, life-threatening, or fatal ***infections***, including opportunistic infections such as pneumonia (including *Pneumocystis jirovecii* and other fungal pneumonia), bacteremia, sepsis, herpes zoster infection, and cytomegalovirus infection have been reported. One-third of patients experience grade 3 or higher infections. Consider antibiotic prophylaxis throughout treatment for vulnerable patient groups. Discontinue polatuzumab vedotin in patients who develop serious infections.[1,2]

Infusion-related reactions, including fever, chills, flushing, dyspnea, hypotension, and urticaria occur in one-third of patients. Most reactions are grade 1 and 2, but severe reactions have been reported. Reactions may also be delayed, occurring as late as 24 hours after administration. Premedication with antihistamine and antipyretic is

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recommended prior to each infusion. If a reaction occurs during the infusion, interrupt the infusion and administer supportive care as needed. Upon resolution of symptoms, the infusion may be resumed at 50% of the prior rate and, if tolerated at the reduced rate, the rate can be incrementally increased by 50 mg/h every 30 minutes. For the next cycle following a reaction, polatuzumab vedotin should be administered over 90 minutes. If tolerated, subsequent infusions may then be administered over 30 minutes. Permanently discontinue polatuzumab vedotin for:

- first instance of grade 3 wheezing, bronchospasm, or generalized urticaria,
- recurrent grade 2 wheezing or urticaria,
- recurrent grade 3 symptoms, OR
- any grade 4 reactions.[1,2]

For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Severe ***myelosuppression***, including neutropenia, febrile neutropenia, thrombocytopenia, and anemia may occur as early as the first cycle of treatment. Consider prophylactic administration of granulocyte colony stimulating factor (GCSF) as needed. Grade 3 or 4 neutropenia and thrombocytopenia may require more frequent lab monitoring, dose delays, and/or treatment discontinuation.[1,2]

Peripheral neuropathy is reported in up to 40% of patients and can occur as early as the first cycle of treatment. Patients with pre-existing peripheral neuropathy may experience worsening of their condition. Risk of developing peripheral neuropathy increases with sequential doses. Peripheral neuropathy associated with polatuzumab vedotin is primarily sensory; however, motor and sensorimotor peripheral neuropathy may also occur. Monitor for symptoms such as hypoesthesia, hyperesthesia, dysesthesia, neuropathic pain, burning sensation, weakness, or gait disturbance. Dose delay, dose reduction, or treatment discontinuation may be required.[1,2]

Progressive multifocal leukoencephalopathy (PML) has been reported. Monitor for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Interrupt treatment if PML is suspected and permanently discontinue polatuzumab vedotin if diagnosis is confirmed.[1,2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[1]	may increase plasma level of monomethyl auristatin E (MMAE)	may inhibit CYP 3A4 metabolism of MMAE in the intestinal wall	monitor for polatuzumab vedotin toxicity

MMAE is a ***substrate of CYP 3A***. Concomitant use with a strong CYP 3A inhibitor may increase the AUC of unconjugated MMAE; monitor for increased toxicity from polatuzumab vedotin. Concomitant use with a strong CYP 3A inducer may decrease the AUC of unconjugated MMAE; clinical significance is unknown.[1,2]

SUPPLY AND STORAGE:

***Injection*:** Hoffman-La Roche Limited supplies polatuzumab vedotin as 30 mg and 140 mg (preservative free) vials of lyophilized powder. Keep in outer carton to protect from light. Refrigerate. Do not shake.[1]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Compatibility: consult detailed reference

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PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[1]
Intermittent infusion	• administer initial dose ***over 90 minutes***; if well tolerated, subsequent infusions may be administered ***over 30 minutes***[1,9] • administer with 0.2-0.22 micron in-line filter [1,9]
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***[1,2,9]:	***1.8 mg/kg*** (range 1.4-1.8 mg/kg) ***IV for one dose on day 1*** (total dose per cycle 1.4-1.8 mg/kg)
Concurrent radiation:	no information found	
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:	CrCl ≥ 30 mL/min: no adjustment required[1] CrCl < 30 mL/min: no information found	
	calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	mild hepatic impairment (bilirubin ≤ 1.5 x ULN and AST > ULN): no adjustment required[1,2] moderate/severe hepatic impairment (bilirubin > 1.5 x ULN): no information found, but increased exposure to MMAE is possible; monitor for toxicity[1,2]	
Dosage in dialysis:	no information found	

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Children: safety and efficacy has not been established[1]

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