NCPE Assessment

Technical Summary

Enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®)

HTA 24038

January 2026

Applicant: Astellas Pharma Co. Ltd

First-line Treatment of Adult Patients with Unresectable or Metastatic Urothelial Cancer who are Eligible for Platinum-Based Chemotherapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®).

Following assessment of the Applicant's submission, the NCPE recommends that enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®) not be considered for reimbursement.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Astellas Pharma Co. Ltd) Health Technology Assessment of enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost, requested by the pharmaceutical company, is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In March 2025, Astellas Pharma Co. Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®) (EV+P) for the first-line treatment of unresectable or metastatic urothelial cancer (u/mUC) in adult patients who are eligible for platinum-based chemotherapy. Astellas Pharma Co. Ltd is seeking reimbursement of enfortumab vedotin on the Oncology Drug Management System.

Enfortumab vedotin is an antibody drug conjugate targeting Nectin-4, that contains the microtubule-disrupting agent monomethyl auristatin E. Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death protein-1 receptor and blocks its interaction with ligands. Combination of enfortumab vedotin with pembrolizumab results in enhanced anti-tumour activity. Both enfortumab vedotin and pembrolizumab are administered intravenously. The recommended dose of enfortumab vedotin is 1.25mg per kilogram once on Days 1 and 8 of each 21-day cycle. The recommended dose of pembrolizumab is 200mg once every 21 days, or 400mg once every 42 days. In line with the licence, treatment should continue until disease progression or unacceptable toxicity.

EV+P is positioned as a first-line treatment for u/mUC in adult patients who are eligible for platinum-based chemotherapy. The current standard of care, for this indication, is gemcitabine in combination with platinum-based chemotherapy. This is followed by avelumab maintenance therapy for patients whose disease has not progressed. Clinical opinion to the Review Group indicated that a proportion of patients who are cisplatin-ineligible may receive atezolizumab or pembrolizumab monotherapy, if they meet the respective biomarker criteria (PD-L1 combined positivity score of ≥10 for pembrolizumab; PD-L1 expression of ≥5% for atezolizumab). These monotherapies were not included as comparators, which the Review Group considered to be a limitation of the assessment.

1. Comparative effectiveness of enfortumab vedotin in combination with pembrolizumab

The clinical efficacy of EV+P was informed by the EV-302 trial, which was a phase III, open-

label, randomised controlled trial. Eligible participants were adults with u/mUC who were eligible for platinum-based chemotherapy. Participants (n=886) were randomised to receive either EV+P (n=442) or gemcitabine in combination with platinum-based chemotherapy (gemcitabine+PBC) (n=444). Participants whose disease did not progress, following gemcitabine+PBC, were eligible for avelumab maintenance therapy. The primary endpoints were progression-free survival (PFS) and overall survival (OS). The secondary endpoints were overall response rate (ORR), duration of response and time to pain progression. Health related quality of life (HRQoL) outcomes were also collected. The most recent data cut was August 2024; median follow-up was 29.1 months.

Results demonstrated that, for all primary and key secondary endpoints, more favourable outcomes were observed for participants in the EV+P arm compared to those in the gemcitabine+PBC arm. Benefits were observed for PFS, OS and ORR in the EV+P arm. Median PFS in the EV+P arm was 12.5 months (95% CI, 10.4 to 16.6), compared with 6.3 months (95% CI, 6.2 to 6.5) in the gemcitabine+PBC arm; p<0.00001. Median OS in the EV+P arm was 33.8 months (95% CI, 26.1 to 39.3), compared with 15.9 months (95% CI, 13.6 to 18.3) in the gemcitabine+PBC arm; p<0.00001. The ORR in the EV+P arm was 67.5% (95% CI, 62.9 to 71.9), compared with 44.2% (95% CI, 39.5 to 49.9) in the gemcitabine+PBC arm; p<0.00001. HRQoL endpoints remained stable in both arms throughout the duration of the trial.

