CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Enfortumab vedotin (Padcev)

Indication: For the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor therapy.

Sponsor: Seagen Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: December 2021
Report Length: 16 Pages

Single Technology

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

ENFORTUMAB VEDOTIN (PADCEV — SEAGEN CANADA INC.)

Therapeutic Area: Locally advanced or metastatic urothelial carcinoma.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that enfortumab vedotin be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (UC) who have previously received a platinum-containing chemotherapy and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label phase III RCT (Study EV-301) comparing enfortumab vedotin to standard salvage chemotherapy with docetaxel, paclitaxel, or vinflunine in adult patients with locally advanced or metastatic UC who had received a platinum-containing chemotherapy and who had experienced disease progression or relapse during or following treatment with PD-1 or PD-L1 inhibitors, demonstrated that treatment with enfortumab vedotin resulted in added clinical benefit with a statistically significantly prolonged overall survival (HR: 0.702 [95% CI: 0.556, 0.886]; P = 0.00142) and progression-free survival (HR = 0.615, 95% CI: 0.505, 0.748; P < 0.00001) compared to chemotherapy. The confirmed overall response rate (ORR) was also statistically significant in favour of enfortumab vedotin with an ORR of 40.6% compared to 17.9% for chemotherapy (P < 0.001).

Patients identified a need for treatment options that could result in longer survival, longer remission, fewer severe side effects, and improved quality of life. pERC agreed there was considerable unmet need in this setting. Results of Study EV-301 suggested no difference between enfortumab vedotin and chemotherapy in measures of health-related quality of life (HRQoL), however, pERC considered the HRQoL results to be immature with low completion rates, thus no conclusions could be drawn on the effect of enfortumab vedotin on these outcomes based on the available evidence. Given the totality of the evidence, pERC concluded that enfortumab vedotin provides an effective treatment, in patients who have experienced disease progression on platinum-based chemotherapy and on PD-1 or PD-L1 inhibitors, that meets some of the needs identified by patients, including a need for treatments that halt disease progression and recurrence. pERC considered that enfortumab vedotin was associated with a significant but manageable toxicity profile.

Using the sponsor submitted price for enfortumab vedotin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for enfortumab vedotin was $506,439 per quality-adjusted life-year (QALY) compared with a taxane comparator (docetaxel or paclitaxel).

At this ICER, enfortumab vedotin is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adult patients with metastatic UC who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. A reduction in price of at least 93% is required for enfortumab vedotin to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Enfortumab vedotin should be reimbursed for adult patients (aged ≥18 years) with locally advanced or metastatic UC who have previously received the following treatments: 1.1. a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting; and 1.2. a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting	Evidence from Study EV-301 demonstrated that enfortumab vedotin resulted in significant improvements in OS, PFS and ORR in patients with locally advanced or metastatic UC who had previously been treated with a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, as well as a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting.
2. Patients should have a good performance status	The CADTH review identified no evidence to demonstrate the benefit of enfortumab vedotin in patients with an ECOG PS greater than 1. Based on the clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.
3. Treatment with enfortumab vedotin should not be initiated in patients with: 3.1. Preexisting grade 2 or higher sensory or motor neuropathy or ongoing clinically significant toxic effects associated with previous treatment. 3.2. Active CNS metastases, uncontrolled diabetes, or active keratitis or corneal ulcerations	This condition reflects the exclusion criteria from Study EV-301. The CADTH review did not identify any evidence to demonstrate the safety and potential benefits in patients with these conditions.
Renewal	
4. Patients should be assessed by the treating physician prior to each treatment cycle with diagnostic imaging conducted every 2 to 3 months.	Imaging assessments for Study EV-301 were performed every 56 days (approximately every 2 months) from the first dose of study treatment throughout the study until radiological disease progression. According to the clinical expert input, in clinical practice, patients would be assessed for toxicity and clinical progression monthly (at each treatment cycle), with imaging assessments conducted every 2 to 3 months.
Discontinuation	
5. Enfortumab vedotin should be discontinued in patients with either of the following: 5.1. Documented disease progression 5.2. Unacceptable toxicity	In Study EV-301, enfortumab vedotin was discontinued based on disease progression (as per RECIST v1.1) or unacceptable toxicity. No additional evidence was identified that support continuing treatment in patients whose disease has progressed. .
Prescribing	
6. Enfortumab vedotin should only be prescribed by clinicians with experience and expertise in treating advanced UC in centres with expertise in the administration of IV drugs with the potential for extravasation, and pharmacy resources to monitor drug interactions.	To ensure that enfortumab vedotin is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner. Given the known complications associated with enfortumab vedotin administration, treatment must be administered in centers where there is experience using a drug at risk for extravasation.

