Drug Monograph

A - Drug Name

enfortumab vedotin

COMMON TRADE NAME(S): Padcev®

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B - Mechanism of Action and Pharmacokinetics

Enfortumab vedotin is an antibody drug conjugate (ADC) targeting Nectin-4, an adhesion protein located on the surface of most urothelial cancer cells. It contains a fully human IgG1-kappa antibody attached to the microtubule-disrupting agent (MMAE) by a protease-cleavable linker. After binding to Nectin-4-expressing cells, the ADC-Nectin-4 complex is internalized, and the MMAE is released via proteolytic cleavage. MMAE disrupts the microtubule network in cells, inducing cell cycle arrest and apoptosis.

Distribution	PPB	68 to 82% (MMAE); MMAE is unlikely to displace or to be displaced by highly protein-bound drugs.
Metabolism	Expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. A small fraction of released MMAE from ADC is metabolized.	
	Main enzymes involved	CYP3A4 (MMAE)
Elimination	MMAE elimination appears to be limited by its rate of release from the ADC; approximately 24% of MMAE is recovered unchanged in feces and urine after a single dose of another ADC.	
	Half-life	3.6 days (ADC); 2.6 days (MMAE)

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C - Indications and Status

Health Canada Approvals:

- Urothelial cancer

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following table lists adverse effects that occurred in ≥ 10% of patients with previously treated unresectable locally advanced or metastatic urothelial cancer, in a randomized Phase III study. It also includes severe or life-threatening adverse effects from other sources and post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Tachycardia (<10%)	E
Dermatological	Alopecia (47%)	E
	Rash (54%) (including hand-foot syndrome) (14% severe)	E D
	Stevens-Johnson syndrome (rare)	E D
	Toxic epidermal necrolysis (rare)	E D
Gastrointestinal	Abdominal pain (20%)	E
	Anorexia, weight loss (41%)	E
	Constipation (28%)	E
	Diarrhea (35%)	E
	Nausea, vomiting (30%) (1% severe)	E

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General	Fatigue (50%)	E
Hematological	Myelosuppression ± infection, bleeding (11%)	E
Hepatobiliary	↑ LFTs (12%)	E
Injection site	Infusion site extravasation (1%) (may be severe)	I E
Metabolic / Endocrine	Hyperglycemia (11%) (7% severe)	E
Musculoskeletal	Musculoskeletal pain (25%)	E
Nervous System	Dysgeusia (26%)	E D
	Insomnia (11%)	E
	Peripheral neuropathy (50%) (5% severe)	E D
Ophthalmic	Dry eye (24%) (1% severe; including keratitis or keratopathy)	E D
Respiratory	Pneumonitis (3%)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for enfortumab vedotin include rash, fatigue, peripheral neuropathy, alopecia, anorexia, weight loss, diarrhea, nausea, vomiting, constipation, dysgeusia and musculoskeletal pain.

Severe **skin reactions**, including epidermal necrosis, SJS, TEN, symmetrical drug-related intertriginous and flexural exanthema, with fatal outcome have been reported with enfortumab vedotin during clinical trials and post-marketing. Adverse reactions mainly occur during the first cycle of treatment, but may occur in subsequent cycles.

Extravasation has been observed following enfortumab vedotin administration. Reactions may be delayed; symptoms may continue to worsen for 2-7 days after extravasation and resolve within 1-4 weeks of the worst symptoms. Ensure good venous access prior to starting treatment. If extravasation occurs during administration, stop the infusion and monitor for adverse reactions.

Hyperglycemia and **diabetic ketoacidosis** (DKA), including fatal events, have been reported in patients with and without pre-existing diabetes mellitus treated with enfortumab vedotin. Hyperglycemia occurred more frequently in patients with pre-existing hyperglycemia or a high BMI (≥30 kg/m^2). The incidence of Grade 3 or 4 hyperglycemia increased consistently in patients with higher BMI or higher baseline HbA1C. Patients with baseline hemoglobin A1C ≥ 8% were excluded from clinical trials.

Peripheral neuropathy, mostly sensory, has been reported in patients with and without pre-existing peripheral neuropathy. The median time to onset was approximately 5 months for Grade ≥ 2.

