NCPE Assessment

Technical Summary

Enfortumab vedotin (Padcev®)

HTA ID 22024

12 July 2023

Applicant: Astellas

Enfortumab vedotin for the treatment of adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 (PD-1) or programmed death-ligand-1 (PD-L1) inhibitor.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of enfortumab vedotin (Padcev®) for this indication. Following assessment of the Applicant's submission, the NCPE recommends that enfortumab vedotin (Padcev®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Astellas) Health Technology Assessment of enfortumab vedotin (Padcev®). 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 November 2022, Astellas submitted a dossier examining the comparative clinical effectiveness, cost-effectiveness and budget impact of enfortumab vedotin for the treatment of adults with locally advanced or metastatic urothelial cancer (UC) who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. Reimbursement is sought under the Oncology Drugs Management System.

Enfortumab vedotin is an antibody-drug conjugate consisting of a monoclonal antibody targeting nectin-4, which is conjugated to the microtubule-disrupting agent monomethyl auristatin E. Disruption of the microtubule network results in cell cycle arrest and apoptotic cell death. The recommended dose of enfortumab vedotin is 1.25mg/kg, administered intravenously, on days one, eight and 15 of a 28-day cycle. Treatment is continued until disease progression or unacceptable toxicity (as per the license).

For individuals with progressive disease after receiving treatment with platinum-based chemotherapy and PD-1/PD-L1 therapies, active treatment options, available in Ireland, are currently limited to taxane chemotherapy. Therefore, taxane chemotherapy is considered the relevant comparator to enfortumab vedotin.

1. Comparative effectiveness of enfortumab vedotin (Padcev®)

EV-301

Direct comparative evidence of enfortumab vedotin versus pre-selected chemotherapy (docetaxel, paclitaxel, or vinflunine), in adults with locally advanced/metastatic UC previously treated with platinum-based chemotherapy and a PD-1 or a PD-L1 inhibitor, is available from the EV-301 randomised controlled trial. Data were presented for two populations. The intention to treat (ITT) population which included all randomised individuals, and the docetaxel/paclitaxel (DP) population. The DP population was a post-hoc subgroup analysis which included only individuals who were pre-assigned to docetaxel or paclitaxel therapy (as vinflunine is not used in Ireland), should they be randomised to the chemotherapy arm. The clinical evidence that supports this assessment is derived from the DP population.

Eligible individuals were randomised 1:1 to enfortumab vedotin (DP population: n=228) or chemotherapy (DP population: n=229). Individuals in both trial arms were treated until disease progression or unacceptable toxicity. Individuals receiving chemotherapy could cross-over to receive

enfortumab vedotin after the primary efficacy analysis (July 2020). The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. Clinical effectiveness results are presented for the final analysis (July 2021), with a median follow-up of 24.25 months. Data from the final analysis were used to inform the cost-effectiveness model.

For the DP population, median OS was 13.2 months with enfortumab vedotin versus 8.9 months with chemotherapy; hazard ratio (HR) of 0.67 (95% confidence interval (CI) 0.54 to 0.84). Median PFS was 5.6 months with enfortumab vedotin versus 3.6 months with chemotherapy; HR of 0.56 (95% CI 0.45 to 0.70). HRQoL data were only available for the ITT population from the primary analysis (July 2020); clinically meaningful differences between enfortumab vedotin and chemotherapy were not observed. The Review Group considers that the open-label nature of EV-301 increases the potential for bias in patient-reported outcomes, this together with high attrition rates in HRQoL outcomes means the effect of enfortumab vedotin on HRQoL remains uncertain. Furthermore, the open-label design could lead to bias in the investigator-led assessment of key secondary endpoints.

2. Safety of enfortumab vedotin (Padcev®)

The safety analysis set included all individuals from the ITT population who received any amount of study drug (n=296 for enfortumab vedotin and n=291 for chemotherapy). Results are presented for the final analysis (July 2021), no major differences were observed in the safety analysis for the DP-population. Safety data for the DP-population were included in the cost-effectiveness model consistent with the population used to inform comparative clinical effectiveness.

Any grade treatment emergent adverse events (TEAEs) were reported in 98.0% of individuals receiving enfortumab vedotin and 99.0% receiving chemotherapy. Drug-related TEAEs were more common with enfortumab vedotin (93.9%) compared to chemotherapy (91.8%). The most reported grade 3 or above TEAEs with enfortumab vedotin were neutrophil count decreased (7.1% versus 15.5% with chemotherapy), maculo-papular rash (7.4% versus 0%), fatigue (7.1 versus 4.8%), anaemia (6.4% versus 12.0%), hyperglycaemia (7.1% versus 1.0%), and peripheral sensory neuropathy (5.1% versus 2.11%). TEAEs of special interest with enfortumab vedotin include skin reactions (severe cutaneous adverse reactions and rash), hyperglycaemia, peripheral neuropathy, and ocular disorders.

