DRUG NAME: Brentuximab vedotin

SYNONYM(S): SGN-35[1]

COMMON TRADE NAME(S): ADCETRIS®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a chimeric monoclonal antibody (cAC10) linked to an anti-tubulin agent, monomethylauristatin E (MMAE). The monoclonal antibody targets CD-30 expressing cells and MMAE is released intracellularly to bind to tubulin. The binding of MMAE to tubulin disrupts the microtubule network, causing cell cycle arrest and apoptosis.[2] Brentuximab vedotin is cell cycle phase-specific (G2/M phase).[3]

PHARMACOKINETICS:

Absorption	monomethylauristatin E (MMAE): time to peak 1-3 days	
Distribution	antibody-drug conjugate (ADC) is primarily limited to vascular space; organ distribution of MMAE in humans is unknown	
	cross blood brain barrier?	no information found
	volume of distribution	6-10 L (ADC); 44 L (MMAE)
	plasma protein binding	68-82% (MMAE)
Metabolism	MMAE: minimal; primarily via oxidation by CYP 3A4/5	
	active metabolite(s)	yes; at concentrations less than 10% of MMAE
	inactive metabolite(s)	no information found
Excretion	primarily as unchanged MMAE; limited by the rate of release from ADC	
	urine	MMAE: 72%
	feces	MMAE: 28%
	terminal half life	4-6 days
	clearance	no information found
Sex	ADC volume of distribution is 14% lower in females	

Adapted from standard reference[3,4] unless specified otherwise.

USES:

Primary uses:
*Lymphoma, Hodgkin's
*Lymphoma, non-Hodgkin's
*Lymphoma, cutaneous T-cell

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

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- history of hypersensitivity reaction to brentuximab vedotin or Chinese hamster ovary cell proteins[3]
- concurrent therapy with bleomycin; due to increased risk of pulmonary toxicity, bleomycin must be discontinued prior to starting brentuximab vedotin treatment[2]
- patients with a diagnosis of progressive multifocal leukoencephalopathy (PML) or a history of PML[3]

Caution:
- patients with rapidly proliferating tumour and high tumour burden are at risk of ***tumour lysis syndrome***[2]
- concurrent medications should be carefully reviewed for potential ***drug interactions***, particularly in regard to CYP 3A4 and CYP 3A5[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test or mammalian *in vitro* mutation test. Brentuximab vedotin is clastogenic in mammalian *in vivo* chromosome tests.[3]

Fertility: In rats, brentuximab vedotin causes partially reversible, dose-dependent testicular toxicity (e.g., seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia).[3]

Pregnancy: FDA Pregnancy Category D.[2] 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).
In rats, brentuximab vedotin has been shown to cross the placenta, causing embryo-fetal toxicities, including early resorption, post-implantation loss, decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). For women of childbearing potential, two contraceptive methods are recommended during treatment.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk.

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.[5] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***infusion-related reactions*** (12%); see paragraph following **Side Effects** table
blood and lymphatic system/ febrile neutropenia	***anemia*** (33-52%, severe 2-10%)
	lymphadenopathy (10-11%)
	neutropenia (54-55%, severe 21%); can be prolonged (≥ 1 week), may require dose modification, delays, or growth factor support[3]
	thrombocytopenia (16-28%, severe 10%); can be prolonged (≥ 1 week), may require dose delays or platelet transfusions[3]
cardiac	myocardial infarction (<1%)[3]
	QT shortening[3]; clinical significance is unknown
	supraventricular arrhythmia (3%)
gastrointestinal	*emetogenic potential: low*[6]

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Revised: 1 August 2022

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (9-25%, severe 1-2%)
	constipation (16-19%, severe 2%)
	diarrhea (29-36%, severe 1-3%)
	nausea (38-42%, severe 2%)
	pancreatitis[7]; sometimes fatal
	vomiting (17-22%, severe 3%)
general disorders and administration site conditions	*extravasation hazard:* irritant[8,9]; see paragraph following **Side Effects** table
	chills (12-13%)
	fatigue (41-49%, severe 2-3%)
	fever (29-38%, severe 2%)
	infusion site extravasation, erythema and blisters[9] (<1%); see paragraph following **Side Effects** table
	night sweats (9-12%)
	peripheral edema (4-16%)
infections and infestations	septic shock (3%)
	upper respiratory tract infection (12-47%)
	urinary tract infection (3%)
metabolism and nutrition	anorexia (11-16%, severe 2%)
	tumour lysis syndrome[3] (<1%); see paragraph following **Side Effects** table
	weight loss (1-12%, severe 3%)
musculoskeletal and connective tissue	arthralgia (9-19%)
	back pain (10-14%, severe 2%)
	muscle spasms (9-10%, severe 2%)
	myalgia (16-17%, severe 2%)
	pain (7-28%, severe 5%)
	pain in extremity (10%, severe 4%)
nervous system	anxiety (7-11%, severe 2%)
	dizziness (11-16%)
	headache (16-19%, severe 2%)
	insomnia (14-16%)
	peripheral motor neuropathy (7-16%, severe 3-4%); see paragraph following **Side Effects** table
	peripheral sensory neuropathy (52-53%, severe 8-10%); see paragraph following **Side Effects** table
	progressive multifocal leukoencephalopathy (< 1%); see paragraph following **Side Effects** table
renal and urinary	pyelonephritis (2%)
respiratory, thoracic and mediastinal	cough (17-25%)
	dyspnea (13-19%, severe 1-2%)
	oropharyngeal pain (9-11%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pneumonitis (2%)
	pneumothorax (2%)
	pulmonary embolism (2%)
skin and subcutaneous tissue	alopecia (13-14%)
	dry skin (4-10%)
	pruritus (17-19%)
	rash (27-31%)
	Stevens-Johnson syndrome

Adapted from standard reference[2] unless specified otherwise.

