DRUG NAME: Enfortumab vedotin

SYNONYM(S):

COMMON TRADE NAME(S): PADCEV®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Enfortumab vedotin is a fully human IgG1 kappa antibody-drug conjugate directed against Nectin-4, an adhesion protein located on the surface of cells. The monoclonal antibody component (AGS-22C3) is conjugated to the small molecule microtubule-disrupting agent (monomethyl auristatin E or MMAE) via a protease-cleavable linker. Internalization of the antibody-drug conjugate leads to cleavage of the linker and the release of MMAE within the cell. In the cell, MMAE disrupts the microtubule network, which subsequently induces cell cycle arrest and apoptotic cell death.[1] MMAE is cell cycle phase-specific and stalls cell cycle progression at G_2/M phase.[2]

PHARMACOKINETICS:

Absorption	monomethyl auristatin E (MMAE) time to peak ~2 d after dose[3]	
Distribution	in animal studies, MMAE was well distributed into tissues[4]	
	cross blood brain barrier?	no information found
	volume of distribution	enfortumab vedotin: 12.8 L
	plasma protein binding	MMAE: 68-82%
Metabolism	expected to undergo catabolism to small peptides, amino acids, and unconjugated MMAE and MMAE-related catabolites[3]; metabolism occurs primarily via oxidation by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	elimination of MMAE appears to be limited by rate of release from the antibody-drug conjugate; ~24% of total MMAE administered is recovered unchanged in feces and urine over 1 week	
	urine	MMAE[3]: 6%
	feces	MMAE[3]: 17%
	terminal half life	enfortumab vedotin: 3.6 d; MMAE: 2.6 d
	clearance	enfortumab vedotin: 0.114 L/h; unconjugated MMAE: 2.11 L/h
Sex	no clinically meaningful difference	
Elderly	no clinically meaningful difference	
Ethnicity/race	no clinically meaningful difference	

Adapted from standard reference[5] unless specified otherwise.

Developed: 22 June 2021
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USES:

Primary uses:

*Urothelial cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***hyperglycemia*** and ***diabetic ketoacidosis***, including fatal events, have been reported in patients with and without pre-existing diabetes mellitus[1]
- incidence of ***grade 3-4 hyperglycemia*** is higher in patients with higher body mass index or baseline A1C[1]

Carcinogenicity: No information found; carcinogenicity studies for enfortumab vedotin or MMAE were not conducted.[5]

Mutagenicity: Monomethyl auristatin E (MMAE) was not mutagenic in Ames test or mammalian *in vitro* mutation test. MMAE is genotoxic in a mammalian *in vivo* chromosome test through an aneugenic mechanism (which is consistent with its effect as a microtubule disrupting agent).[5]

Fertility: In animal studies, testicular toxicity was observed at systemic exposures approximately equal to the expected human systemic exposure with clinically recommended doses.[5]

Pregnancy: There is no available human data to inform a drug-associated risk. However, based on findings from animal studies, enfortumab vedotin is expected to cause fetal harm in humans. In embryo-fetal development studies in animals, embryo-fetal lethality, structural malformations, skeletal anomalies, reduced litter sizes and viable fetuses, and increased early resorptions were reported at maternal exposures similar to the expected human systemic exposure with clinically recommended doses. Female patients of reproductive potential should use contraception during treatment with enfortumab vedotin and for at least 6 months after treatment has ended. Male patients with female partners of reproductive potential should use contraception during treatment with enfortumab vedotin and for at least 4 months after treatment has ended.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Breastfeeding is not recommended during treatment with enfortumab vedotin and for at least 6 months after treatment has ended.[5]