3. Cost effectiveness of enfortumab vedotin (Padcev®)

Methods

A cost-utility analysis, using a partitioned survival model, with cycle length of one month and a lifetime horizon, was submitted. A half cycle correction was applied. The model included three mutually exclusive health states: pre-progression, post-progression and death. Standard parametric models were used to extrapolate PFS and OS data for the DP-population from the EV-301 trial. Enfortumab vedotin and chemotherapy data were extrapolated independently. Standard parametric distributions were used to extrapolate PFS. A piecewise approach was used for OS, which the Applicant justified with reference to heavy censoring resulting in low numbers of individuals at risk in the tail of the survival curve. The Review Group considered this to be reasonable and note that switching to a fully parametric approach did not have a major impact on the ICER. Although the July 2021 OS data is relatively mature, the cost-effectiveness model is very sensitive to the choice of distribution for the tail of the OS curve. There is a potential of overestimation of treatment effects for enfortumab vedotin with the Applicant's choice of the exponential distribution, due to the implicit assumption of a lifetime duration of treatment effectiveness.

Utility data were derived from EQ-5D-5L data, from the EV-301 trial, mapped to EQ-5D-3L. Treatment-specific utility values were applied for the pre-progression health state, with a non-treatment-specific utility applied for both treatment arms in the post-progression health state. Utility decrements were not included for TEAEs or increasing age. The Review Group has concerns that the use of treatment-specific utilities in the pre-progression health state may not be fully justifiable based on numerical differences in HRQoL outcomes in the open-label EV-301 trial.

Direct medical costs were included for drug acquisition (including administration), disease management, routine care and monitoring, end-of-life care and the management of TEAEs. Irish cost data were used where possible. The Review Group had concerns regarding the method used to calculate administration costs in the cost-effectiveness model. The model was very sensitive to the assumptions made.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group made several changes to the Applicant base case based on plausible alternative assumptions. These included, using a flat drug administration cost, non-treatment-specific utility in the pre-progression health state for both treatment arms, lower paclitaxel costs and a later (26-month) cut-point for the

piecewise model in line with patient numbers at the final (July 2021) data-cut. The Applicant incremental cost-effectiveness ratio (ICER) and the NCPE-adjusted ICER are shown in Table 1.

Table 1: Incremental cost -effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case					
Enfortumab vedotin	74,139	1.07			
Chemotherapy	24,394	0.76	49,745	0.31	161,060
NCPE-adjusted base case					
Enfortumab vedotin	81,729	1.05			
Chemotherapy	25,477	0.76	56,261	0.29	195,334

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

Mean probabilistic ICERs were aligned with the deterministic ICERs. Enfortumab vedotin had a 0% probability of cost-effectiveness at both the €20,000 per QALY and €45,000 per QALY thresholds, for the Applicant and NCPE-adjusted base case.

Sensitivity analysis indicated that the main drivers of cost-effectiveness in both the Applicant and NCPE-adjusted base case were related to the extrapolation of OS, duration of treatment, dose intensity, and health state utility values. When OS was extrapolated using the Weibull distribution, considered by the Review Group to be a conservative but plausible alternative scenario, the ICER under the NCPE adjusted base case assumptions increased to €237,436 per QALY.

An analysis of the price-ICER relationship was conducted using the NCPE-adjusted base case. The price reductions (inclusive of 8.25% Framework Agreement rebate) required to achieve cost effectiveness at the €20,000 and €45,000 per QALY thresholds were approximately 94.0% and 81.70% respectively.

4. Budget impact of enfortumab vedotin

The price-to-wholesaler of enfortumab vedotin is €671.78 for a 20mg vial and €1,007.67 for a 30mg vial. The total cost per patient per treatment course (assuming 100% dose intensity and median treatment duration of five months) is €63,122 (€50,525 excluding VAT), including relevant fees, mark ups and rebates.

The Applicant used several sources to inform the eligible patient estimates. These included the National Cancer Registry Ireland (NCRI) data, clinical opinion, and the published literature. The

Applicant assumed an initial market share of 60%, increasing to 70% in year five. Overall, the Applicant estimated that 41 individuals with locally advanced/metastatic UC would be treated with enfortumab vedotin in year one, rising to 58 in year five. The Applicant also presented a net drug budget impact assuming enfortumab vedotin will displace docetaxel and paclitaxel.

The Applicant estimated the cumulative five-year gross drug budget impact for enfortumab vedotin to be €16.22 million (€12.99 million excluding VAT). The cumulative five-year net drug budget impact for enfortumab vedotin was estimated to be €13.93 million (€11.12 million excluding VAT).

5. Patient Organisation Submission

No Patient Organisation Submissions were received during the course of the assessment**.**

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that enfortumab vedotin (Padcev®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

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