Reimbursement Condition	Reason
7. Enfortumab vedotin should not be used in combination with other drugs.	Enfortumab vedotin was administered as monotherapy in Study EV-301; the CADTH review identified no evidence on the safety and potential benefits of combining enfortumab vedotin with any other treatments.
Pricing	
8. A reduction in price	The ICER for enfortumab vedotin is $506,439 when compared with taxanes. A price reduction of 93% would be required for enfortumab vedotin to be able to achieve an ICER of $50,000 per QALY compared to a taxane.
Feasibility of Adoption	
9. The feasibility of adoption of enfortumab vedotin must be addressed	At the submitted price, the budget impact of enfortumab vedotin is expected to be greater than $40 million in year 3 and overall 3-year budget impact to be $99 million. Furthermore, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER; incremental cost-effectiveness ratio; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS= progression-free survival; ORR = overall response rate; OS = overall survival; QALY = quality-adjusted life years; RECIST= Response Evaluation Criteria in Solid Tumours; UC = urothelial carcinoma

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2. Implementation Guidance from pERC

Condition # from Table 1	Implementation Considerations and Guidance
1	pERC agreed with the clinical expert consulted by CADTH that patients who are not candidates for platinum-based chemotherapy due to comorbidities, and who may have received alternate non-platinum based or single agent chemotherapy, would not be eligible to receive enfortumab vedotin; however, there may be case-by-case exceptions made for patients who are not eligible for platinum chemotherapy. In this case, immunotherapy should be given first, followed by enfortumab vedotin.
1	Based on the input received from the clinical expert consulted by CADTH, pERC agreed that patients who have received platinum-based chemotherapy but did not receive PD-1or PD-L1 inhibitors due to contraindications, would not be eligible for enfortumab vedotin; however, there might be exceptions made for patients with contraindications to immunotherapy.
1	pERC also agreed with the clinical expert consulted by CADTH that patients who have permanently discontinued immunotherapy for toxicity reasons would not be eligible to switch to enfortumab vedotin before experiencing disease progression. Initiation of enfortumab vedotin should be in line with Study EV-301, where patients who discontinued checkpoint inhibitor treatment due to toxicity were required to have evidence of disease progression following discontinuation.
3	PERC agreed that patients with CNS metastases can be treated if they have stable brain metastases prior to treatment on baseline scans. Patients with leptomeningeal disease should not be treated with enfortumab vedotin.
5	pERC noted that decisions to discontinue treatment should be made in consultation with the patient and generally consist of progressive disease, worsening symptoms, dose-limiting toxicity resulting in intolerable

Condition # from Table 1	Implementation Considerations and Guidance
	serious adverse events, patient wishes to discontinue treatment for personal reasons, or deterioration to end of life.
6	Input from public drug programs indicated that vial sharing is not expected given the enfortumab vedotin vial sizes (i.e., 20 mg and 30 mg vials) and the size of the patient population, and it is anticipated that drug wastage will occur, especially at the maximum dose of 125 mg/kg. Using small (20 mg) vial sizes may minimize wastage; however, additional pharmacy resources would be required to reconstitute a higher number of vials for final preparation. Input from public drug plans also noted that administration of weekly doses is more labour-intensive and would require frequent patient visits. In addition, treatment may need to be administered at facilities where sterile compounding pharmacies are nearby or on-site. pERC acknowledged the issues around drug wastage and administration of enfortumab vedotin and noted that these issues may be unavoidable given the patient population, the drug vial sizes, and the chemical/physical instability of the prepared compound.

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; pERC = pCODR Expert Review Committee

