Enfortumab vedotin Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who have previously received a platinum-containing chemotherapy and a programmed death receptor 1 (PD-1) or programmed death ligand 1 inhibitor (PD-L1).	C67	00846a	ODMS 01/12/2023

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Enfortumab vedotin is administered on Days 1, 8 and 15 of a 28-day cycle. Treatment should be continued until disease progression or unacceptable toxicity.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 8, 15	Enfortumab vedotin	1.25mg/kg	IV infusion	50ml 0.9% NaCl over 30 mins	Every 28 days
For patient weight ≥100kg, the dose calculation should use 100kg (maximum dose=125mg).					
Final concentration of enfortumab vedotin should be 0.3-4mg/ml.					
In-line filters or syringe filters of pore size: 0.2-1.2 µm are recommended to be used during administration.					
Dextrose 5% or Lactated Ringer's solution for Injection may also be used as diluent.					

ELIGIBILITY:

- Indication as above
- Histologically or cytologically confirmed urothelial carcinoma (including differentiation in squamous cells or in multiple cell types)
- Radiologically documented unresectable locally advanced or metastatic urothelial carcinoma
- Previous treatment with platinum-containing chemotherapy in either the neo-adjuvant, adjuvant or metastatic setting
- Progression during or following treatment with programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor
- Adequate haematological and organ function
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to enfortumab vedotin or to any of the excipients
- Active CNS metastases
- Pre-existing ≥ Grade 2 sensory or motor neuropathy
- Uncontrolled diabetes mellitus
- Active keratitis or corneal ulcerations
- Pregnancy / breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal, liver profile and blood glucose
- Lipase, phosphate, HbA1c
- Assessment of pre-existing neuropathy
- Ophthalmology assessment if clinically indicated
- Skin assessment

Regular tests:

- FBC, renal, liver profile and blood glucose on Day 1, 8 and 15 of Cycle 1, then on Day 1 of each subsequent cycle
- Phosphate on day 1
- Lipase and HbA1c, on day 1 if clinically indicated
- Ophthalmology assessment if clinically indicated
- Skin assessment should be carried out throughout treatment

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Recommended dose reductions for enfortumab vedotin are outlined in Table 1
- Dose interruption, reduction and discontinuation recommendations for enfortumab vedotin are outlined in Tables 2, 3 and 4

Table 1: Recommended dose reductions for enfortumab vedotin for adverse reactions

	Dose level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Haematological:

Table 2: Dose modification of enfortumab vedotin in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.5	**and**	**≥75**	100% dose
1.0–1.49	**or**	**50-74**	100% dose, except: If platelets 50-74 x 10^9/L, withhold dose until platelets ≥75 x10^9/L or have returned to baseline, then resume treatment at the same dose level.
0.5-0.99	**or**	**25-49**	Withhold dose until ANC ≥ 1.5 x 10^9/L and platelets ≥75 x 10^9/L or returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level*.
<0.5	**or**	**<25**	Withhold dose until ANC ≥ 1.5 x 10^9/L and platelets ≥75 x 10^9/L or returned to baseline, then reduce dose by 1 dose level and resume treatment* or consider discontinuation. For anaemia, treatment discontinuation should be strongly considered
* Use of transfusions or growth factors may be considered **(Refer to local policy).**			

Renal and Hepatic Impairment:

Table 3: Dose modification of enfortumab vedotin in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
CrCl ml/min	**Dose**	**Severity**	**Dose**
≥ 15ml/min	No dose adjustment is needed	**Mild**	No dose adjustment is needed
< 15ml/min	No need for dose adjustment is expected	**Moderate/Severe**	Not recommended
Haemodialysis	No need for dose adjustment is expected		

Management of adverse events:

Table 4: Dose interruption, reduction and discontinuation recommendations for enfortumab vedotin for non-haematological toxicity

Adverse reaction	Severity*	Dose modification*
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	• Immediately withhold and refer to specialised care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	• Permanently discontinue.
	Grade 2 worsening or Grade 2 with fever or Grade 3	• Withhold until Grade ≤1 • Referral to specialised care should be considered • Resume at the same dose level or consider dose reduction by one dose level (see Table 1)
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) • Resume treatment at the same dose level
Pneumonitis/ interstitial lung disease (ILD)	Grade 2	• Withhold until Grade ≤1, then resume at the same dose or consider dose reduction by one dose level (see Table 1)
	Grade ≥3	• Permanently discontinue.
Peripheral neuropathy	Grade 2	• Withhold until Grade ≤1 • For first occurrence, resume treatment at the same dose level • For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level (see Table 1)
	Grade ≥3	• Permanently discontinue.
*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life-threatening		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low **(Refer to local policy).**

PREMEDICATIONS:

- For patients who have experienced a prior infusion reaction, premedication consisting of an oral anti-pyretic, antihistamine and IV corticosteroid should be administered 30 minutes prior to subsequent infusions of enfortumab vedotin **(Refer to local policy)**

OTHER SUPPORTIVE CARE:

- Consider artificial tears for prophylaxis of dry eye **(Refer to local policy)**
- Consider topical corticosteroids and antihistamines for mild to moderate skin reactions **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Enfortumab vedotin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Skin reactions:** Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Mild to moderate skin reactions, predominantly maculopapular rash, have been reported. Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. Refer to Table 3 for dose interruption, reduction and discontinuation recommendations for skin reactions.
- **Pneumonitis / ILD:** Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin. Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Refer to Table 3 for dose interruption, reduction and discontinuation recommendations for pneumonitis / ILD.
- **Hyperglycaemia:** Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, have occurred in patients with and without pre-existing diabetes mellitus, treated with enfortumab vedotin. Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2). Patients with baseline HbA1c ≥8% were excluded from clinical trials. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia.
- **Peripheral neuropathy:** Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions. Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical trials. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin (see Table 3).
- **Ocular disorders:** Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin. Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.
- **Infusion site extravasation:** Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred. Ensure good venous access prior to starting enfortumab vedotin and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.
- **Embryo-foetal toxicity and contraception:** Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 12 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following the last dose of enfortumab vedotin.

DRUG INTERACTIONS:

- Formal drug-drug interaction studies with enfortumab vedotin have not been conducted.
- Concomitant administration of enfortumab vedotin and CYP3A4 (substrates) metabolised medicinal products, has no clinically relevant risk of inducing pharmacokinetic interactions
- Concomitant use of CYP3A4 inhibitors may exposure of unconjugated monomethyl auristatin E (MMAE). Enfortumab vedotin is an antibody-drug conjugate, consisting of a monoclonal antibody component (AGS-22C3) conjugated to the small molecule microtubule-disrupting agent MMAE. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities due to increased exposure to MMAE.
- Strong CYP3A4 inducers may decrease the exposure of unconjugated MMAE with moderate effect.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Pack and Educational Letter
https://www.hpra.ie/img/uploaded/swedocuments/12d6a7b3-98e0-4d29-b8d6-9054293463ba.pdf

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2. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
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Version	Date	Amendment	Approved By
1	01/12/2023		Prof Maccon Keane
2	15/12/2023	Addition of skin assessment to baseline and regular tests	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.