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Severe or life-threatening **pneumonitis** have been reported with enfortumab vedotin. During clinical trials, the median time to onset was approximately 3 months; two patients experienced fatal events.

Ocular events, mostly corneal disorders or dry eyes, have occurred in clinical trials. The median time to onset was approximately 2 months. Consider prophylaxis for dry eyes with artificial tears. An ophthalmologic referral should be considered if symptoms do not resolve or worsen.

Higher incidences of skin reactions, peripheral neuropathy, and pneumonitis occurred when enfortumab vedotin was given in combination with pembrolizumab, compared to enfortumab vedotin as a single agent.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Premedication (Prophylaxis for Infusion Reactions):

- Routine premedication is not recommended. No premedication was given for the first dose of enfortumab vedotin during clinical trials.
- Patients who experience an infusion reaction may be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid given 30–60 minutes prior to each infusion. (Powles 2021)

Adults:

Monotherapy:

Intravenous: 1.25 mg/kg* days 1, 8, and 15 q28days

Subsequent doses should NOT be administered less than 1 week apart.

*Dose is capped at a weight of 100 kg.

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Combination therapy:

Various dosing and schedules are used depending on the indication. Refer to the product monograph or related regimen monographs for details.

Dosage with Toxicity:

Dose Level	Enfortumab Vedotin Dose (mg/kg)*
0	1.25
-1	1
-2	0.75
-3	0.5
-4	Discontinue

*For patients ≤ 100 kg. If weight is > 100 kg, dose should be based on 100 kg.

Toxicity	Grade/Severity	Action
Skin Reactions	Grade 1 or 2	Consider topical corticosteroids and antihistamines as needed.
	Grade 3, worsening reactions, or suspected SJS or TEN	Hold*. Consider dermatological referral. Resume at same dose or consider 1 dose level ↓.
	Grade 4, recurrent Grade 3, or confirmed SJS or TEN	Discontinue.
Hyperglycemia	Blood glucose > 13.9 mmol/L	Hold*. Resume at same dose.
Pneumonitis	Grade 2	Hold*. Resume at the same dose or consider 1 dose level ↓.
	Grade 3 or 4	Discontinue.
Peripheral Neuropathy	Grade 2	Hold*. 1st occurrence: resume at same dose. Recurrence: resume at 1 dose level ↓.
	Grade 3 or 4	Discontinue.

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Ocular Toxicity	Any	Consider holding or reducing dose. Consider ophthalmology referral if symptoms do not resolve or worsen.
Other Non-hematologic Toxicity	Grade 3	Hold*. Resume at same dose or consider 1 dose level ↓.
	Grade 4	Discontinue.
Hematologic Toxicity	Grade 2 thrombocytopenia	Hold*. Resume at same dose or consider 1 dose level ↓.
	Grade 3	
	Grade 4	Hold*. Resume at 1 dose level ↓ or discontinue.

*Do not restart treatment until blood glucose resolved to ≤ 13.9 mmol/L, and other toxicities ≤ Grade 1.

Dosage with Hepatic Impairment:

MMAE exposure is likely increased in patients with moderate or severe hepatic impairment.

Hepatic Impairment	Enfortumab Vedotin Dose
Child-Pugh A	No adjustment required.
Child-Pugh B	Not studied; avoid use.
Child-Pugh C	

Dosage with Renal Impairment:

No dosage adjustment is required with renal impairment. The effect of end stage renal disease with or without dialysis on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

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Dosage in the elderly:

No dose adjustment is required in patients ≥ 65 years of age. No overall differences in efficacy were observed between patients ≥ 65 years and those < 65 years. Patients ≥ 65 years were more likely to experience serious adverse events or treatment discontinuation.

Dosage based on gender:

No clinically significant differences on the pharmacokinetics of enfortumab vedotin were observed based on gender.

Dosage based on ethnicity:

No clinically significant differences on the pharmacokinetics of enfortumab vedotin were observed based on ethnicity.

Children:

Safety and effectiveness have not been evaluated in children < 18 years of age.