Discussion Points

- Evidence from Study EV-301 showed that enfortumab vedotin was associated with a significantly prolonged OS, with a median OS of 12.88 months for enfortumab vedotin compared to 8.97 months with chemotherapy (HR: 0.702 [95% CI: 0.556, 0.886]). Though statistically significant, pERC considered the results for OS moderate, which was a concern given that Study EV-301 was stopped early for efficacy based on an information fraction of 68.6%; thus, the moderately meaningful OS benefit seen might be an overestimation of the true benefit that could be conferred by enfortumab vedotin. Results for PFS and ORR were consistent with the primary endpoint. However, pERC noted that there are no treatments for patients that have failed platinum-based chemotherapy and experienced disease progression on PD-1 or PD-L1 inhibitors that has demonstrated improved survival; thus, the committee considered the benefit of OS and PFS to be clinically meaningful.
- Safety results from Study EV-301 were deliberated by pERC. The incidence of serious adverse events (SAEs) was higher in the enfortumab vedotin arm compared to taxane chemotherapy (46.6% vs. [redacted]). Notable harms of skin reactions, peripheral neuropathy, and ocular disorders were more frequent in the enfortumab vedotin arm compared to the taxane chemotherapy group (53.7% vs. [redacted], 50.3% vs. [redacted], and 28.0% vs. [redacted], respectively). pERC also considered the potential requirement for regular ophthalmological examinations due to the ocular disorders associated with enfortumab vedotin; however, it was noted that these conditions are generally treatable using readily available eye medications.
- The patient group input submitted for this review indicated that patients desire treatments with a reduced incidence of treatment-related infections. pERC noted that the occurrence of infections was low in Study EV-301 and overall, agreed that the safety profile of enfortumab vedotin was manageable. Patients also noted the avoidance of surgery as an important outcome. Based on the clinical expert opinion, pERC concluded that for the current indication enfortumab vedotin would have no impact on the avoidance of cystectomy because cystectomy is expected to occur prior to the administration of enfortumab vedotin for the patient population under review.
- The comparator used in Study EV-301 was standard chemotherapy consisting of paclitaxel, docetaxel, or vinflunine which generally aligns with the recommended standard of care guidelines in Canada. However, vinflunine is not available as a treatment option in the current Canadian clinical practice and, therefore, the trial results for the chemotherapy arm should be interpreted after taking the proportion of patients who received this treatment into consideration. In Study EV-301, vinflunine was administered to 75 (25.8%) patients in the chemotherapy arm. However, pERC felt that this would not affect the overall interpretation of the study results.
- pERC considered the sequencing of treatments given the newly recommended listing for avelumab as maintenance therapy following the first-line platinum-based chemotherapy in the locally advanced or metastatic setting. As per the eligibility criteria of Study EV-301, patients are required to fail platinum-containing chemotherapy, and PD-1/PD-L1 inhibitor therapy. pERC noted that unless there is a re-treatment with a PD-1/PD-L1 inhibitor, patients would fulfill the eligibility criteria for treatment with enfortumab vedotin, thus a significant portion of patients would be eligible to receive enfortumab vedotin as second-line therapy. Conversely, it was also noted that if the treatment-free interval is of sufficient length following treatment with

avelumab maintenance therapy, second-line treatment with a PD-1/PD-L1 inhibitor (i.e., pembrolizumab) would be justified prior to enfortumab vedotin.

- pERC discussed the public drug plans' request for clarification on whether erdafitinib could be considered as a relevant comparator in patients with *FGFR* genetic alterations who have previously received PD-1 or PD-L1 inhibitors and chemotherapy. pERC considered this issue to be out of scope of the current review.
- pERC discussed the patient-reported outcomes from Study EV-301 and noted that there was no difference in HRQoL between treatment groups throughout the trial. Given the limitations associated with the HRQoL results from Study EV-301, including immature data and low completion rates, pERC was unable to comment with certainty on the impact of enfortumab vedotin on HRQoL.
- pERC discussed that there would be no need for diagnostic testing for Nectin-4 in this population, given that Nectin-4 is not a prognostic or predictive factor. Based on the clinical expert opinion, greater than 90% of patients with UC express this cell surface antigen.
- Approval of enfortumab vedotin may introduce concerns about feasibility of adoption. The estimated budget impact in year 3 is greater than $40 million, a value identified by participating plans as unaffordable. Additionally, there is a high degree of uncertainty evident in the difference between the sponsor's estimate of the 3-year budget impact ($35,386,568) and the value estimated by CADTH ($99,379,089). These findings are driven by assumptions about enfortumab vedotin's market share.

Background

Enfortumab vedotin has a Health Canada indication for the treatment of adult patients with unresectable locally advanced or metastatic UC who have previously received a platinum-containing chemotherapy and PD-1 or PD-L1 inhibitor therapy.

Enfortumab vedotin is a fully human immunoglobulin G1K antibody and microtubule-disrupting agent monomethyl auristatin E (MMAE) antibody-drug conjugate (ADC) via a protease-cleavable linker directed against Nectin-4. It is available as 20 mg and 30 mg single-use vial lyophilized powder for solution for IV infusion only, at a dose of 1.25 mg/kg (up to a maximum for 125 mg for patients ≥100 kg) administered as an IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 open-label, phase III RCT in locally advanced or metastatic urothelial cancer
- Patients' perspectives gathered by patient groups, Bladder Cancer Canada
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- One clinical specialist with expertise diagnosing and treating patients with locally advanced or metastatic urothelial cancer
- Input from 2 clinician groups, including Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee, and a group of 17 Canadian physicians who treat bladder cancer
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient advocacy group; Bladder Cancer Canada (BCC) provided input for the review of enfortumab vedotin in locally advanced/metastatic UC. Bladder Cancer Canada is a nationally registered Canadian charity and is the first and only Canadian patient advocacy organization dedicated to bladder cancer issues. Supported by a Medical Advisory Board and a Medical Research Board consisting of the top bladder cancer specialists across Canada, its mission aims to help bladder cancer patients and their support teams address the day-to-day issues of this disease; increase awareness among the public and medical community; and

fund research into the diagnosis, treatment, and elimination of the disease. BCC's vision is patient support, awareness, and research to create a world where bladder cancer is "just a memory".