Extravasation of brentuximab vedotin has been reported to cause erythema and blisters in one patient which progressed to demyelinating neuropathy over the week following the extravasation and then fully resolved by 8 weeks. No tissue necrosis or ulceration were observed. The mechanism for this reaction is unknown; however, it was hypothesized that it could be caused by MMAE released from the antibody-drug conjugate (ADC) by enzymes in the normal tissue cells surrounding the extravsation area.Therefore, brentuximab vedotin can be considered an ***irritant*** with potential for vesicant-like properties.[9] For more information on the management of extravasation reactions, see BC Cancer Systemic Therapy Policy III-20 ***Prevention and Management of Extravasation of Chemotherapy***.

Infusion-related reactions, including anaphylaxis, have been reported. Reactions may be immediate or delayed, with symptoms occurring within 2 days after administration.[3] Symptoms include chills, nausea, dyspnea, pruritus, pyrexia and cough.[2] Severe reactions present as wheezing, difficulty breathing, hives, itching, and swelling.[3] If a reaction occurs, interrupt the infusion and institute appropriate medical management. Patients with a prior reaction should be premedicated with acetaminophen, antihistamine, and corticosteroid for subsequent infusions. If anaphylaxis occurs, the infusion should be immediately and permanently discontinued, and appropriate medical management instituted.[2,3] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Peripheral neuropathy is usually sensory in nature, but motor neuropathy has also been reported. Peripheral neuropathy is dose-cumulative[2] and usually occurs several months into therapy.[10] Improvement or resolution of symptoms usually takes an average of seven weeks.[10] About half of patients who experience neuropathy may have residual symptoms of neuropathy. Symptoms include hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Dose modifications or discontinuation may be needed.[2]

Progressive multifocal leukoencephalopathy (PML) and death have been reported following active John Cunningham (JC) virus infection in patients treated with brentuximab vedotin. Other risk factors include prior immunosuppressive therapies or underlying immunosuppressive disease. PML should be considered in any patient treated with brentuximab vedotin who presents with new onset of signs and symptoms of central nervous system abnormalities. Symptoms include changes in mood or usual behaviour, confusion, thinking problems, loss of memory, changes in vision, speech or walking, and decreased strength or weakness on one side of the body. Brentuximab vedotin should be held if PML is suspected, and discontinued permanently if diagnosis is confirmed.[2]

Tumour lysis syndrome has been reported; patients with rapidly proliferating tumour or high tumour burden may be at increased risk. Monitor patient closely; symptoms include nausea, vomiting, edema, shortness of breath, heart rhythm disturbances, and acute renal failure.[3]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[3]	may increase plasma level of monomethylauristatin E (MMAE)	may inhibit CYP 3A4 metabolism of MMAE in the intestinal wall	monitor for brentuximab vedotin toxicity
ketoconazole[3]	increased AUC of MMAE by 34%	potent inhibition of CYP 3A4 and P-gp by ketoconazole	monitor for brentuximab vedotin toxicity
rifampin[3]	decreased AUC of MMAE by 46%	potent induction of CYP 3A4 by rifampin	avoid concurrent therapy if possible

Monomethylauristatin E (MMAE) is a substrate of CYP 3A4/5. Co-administration with potent inhibitors or inducers of CYP enzymes may affect plasma levels of MMAE. Monitor for brentuximab vedotin toxicity in patients receiving strong CYP 3A4/5 inhibitors.[3]

MMAE inhibited CYP 3A4/5 in certain *in vitro* studies, however it is not expected to alter the exposure of other drugs metabolized by CYP 3A4 enzymes.[3]

Brentuximab vedotin is a substrate of p-glycoprotein. Monitor for brentuximab vedotin toxicity in patients receiving strong inhibitors of p-glycoprotein.[3]

SUPPLY AND STORAGE:

***Injection*:** GMD Distribution Inc. (for Seattle Genetics Inc.) supplies brentuximab vedotin as a lyophilized cake or powder in 50 mg single-use (preservative-free) vials. Refrigerate. Do NOT freeze. Protect from light.[2]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[2,3]
Intermittent infusion	***over 30 minutes***[1-3,11]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found

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Revised: 1 August 2022

BCCA administration guideline noted in ***bold***, ***italics***

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:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks***[2,3,10-12]:	***1.8 mg/kg IV for one dose on day 1*** (total dose per cycle 1.8 mg/kg) (for weight > 100 kg: calculate dose based on a weight of 100 kg)
	4 weeks[13-15]:	***1.2 mg/kg IV for one dose on days 1 and 15*** (total dose per cycle 2.4 mg/kg) (for weight > 100 kg: calculate dose based on a weight of 100 kg)
Dosage in myelosuppression	modify according to protocol by which patient is being treated[11]; if no guidelines are available, the following have been suggested[2,3]: • for grade 3 or 4 neutropenia: hold dose until resolution to baseline or grade 2 or lower; consider filgrastim support for subsequent cycles • for recurrent grade 4 neutropenia despite filgrastim support: discontinue or reduce dose to 1.2 mg/kg • for grade 3 or 4 thrombocytopenia: consider platelet transfusion or dose delay	
Dosage in severe peripheral neuropathy[2,3]:	• for new or worsening grade 2 or 3 neuropathy: hold dose until neuropathy improves to grade 1 or baseline; then restart at 1.2 mg/kg • for grade 4 neuropathy: discontinue treatment	
Dosage in renal failure:	no information found	
Dosage in hepatic failure:	no information found	

Children: no information found

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