Technology Guidance

Enfortumab vedotin

in combination with pembrolizumab for untreated locally advanced or metastatic urothelial cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

✓ Enfortumab vedotin 20 mg and 30 mg powder for concentrate for solution for infusion, in combination with pembrolizumab, for untreated locally advanced or metastatic urothelial cancer.

Funding status

Enfortumab vedotin 20 mg and 30 mg powder for concentrate for solution for infusion are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 September 2026.

MAF assistance **does not** apply to pembrolizumab for this indication.

Clinical indication, subsidy class and MediShield Life claims eligibility for enfortumab vedotin are provided in the Annex.

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Technology Evaluation

1.1. At the April 2026 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of enfortumab vedotin, in combination with pembrolizumab, for untreated locally advanced or metastatic urothelial cancer. The evaluation considered the company's evidence submission by Astellas for enfortumab vedotin (Padcev), for use in combination with pembrolizumab, and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from the MOH Cancer Drug Subcommittee helped ACE ascertain the clinical value of enfortumab vedotin in combination with pembrolizumab. Local patient and voluntary organisations were also invited to provide their lived experiences to inform the evaluation, however, no submissions were received.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. Urothelial cancer (UC) arises from urothelial cells lining the bladder, urethra, ureter, or renal pelvis. In Singapore, approximately 100 patients each year are diagnosed with locally advanced or metastatic UC and require first-line systemic treatment.

2.2. The current standard first-line treatment is chemotherapy comprising a platinum plus gemcitabine. Among patients who do not experience disease progression following chemotherapy, some may opt to receive maintenance treatment with avelumab, a programmed cell death ligand 1 (PD-L1) inhibitor. In this population, avelumab maintenance treatment has been shown to improve overall survival compared to best supportive care.

2.3. The Committee noted the regulatory approval for a new combination treatment comprising enfortumab vedotin (a nectin-4 targeted antibody drug conjugate) plus pembrolizumab (a programmed cell death protein 1 [PD-1] inhibitor). The company's evidence submission for this treatment had requested a listing for patients with untreated locally advanced or metastatic UC, in line with the pivotal trial population. The Committee considered the submission's nominated comparator, platinum plus gemcitabine with or without avelumab maintenance treatment, to be appropriate.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence from a phase III trial (EV-302) involving 886 patients with untreated locally advanced or metastatic UC. Patients were randomised to receive either enfortumab vedotin plus pembrolizumab, or chemotherapy (platinum plus gemcitabine). In addition, 30.4% of patients in the chemotherapy arm received avelumab maintenance treatment.

3.2. In the primary analysis (median follow-up of 17.2 months), enfortumab vedotin plus pembrolizumab demonstrated statistically significant improvements in progression-free survival (PFS) and overall survival (OS) compared with chemotherapy. Median PFS was 12.5 versus 6.3 months (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.38 to 0.54). Median OS was 31.5 versus 16.1 months (HR 0.47; 95% CI 0.38 to 0.58).

3.3. The Committee noted that, in an updated analysis (median follow-up of 29.1 months), the survival benefits of enfortumab vedotin plus pembrolizumab were maintained. However, the individual contribution of each drug (enfortumab vedotin versus pembrolizumab) to the overall treatment effect remained uncertain, as this was not assessed in the evidence submission.

3.4. Based on the evidence presented, the Committee considered the submission's claim of superior clinical effectiveness to be supported for enfortumab vedotin plus pembrolizumab compared with chemotherapy (with or without avelumab maintenance treatment). However, the Committee noted that the rate of avelumab maintenance use in local practice was likely higher than that observed in the chemotherapy arm of the trial, which may have underestimated the effectiveness of current standard treatment in Singapore. As a result, the magnitude of benefit observed with enfortumab vedotin plus pembrolizumab in the trial may not be fully realised in the local target population.

3.5. Regarding safety, the submission described enfortumab vedotin plus pembrolizumab as superior, based on adverse event rates that were adjusted for treatment exposure. However, the Committee considered that unadjusted rates would be more reflective of clinical practice, given the longer treatment durations of enfortumab vedotin (administered until disease progression) and pembrolizumab (maximum 35 cycles), compared with chemotherapy (maximum 6 cycles).

3.6. Based on unadjusted event rates, the enfortumab vedotin plus pembrolizumab arm had higher incidence of serious treatment-emergent adverse events (TEAEs; 53.2% versus 39.0%), and TEAEs leading to study drug discontinuation (48.2% versus 21.5%) compared with the chemotherapy arm. Overall, the Committee considered that the submission's claim of superior safety was not adequately supported, and that a claim of inferior safety was more appropriate.

Cost effectiveness

4.1. The Committee reviewed the submission's cost-utility analysis that compared enfortumab vedotin plus pembrolizumab versus chemotherapy (with or without avelumab maintenance treatment) based on EV-302 trial data. Key components of the base-case economic evaluation are summarised in Table 1.