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F - Administration Guidelines

- Reconstitute each vial with Sterile Water for Injection. Swirl gently; do not shake the solution.
- Dilute in D5W, NS, or Ringer's lactate. Invert infusion bag gently to mix.
- Final concentration should be 0.3 mg/mL to 4 mg/mL.
- Administer as an IV infusion over 30 minutes. Do NOT administer as an IV push or bolus.
- If given with pembrolizumab on the same day, administer enfortumab vedotin first, with an interval of 30 minutes between infusions (for at least Cycle 1, Day 1). If well tolerated, subsequent intervals between infusions may be reduced to 15 minutes.
- Do NOT administer other drugs through the same IV line.
- If extravasation occurs during administration, stop the infusion and monitor for adverse reactions (e.g., skin and soft tissue injury).
- Do not expose the vials or diluted drug to direct sunlight.
- Store unopened vials in a refrigerator at 2-8^{o}C. Do not freeze.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Do NOT start enfortumab vedotin in patients with pre-existing grade ≥ 2 neuropathy, ongoing clinically significant toxicity from previous treatment, active CNS metastases, uncontrolled diabetes, active keratitis or corneal ulcerations.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Mutagenicity: No
- Genotoxicity: Yes
  Enfortumab vedotin is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **4 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **6 months** after the last dose.
- Fertility effects: Probable
  Testicular toxicity was observed in animals.

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H - Interactions

No drug interaction studies have been conducted.

In vitro, MMAE is a substrate of P-gp and does not inhibit P-gp.

In vitro, MMAE inhibits CYP3A4/5 but not other CYP450 enzymes, and does not induce major CYP450 enzymes. MMAE is predicted not to alter the exposure of CYP3A4 substrates (e.g., midazolam).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Combined strong P-gp and CYP3A4 inhibitors (i.e. ketoconazole)	↑ MMAE exposure by 38%, no changed in ADC exposure (with ketoconazole)	↓ metabolism of MMAE	No enfortumab vedotin dose adjustment required. Monitor for adverse reactions closely.
Strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, posaconazole, ritonavir, voriconazole)	↑ MMAE exposure (theoretical)	↓ metabolism of MMAE	Monitor for adverse reactions closely.
Strong CYP3A4 inducers (i.e. rifampin)	↓ MMAE exposure by 53%, no change in ADC exposure (with rifampin)	↑ metabolism of MMAE	Caution; monitor for enfortumab vedotin ↓ therapeutic response.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each dose, and as clinically indicated
Liver function tests	Baseline, before each dose, and as clinically indicated
Blood glucose	Baseline and as clinically indicated (more frequently in patients with or at risk for diabetes mellitus or hyperglycemia)
Clinical toxicity assessment for infection, bleeding, extravasation, peripheral neuropathy, GI, ocular, respiratory and skin effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Enfortumab Vedotin - Previously Treated Advanced or Metastatic Urothelial Cancer

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K - References

ASCO Guidelines: Emetic Risk of Single Intravenous Antineoplastic Agents in Adults. American Society of Clinical Oncology 2020.

Butler, J. et al. Extravasation injury from chemotherapy and other non-antineoplastic vesicants. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed on June 13, 2022.

CADTH reimbursement recommendation: Enfortumab vedotin (unresectable, locally advanced or metastatic urothelial cancer). January 2022.

Enfortumab vedotin and Rifampin. Lexicomp: Interactions. UpToDate, Inc. 2022. Accessed on June 20, 2022.

National Library of Medicine (U.S.). (2018, June - 2020, July). An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301). Identifier NCT03474107. https://https://clinicaltrials.gov/ct2/show/NCT03474107.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis. Version 2.2022, March 23, 2022.

Powles T. et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021;384:1125-35.

Prescribing Information: Padcev® (enfortumab vedotin-ejfv). Seagen Inc, Inc. May 2022.

Product Monograph: Padcev® (enfortumab vedotin). Seagen Canada Inc. August 20, 2024.

Summary of Product Characteristics. Padcev® (enfortumab vedotin). Astellas Pharma Ltd. December 5, 2022.

January 2025 Updated Adverse effects, Dosing, and Administration sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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