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.[6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (20-41%, severe 2-6%)[5]
	febrile neutropenia (4%)
	leukopenia (14%, severe 4%)
	lymphopenia (46%, severe 9%)[5]
	neutropenia (11-24%, severe 4-7%)[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	cardiac disorder (1%); fatalities reported
	tachycardia[5] (<10%)
endocrine	***diabetic ketoacidosis***; fatalities reported, see paragraph following **Side Effects** table
eye (see paragraph following **Side Effects** table)	dry eye (24%, severe 1%)[5]
	blurred vision (14%)
	ocular disorders (40%)[5]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain[5] (20%, severe 1%)
	constipation[5] (28%, severe 1%)
	diarrhea (35%, severe 4%)
	nausea (30%, severe 1%)[5]
	vomiting (14%, severe 1%)[5]
general disorders and administration site conditions	*extravasation hazard:* irritant[9-11] ; see paragraph following **Side Effects** table
	fatigue (50%, severe 9%)[5]
	infusion site extravasation, skin and soft tissue reactions (1-2%, severe <1%); see paragraph following **Side Effects** table
	pyrexia[5] (22%, severe 2%)
infections and infestations	cellulitis (5%)
	sepsis (3%); fatalities reported
	urinary tract infection (17%, severe 6%)[5]
injury, poisoning, and procedural complications	infusion-related reaction[12,13] (9%, severe 1%)
investigations	ALT increase[5] (20%)
	AST increase[5] (12-47%, severe 1%)
	creatinine increase (50%, severe <1%)[5]
	glucose increase, nonfasting[5] (47%, severe 7%); see paragraph following **Side Effects** table
	lipase increase (17%, severe 6%)[5]
	phosphate decrease (26%, severe 5%)
	platelet decrease[5] (22%, severe 0%)
	potassium decrease (19%, severe 1%)
	potassium increase[5] (13%, severe 3%)
	sodium decrease (32%, severe 7%)[5]
	urate decrease (severe 7%)
	weight loss (16%, severe <1%)[5]
metabolism and nutrition	appetite decrease (41%, severe 5%)[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperglycemia (11-14%, severe 7%)[5]; see paragraph following **Side Effects** table
musculoskeletal and connective tissue	musculoskeletal pain[5] (25%, severe 2%)
nervous system disorders	dysgeusia (26%)[5]
	peripheral neuropathy, primarily sensory (50%, severe 5%)[5]; see paragraph following **Side Effects** table
psychiatric	insomnia[5] (11%)
renal and urinary	acute kidney injury (3%)
respiratory, thoracic and mediastinal	acute respiratory failure (1%); fatalities reported
	aspiration pneumonia (1%); fatalities reported
	dyspnea (3%)
	pneumonitis[5] (3%, severe 1%); fatalities reported
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	***alopecia*** (47%)[5]
	dry skin (17%)[5]
	epidermal necrosis[14]
	maculopapular rash (26%)
	pruritus (34%, severe 2%)[5]
	rash (54%, severe 14%)[5]
	skin reactions (55%, severe 13%); see paragraph following **Side Effects** table
	Stevens-Johnson syndrome[14]
	toxic epidermal necrolysis[14]
vascular	hemorrhage[5] (17%, severe 3%); includes also hematuria, epistaxis, hemoptysis

Adapted from standard reference[1] unless specified otherwise.

Extravasation may cause skin and soft tissue reactions such as erythema, swelling, pain, secondary cellulitis, bullae, and exfoliation.[1,5,14] A few patient cases have been reported where the initial presentation of erythema and blister developed into an erythematous plaque with a central area of erosion and desquamation. Because of these cases, enfortumab vedotin may be considered to be an irritant with the potential for vesicant-like properties.[11] Onset of symptoms may be delayed (e.g., 24 hours after the extravasation). Symptoms may initially worsen for 2-7 days after extravasation, but resolve within 1-4 weeks of symptom peak. If extravasation occurs, stop the infusion and monitor for reactions.[1,5,14] For more information on the management of extravasation reactions, see BC Cancer Systemic Therapy Policy III-20 ***Prevention and Management of Extravasation of Chemotherapy***.

Hyperglycemia is reported in 14% of patients treated with enfortumab vedotin. Median time to onset is about 0.6 months (range 0.1 to 20.3 months). Hyperglycemia occurs more frequently in patients with preexisting hyperglycemia or body mass index of 30 kg/m^2 or greater, but it has also been reported in patients without a prior history of diabetes mellitus. Grade 3 or 4 events are consistently reported with a higher incidence in patients with higher baseline A1C or body mass index. However, ***diabetic ketoacidosis***, a serious and life threatening complication of hyperglycemia, has been reported in patients with or without preexisting diabetes mellitus, and some cases were fatal. Educate patients about the importance of recognizing symptoms of hyperglycemia and the potential for serious complications. Because hyperglycemia can lead to ketoacidosis, monitor blood glucose in all