Table 1: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with untreated locally advanced or metastatic urothelial cancer
Outcomes	Total and incremental costs; total and incremental LYs; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	10 years in the base case, based on a median follow-up of 29.1 months in EV-302 trial
Health states	Pre-progression; post-progression; death
Cycle length	3 weeks
Extrapolation methods used to generate results	One-piece parametric extrapolations of patient-level data from EV-302 trial were used for PFS (generalised gamma for enfortumab vedotin plus pembrolizumab arm; log-logistic for chemotherapy arm) and OS (log-logistic for both treatment arms). ToT was extrapolated using standard parametric distributions for enfortumab vedotin (log-logistic) and avelumab maintenance (Weibull), while KM data was used for pembrolizumab and chemotherapy.
Health-related quality of life	Health state utilities based on EV-302 trial EQ-5D data, adjusted for age mapped with South Korea value set in the base case. AE disutilities were applied in the base case.
Types of healthcare resources included	• Drug acquisition and drug administration • Disease management costs • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; ToT, time on treatment.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$45,000 and SG$75,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be uncertain and likely underestimated, in view of the following:

- The submission applied a higher proportion of avelumab maintenance use in the model compared to the trial, by adjusting only the costs without corresponding adjustments to the efficacy data, resulting in underestimation of the ICER.

- The extrapolations of Kaplan-Meier curves in the model were uncertain. While the submission's choice of parametric extrapolation for OS in the enfortumab vedotin plus pembrolizumab arm demonstrated reasonable fit, the choice was not clearly justified and may be optimistic compared to alternative well-fitting extrapolations. In addition, the choice of extrapolation for avelumab time-on-treatment likely overestimated avelumab's treatment duration in the chemotherapy arm.

- The submission applied health state utility values favouring enfortumab vedotin plus pembrolizumab without adequate justification. In addition, treatment-specific pre-progression utility values were used even though differences in patient-reported outcomes between treatment arms were not tested for significance within the EV-302 trial. The higher utility value applied for enfortumab vedotin plus pembrolizumab was also inconsistent with a claim of inferior safety versus chemotherapy.

- The submission applied inaccurate drug and administration costs in the model, and there was erroneous inclusion of some adverse event disutility values and durations.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the model included aligning the proportion of avelumab maintenance use with the EV-302 trial, applying a more probable treatment duration for avelumab in the chemotherapy arm, revising health state utility values, and updating cost inputs. These changes increased the ICER to between SG$75,000 and SG$105,000 per QALY gained.

4.4. The Committee noted that based on scenario analyses of the revised base case, the key model drivers were the choice of parametric extrapolations for OS and the health state utility values. The ICERs remained unfavourably high across the scenarios.

4.5. Overall, the Committee considered that enfortumab vedotin plus pembrolizumab did not represent a cost-effective use of healthcare resources for untreated locally advanced or metastatic UC.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be between SG$5 million and SG$10 million in the first year, increasing to more than SG$10 million in the fifth year of listing enfortumab vedotin plus pembrolizumab on the MOH List of Subsidised Drugs for untreated locally advanced or metastatic UC.

5.2. The Committee considered that the submission estimates were uncertain and likely overestimated, due to an overestimation of patients with early-stage UC who eventually progress to locally advanced or metastatic disease, uncertainty in the proportion of patients who would receive first-line systemic treatment, application of a higher relative dose intensity for enfortumab vedotin based on earlier trial data, and overestimation of drug costs.

5.3. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, increasing to between SG$5 million and SG$10 million in the fifth year of listing enfortumab vedotin plus pembrolizumab. The Committee also considered that the submission's price-volume agreement (PVA) caps for enfortumab vedotin were unacceptably high and inadequate to provide budget certainty.

Recommendations

6.1. Based on the evidence submitted and the company's pricing proposal, the Committee indicated that enfortumab vedotin could be considered for listing on the MOH List of Subsidised Drugs contingent upon the company offering a revised pricing proposal that improves the ICER and provides budget certainty. The company subsequently submitted a revised proposal to address the Committee's concerns. Accordingly, the Committee recommended enfortumab vedotin 20 mg and 30 mg powder for concentrate for solution for infusion be listed on the Medication Assistance Fund (MAF) for untreated locally advanced or metastatic UC.

6.2. While enfortumab vedotin is indicated for use in combination with pembrolizumab for untreated locally advanced or metastatic UC, pembrolizumab for this indication is eligible only for MediShield Life claims, with no MAF assistance available.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indication	Subsidy class (implementation date)	Eligible for MediShield Life claims (implementation date)
Enfortumab vedotin 20 mg and 30 mg powder for concentrate for solution for infusion	Enfortumab vedotin in combination with pembrolizumab for untreated locally advanced or metastatic urothelial cancer	MAF (1 Sep 2026)	Yes[1] (1 Sep 2026)

Abbreviation: MAF, Medication Assistance Fund.
[1]Please refer to MOH's website for the MediShield Life claim limit starting from the implementation date.