The information provided by BCC was gathered through an online survey and telephone interviews conducted between May 27 and June 11, 2021. Most survey respondents were from Canada, with a small number from the United States. Additionally, telephone interviews were conducted in June 2021 with two patients from Canada who had experience with enfortumab vedotin. In total, 38 patients and 6 caregivers diagnosed with or caregiver to someone diagnosed with Stage II or higher muscle-invasive bladder cancer, of which one-third of patients reported living with locally advanced or metastatic bladder cancer, completed the survey.

Many patients and caregivers reported that symptoms of bladder cancer including fatigue, lack of sleep, and loss of strength and stamina were problematic, but manageable, while some patients indicated that having bladder cancer has had a minimal impact on their day-to-day lives. Additional symptoms including blood in the urine, pain in the abdomen and bones, decreased mobility and difficulty/pain when urinating were also commonly reported. Issues related to continence including frequent need for urination and loss of control, urostomy and catheter management, and urinary tract infections were the most commonly reported to impact day-to-day life of patients which resulted in additional planning, discomfort, and time lost. Moreover, financial impacts related to the costs of catheter and urostomy supplies that are not covered by some provincial governments were reported to impact the already limited financial resources of patients and caregivers.

Patients cited experiencing a number of side effects with current treatments including fatigue, constipation, low blood cell count, loss of appetite, neuropathy, nausea/vomiting, hair loss, insomnia, diarrhea, and mouth sores. Most patients also reported that there were minimal barriers to access treatment for their bladder cancer, however, some mentioned they did have difficulties due to travel distance, treatment cost, unavailability of treatment in Canada, no access to a physician, and requiring time off work to receive treatment. Two patients had experience with enfortumab vedotin through a clinical trial. Patients noted that side-effects of treatment with enfortumab vedotin were temporary and manageable compared to previous treatments received. When asked what key values about enfortumab vedotin have been important to them as patients, they said that the treatment has given them their "life back again" – allowing them to resume the activities that they enjoy. Patients with experience with enfortumab vedotin highlighted the importance to have publicly funded access for this treatment.

Overall, patients and caregivers hoped for fewer and less severe side effects than those experienced with current bladder cancer treatments, as well as treatments that induced remission or were curative. Specifically, patients cited that new treatments would ideally slow or stop disease progression, recurrence and spread, reduce pain, fatigue, and impaired sexual function, increase energy levels/strength, improve mental health, continence/urination control, and result in fewer/no infections and avoidance of surgery.

Clinician Input

Input from Clinical Experts Consulted by CADTH

In patients with incurable locally advanced/metastatic UC, the clinical expert identified an unmet need for an effective third-line treatment option after progression with platinum chemotherapy and a PD-1/PD-L1 inhibitor. The mainstay of treatment for incurable patients is cytotoxic platinum-based chemotherapy with gemcitabine with or without cisplatin. Maintenance avelumab was reported to show an overall survival (OS) benefit and is likely to become a funded standard of care. Pembrolizumab is now a funded second-line standard of care in Canada following demonstration of a survival benefit after progression despite first line chemotherapy, displacing second-line taxane therapy. The only options following immunotherapy are paclitaxel and docetaxel which have modest response rates and treatment durations, and enfortumab vedotin would provide a new option to taxane therapy. The clinical expert noted that identifying patients who would respond to enfortumab could not be done, and that patients at this stage are typically under the care of expert medical oncologists, who would be able to identify progressive disease to initiate new treatment. Response to treatment would rely on improvement in symptoms, which would be assessed prior to treatment and/or evidence of objective tumor shrinkage on imaging. The clinical expert also stated that there are additional adverse events with enfortumab vedotin that may require assessment by ophthalmologists or dermatologists.