A key limitation of EV-302 was the low proportion of participants in the gemcitabine+PBC arm who received avelumab maintenance (30%). This is lower than expected in Irish clinical practice. Median OS was longer for those eligible for and receiving avelumab maintenance compared with eligible non-recipients (26.22 vs 18.76 months). Consequently, the effects observed in the comparator arm may underestimate those anticipated in Irish clinical practice. The median OS for participants ineligible for and not receiving avelumab maintenance was 7.1 months.

2. Safety of enfortumab vedotin in combination with pembrolizumab

The clinical safety of EV+P was informed by the EV-302 trial. The safety analysis set (n=873) was defined as participants who received any part of study treatment; it comprised 440 participants in the EV+P arm and 433 in the gemcitabine+PBC arm.

The majority of participants in both arms experienced at least one treatment-related adverse event (TRAE); 97.3% in the EV+P arm and 95.6% and gemcitabine+PBC arm. TRAEs leading to permanent discontinuation occurred more frequently in the EV+P arm (42.7% versus 18.5%). The most common TRAEs in the EV+P group were peripheral sensory neuropathy (51.8%), pruritus (40.7%), and alopecia (33.2%). The most common TRAEs in the gemcitabine+PBC arm were anaemia (56.6%), neutropenia (41.6%), and nausea (38.8%). Skin reactions, peripheral neuropathy, hyperglycaemia, ocular disorders, and infusion-related reactions are all TRAEs of special interest for enfortumab vedotin. In the EV+P group, the most common grade ≥3 TRAEs of special interest were skin reactions (16.6%), peripheral neuropathy (8.4%), and hyperglycaemia (8.9%).

3. Cost effectiveness of enfortumab vedotin in combination with pembrolizumab

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a partitioned survival model developed in Microsoft Excel®. The modelled population in the cost-effectiveness model (CEM) was adult patients with previously untreated u/mUC who were eligible for platinum-based chemotherapy. The modelled intervention was EV+P. The modelled comparators were gemcitabine plus cisplatin and gemcitabine plus carboplatin, combined into a single weighted comparator (gemcitabine+PBC), with a proportion of patients receiving subsequent avelumab maintenance after a washout period.

The CEM comprised three mutually exclusive health states: progression-free, progressed disease and death. All patients entered the model in the progression-free health state and were assigned to treatment with either EV+P or gemcitabine+PBC. During each model cycle, patients could remain progression-free or transition to progressed disease or death; transitions to improved health states were not permitted. Weekly cycles, a 30-year time horizon, and a half-cycle correction were applied.

OS and PFS were modelled independently using EV-302 data. OS was constrained by Irish general population mortality; PFS was constrained by the selected OS distribution. The Applicant selected the log-logistic distribution to extrapolate OS for both arms, which the Review Group considered reasonable. For PFS, the Applicant selected the two-knot cubic

spline hazards model for the EV+P, and the three-knot cubic spline odds model for the gemcitabine+PBC. The Review Group considered the standard parametric model approach to be more appropriate and selected the log-logistic distribution for both arms as the NCPE-adjusted base case.

Treatment-related costs were based on time on treatment (ToT) data from EV-302. ToT for enfortumab vedotin and comparator regimens were modelled, while fully mature pembrolizumab ToT data were used directly without extrapolation. The Review Group noted that although pembrolizumab was capped at 35 cycles in EV-302, no such stopping rule appears in the product licence. Enfortumab vedotin ToT was modelled using a log-logistic distribution, which the Review Group considered reasonable. ToT for the gemcitabine+PBC arm was modelled in three stages: observed ToT from Kaplan–Meier data, a 4.87-week washout derived from a post-hoc EV-302 analysis, and extrapolated avelumab maintenance ToT using standard parametric models. The Applicant selected a Weibull curve for avelumab ToT; despite Review Group concerns regarding uncertainty, sensitivity analyses showed results were insensitive to alternative distributions. The Review Group also noted that avelumab use in EV-302 was lower than expected in Irish clinical practice.