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patients at risk of hyperglycemia.[5,13] Insulin therapy may be required to manage elevated blood glucose. Withhold enfortumab vedotin if blood glucose exceeds 13.9 mmol/L (or 250 mg/dL).[5] Diabetic ketoacidosis, if it occurs, is a medical emergency and requires immediate care.[6]

Ocular disorders are frequently reported. The majority of events involve the cornea and include events associated with dry eye such as keratitis, keratopathy, blurred vision, limbal stem cell deficiency, conjunctivitis, and increased lacrimation. Median time to onset is 1.7 months (range 0 to 19.1 months).[5] Contact lens use may increase the risk of developing keratitis.[15] Consider artificial tears for prophylaxis of dry eyes. Ocular disorders may require treatment with topical ophthalmic steroids. Consider dose interruption or dose reduction for symptomatic disorders. Ophthalmologic consult may be required.[5]

Peripheral neuropathy is reported in approximately 50% of patients, although grade 3 reactions are uncommon. Peripheral neuropathy can occur in patients with or without preexisting neuropathy, and is predominantly sensory. Median time to onset of grade 2 (or higher) neuropathy is 4.6 months (range 0.1 to 15.8 months).[5] Early recognition of symptoms is important to limit the potential for severe or irreversible peripheral neuropathy.[15] Consider dose interruption or dose reduction if symptoms develop, and permanently discontinue enfortumab vedotin for grade 3 or 4 events. Some patients may not see improvement or complete resolution of their symptoms after enfortumab vedotin is stopped.[5]

Skin reactions are expected as on-target events with enfortumab vedotin because Nectin-4 is expressed in the skin.[5] Reactions are reported in approximately 50% of patients and are predominantly mild to moderate maculopapular rash. Grade 3 or 4 reactions are reported in about 10% of patients and have included symmetrical intertriginous and flexural exanthema, bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. Fatal cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred during treatment. Median time to onset of severe reactions is 0.6 months (range 0.1 to 6.4 months). Reported cases of SJS and TEN occurred predominantly during the first cycle, but can also occur later in treatment. Consider topical corticosteroids and antihistamines for mild to moderate skin reactions. Withhold enfortumab vedotin for a worsening skin reaction, any grade 3 reaction, and suspected SJS and TEN. Permanently discontinue enfortumab vedotin for grade 4 or recurrent grade 3 reactions and for confirmed SJS and TEN.[1,14]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[5]	*predicted* to increase unconjugated MMAE Cmax by 15% and AUC by 38% with no change in antibody-drug conjugate exposure	combined strong inhibition of CYP 3A4 and inhibition of P-glycoprotein by ketoconazole	no dose adjustment required; monitor for toxicity from enfortumab vedotin
rifampin[5]	*predicted* to decrease unconjugated MMAE Cmax by 28% and AUC by 53% with no change in antibody-drug conjugate exposure	combined strong induction of CYP 3A4 and induction of P-glycoprotein by rifampin	no action needed

MMAE is a substrate of CYP 3A4 and P-glycoprotein. Based on pharmacokinetic modelling predictions, strong CYP 3A4 inhibitors and inducers of CYP 3A4 are predicted to alter the Cmax and AUC of unconjugated MMAE but with no change in antibody-drug conjugate exposure.[5]

MMAE inhibits CYP 3A4/5 *in vitro*[5]; clinical significance is unknown.

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SUPPLY AND STORAGE:

Injection: Seagen Canada Inc. supplies enfortumab vedotin as 20 mg and 30 mg preservative free vials of lyophilized powder. Refrigerate. Store in original packaging. Do not shake.[5]

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.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[5,16]	do NOT use
Intermittent infusion[5,16]	***over 30 minutes***
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***

	Cycle Length:	
Intravenous:	***4 weeks***[5,16]:	***1.25 mg/kg*** (range 0.5-1.25 mg/kg) IV ***for one dose on days 1, 8, and 15*** (max dose = 125 mg) (total dose per cycle 3.75 mg/kg [range 1.5-3.75 mg/kg]) (for weight ≥100 kg: calculate dose based on a weight of 100 kg)

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

	Cycle Length:
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	no adjustment required[5]
Dosage in hepatic failure:	mild impairment (Child-Pugh A): no adjustment required[5] moderate to severe impairment (Child-Pugh B or C): no information found; however, patients with hepatic impairment are considered likely to have increased exposure to MMAE (monitor for toxicity)[5]
Dosage in dialysis:	no information found

Children: safety and efficacy not established[5]

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