DRUG NAME: Enfortumab vedotin

SYNONYM(S):

COMMON TRADE NAME(S): PADCEV® (USA)

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]

USES:

Primary uses:

Urothelial cancer[1]

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- greater incidence of ***grade 3-4 hyperglycemia*** in patients with higher body mass index or baseline A1C[1]
- ***diabetic ketoacidosis*** has been reported in patients with and without pre-existing diabetes mellitus[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, 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***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (34%, severe 10%)
	febrile neutropenia (4%)
	leukopenia (14%, severe 4%)
	lymphopenia (32%, severe 10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neutropenia (14%, severe 5%)
cardiac	cardiac disorder (1%); fatalities reported
endocrine	***diabetic ketoacidosis***
eye see paragraph following **Side Effects** table	dry eye symptoms (36-40%)
	blurred vision (14%)
	ocular disorders (46%)
gastrointestinal	*emetogenic potential:* low[2]
	diarrhea (42%, severe 6%)
	nausea (45%, severe 3%)
	vomiting (18%, severe 2%)
general disorders and administration site conditions	*extravasation hazard:* irritant[3,4]
	fatigue (56%, severe 6%)
	infusion site extravasation, skin and soft tissue reactions (1-2%, severe 1%); see paragraph following **Side Effects** table
infections and infestations	cellulitis (5%)
	sepsis (3%) ; fatalities reported
	urinary tract infection (6%)
investigations	***creatinine increase*** (20%, severe 2%)
	lipase increase (14%, severe 9%)
	phosphate decrease (34%, severe 10%)
	potassium decrease (19%, severe 1%)
	sodium decrease (severe 8%)
	urate decrease (severe 7%)
metabolism and nutrition	appetite decrease (52%, severe 2%)
	hyperglycemia (severe 8%)
nervous system disorders	dysgeusia (42%)
	peripheral neuropathy, primarily sensory (49-56%, severe 2-4%); see paragraph following **Side Effects** table
renal and urinary	acute kidney injury (3%)
respiratory, thoracic and mediastinal	acute respiratory failure (1%); fatalities reported
	aspiration pneumonia (1%); fatalities reported
	dyspnea (3%)
skin and subcutaneous tissue	***alopecia*** (50%)
	dry skin (26%)
	epidermal necrosis[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	maculopapular rash (26%)
	pruritus (26-30%, severe 2%)
	rash (52%, severe 13%)
	skin reactions (54%, severe 10%); see paragraph following **Side Effects** table
	Stevens-Johnson syndrome[5]
	toxic epidermal necrolysis[5]

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. Onset may be delayed (e.g., 24 hours). Symptoms may 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] For more information on the management of extravasation reactions, see BC Cancer Systemic Therapy Policy III-20 ***Prevention and Management of Extravasation of Chemotherapy***.

Ocular disorders are frequently reported. The majority of events involve the cornea and include keratitis, blurred vision, limbal stem cell deficiency, and events associated with dry eyes. Median time to onset is 1.9 months (range 0.3 to 6.2 months). 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.[1]

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 3.8 months (range 0.6 to 9.2 months). 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.[1]

Skin reactions are reported in approximately 50% of patients. 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 0.8 months (range 0.2 to 5.3 months). SJS and TEN occurred predominantly during the first cycle, but can also occur later. Of the patients who experience rash, the majority will experience complete or partial resolution of their symptoms. Withhold enfortumab vedotin for grade 3 reactions and suspected SJS and TEN. Topical corticosteroids and antihistamines may be required. Permanently discontinue enfortumab vedotin for grade 4 or recurrent grade 3 reactions, and for confirmed SJS and TEN.[1,5]

INTERACTIONS:

No clinical studies evaluating drug interactions with enfortumab vedotin have been conducted. However, MMAE is a substrate of CYP 3A4. Data from other antibody-drug conjugates containing MMAE have indicated that concomitant administration of CYP 3A4 inhibitors and inducers may affect the AUC and C_{max} of MMAE. Concomitant administration with strong CYP 3A4 inhibitors may increase free MMAE exposure; monitor for signs of enfortumab vedotin toxicity. Concomitant administration with strong CYP 3A4 inducers may decrease free MMAE exposure and should be avoided if possible as the effect on clinical treatment outcome is not known.[5]

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SUPPLY AND STORAGE:

Injection: Astellas Pharma US, Inc.(Seattle Genetics, Inc.) supplies enfortumab vedotin as 20 mg and 30 mg 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[1]	do NOT use
Intermittent infusion[1]	***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***

Intravenous:	Cycle Length: 4 weeks[1,5]:	***1.25 mg/kg*** (range 0.5-1.25 mg/kg) IV ***for one dose on day 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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REFERENCES:

1. Astellas Pharma US Inc. PADCEV® full prescribing information. Northbrook, Illinois, USA; December 2019.
2. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020.
3. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; 1 March 2021.
4. Lexi-Drugs® - Lexicomp Online (database on the Internet). Enfortumab vedotin. Wolters Kluwer Clinical Drug Information Inc., 25 May 2021. Available at: http://online.lexi.com. Accessed 17 June 2021.
5. Astellas Pharma US Inc. PADCEV® full prescribing information. Northbrook, Illinois, USA; March 2021.

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