A systematic literature review (SLR) was used to identify HRQoL data. The Applicant stated that the EV-302 trial was the most appropriate data source but did not provide a critical evaluation of the identified sources to support this decision. The Review Group considered this a limitation. EQ-5D-5L data from EV-302 were converted to EQ-5D-3L using the Hernandez-Alva algorithm. The Review Group noted differences in compliance rates between treatment arms and considered this insufficient to justify treatment-specific utility values in the progression-free health state. Treatment-independent utility values were used in the NCPE-adjusted base case. The Review Group also noted the increased risk of bias associated with patient-reported outcomes in open-label trials.

Costs and resources included were drug costs, drug administration costs, subsequent treatment costs, AE costs and disease management costs. A once-off, end-of-life cost was also included.

Results

Results of the Applicant base case deterministic cost-effective analysis are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Gemcitabine+PBC	141,164	1.60	-	-	-
EV+P	301,769	3.00	160,605	1.40	114,676

EV+P: Enfortumab vedotin + pembrolizumab, **PBC:** Platinum-based chemotherapy, **QALY:** Quality adjusted life-year, **ICER:** Incremental cost effectiveness ratio.
[a] Corresponding probabilistic ICER using 1,000 iterations = €121,101/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.
[b] PAS are in place for enfortumab vedotin, pembrolizumab, and avelumab; not included in this table.

Several changes were made to inform the NCPE adjusted base case. These included changing utility values from treatment-dependent to treatment-independent, selecting the log-logistic distribution for extrapolation of PFS in both arms, changing to a time-independent relative dose intensity (RDI) for enfortumab vedotin, and replacing hourly chemotherapy administration costs with a flat rate. Results of the NCPE adjusted base case are presented in Table 2.

Table 2: NCPE-adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Gemcitabine+PBC	155,107	1.58	-	-	-
EV+P	337,609	2.91	182,502	1.33	137,368

PBC: Platinum based chemotherapy, **EV+P:** Enfortumab vedotin + pembrolizumab, **ICER:** Incremental cost-effectiveness ratio
[a] Corresponding probabilistic ICER using 1,000 iterations =€141,374/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.
[b] PAS are in place for enfortumab vedotin, pembrolizumab, and avelumab; not included in this table.

Sensitivity analysis

Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE-adjusted base case related to RDI of pembrolizumab, RDI of avelumab, proportion of patients receiving avelumab maintenance and discount rate (on outcomes).

A price-ICER analysis, conducted using the NCPE-adjusted base case, demonstrated that enfortumab vedotin (given in combination with pembrolizumab) could not achieve cost-effectiveness, at a €45,000 per QALY threshold, at any discount.

4. Budget impact of enfortumab vedotin in combination with pembrolizumab

The price to wholesaler of enfortumab vedotin is €649.41 per 20mg vial and €974.11 per 30mg vial. The price to wholesaler of pembrolizumab is €3,015.61 per 100mg vial. Total estimated cost per patient per treatment course of EV+P is €275,078 (including VAT). This estimate is based on a mean treatment duration of 14.39 months for enfortumab vedotin and 11.58 months for pembrolizumab, derived from modelled ToT data.

Eligible patients were adults with untreated u/mUC who are eligible for platinum-based chemotherapy. In the absence of Irish epidemiology data for u/mUC, bladder cancer figures were used to estimate eligible patients. Eligible patient numbers were estimated to be 100 in Year One, increasing to 104 by Year Five. Estimates of the eligible patient population and the market share for EV+P, as well as for comparator treatments, were highly uncertain. The Applicant-estimated five-year cumulative gross and net drug-budget impacts for EV+P were €95.4 million and €81.0 million, respectively, including VAT.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that enfortumab vedotin (Padcev®) in combination with pembrolizumab (Keytruda®) not be considered for reimbursement.*

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.