Clinician Group Input

Two clinicians from the Ontario Health (Cancer Care Ontario) (OH-CCO) Genitourinary Cancer Drug Advisory Committee and a group of Canadian physicians (total 17) who treat bladder and who, with the support of Bladder Cancer Canada, a Canadian patient advocacy organization dedicated to bladder cancer issues (https://bladdercancercanada.org/en/), provided input for this review. The OH-CCO's Drug Advisory Committees provides timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program. On the other hand, the group of Canadian physicians represent the specialty from across Canada in both academic and community settings and share Bladder Cancer Canada's goal to improve the management of bladder cancer.

The clinicians agreed that there was no standard of care for patients with advanced urothelial cancer post-platinum chemotherapy, post-immunotherapy, representing an unmet need in these patients. Enfortumab vedotin is indicated in the third-line setting. Alternative third-line options would be non-platinum chemotherapy, for which there is little evidence of efficacy and for which the toxicity rate is much higher, or FGFR-targeted therapy, which would not be favoured for the reasons of unavailability of FGFR testing in Canada. Experts agree that enfortumab vedotin will redefine the current treatment paradigm as other than taxanes, which are associated with significant toxicity, there are no other beneficial therapies in this setting. Offering enfortumab vedotin to all eligible patients would provide them with hope for improved life expectancy with tolerable side effects. The clinician group stated that throughout treatment, patients would be assessed for toxicity and clinical progression every month, with imaging every 2 to 3 months. Blood work should be performed prior to each treatment cycle, and patients should be seen by their treating oncologist following each cycle. Patients with disease that has metastasized to the bones should also have a bone scan. When considering treatment discontinuation, the clinician group noted that decisions to discontinue treatment should be made in consultation with the patient and would include progressive disease, worsening symptoms, severe adverse events, deterioration to end of life, dose-limiting toxicity resulting in intolerable adverse effects such as significant neuropathy, or the patient wishes to discontinue treatment for any number of personal reasons.

Although no marked experience with enfortumab vedotin was mentioned, the clinicians consider this drug of great importance in the management of bladder cancer, filling an unmet need for patients requiring treatment following progression on platinum-based chemotherapy and immunotherapy. The approval of enfortumab vedotin would give medical oncologists an option to offer to patients with advanced urothelial cancer that has progressed on first- and second-line therapy. Enfortumab vedotin offers significant overall survival benefit compared to taxane chemotherapy, with tangible benefits for patients. Enfortumab vedotin would offer a longer life expectancy with preservation of quality of life, as the drug is generally well tolerated. For a patient population with such a poor prognosis, the inclusion of enfortumab vedotin in the treatment algorithm has the potential to significantly improve the outcomes associated with bladder cancer.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 3. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
Erdafitinib is approved by Health Canada for patients with metastatic UC whose tumors have FGFR genetic alterations, and who have disease progression during or following at least 1 line of prior chemotherapy and may be available through a manufacturer patient support program but has not been reviewed by CADTH yet and is not publicly funded. Erdafitinib could also be considered a relevant comparator in patients with FGFR genetic alterations for patients previously treated with PD-1/PD-L1 inhibitors and chemotherapy.	This issue was considered to be out of scope for the current review of enfortumab vedotin.
Considerations for Initiation of Therapy	
Some patients may not be candidates for platinum-based chemotherapy due to comorbidities and may have received alternate non-platinum based or single agent chemotherapy. Should patients who have not received previous platinum-based chemotherapy be eligible for enfortumab vedotin?	pERC agreed with the clinical expert consulted by CADTH that these patients would not be eligible for enfortumab vedotin, however, there may be case-by-case exceptions made for patients who are not eligible for platinum chemotherapy. In such cases, immunotherapy should be given first, followed by enfortumab vedotin.
Some patients may have a contraindication or may not be candidates for immunotherapy or experience immune toxicity necessitating discontinuation of immunotherapy. Should patients who received platinum-based chemotherapy, but did not receive PD-1/PD-L1 inhibitors be eligible for enfortumab vedotin?	pERC agreed with the clinical expert consulted by CADTH that these patients would not be eligible to receive enfortumab vedotin, however, there might be exceptions made for patients with contraindications to immunotherapy.
Should patients who have immunotherapy permanently discontinued for toxicity reasons be eligible for enfortumab vedotin at the time of disease progression or could they be switched to enfortumab vedotin before disease progression?	pERC agreed with the clinical expert consulted by CADTH that initiation of enfortumab vedotin should be in line with the EV-301 study, where patients who discontinued checkpoint inhibitor treatment due to toxicity were eligible for enfortumab vedotin provided that they had evidence of disease progression following discontinuation.
Considerations for prescribing of therapy	
The dosing of enfortumab vedotin is 1.25 mg/kg IV over 30 minutes on Days 1, 8, 15 every 28 days (maximum dose of 125 mg for patients >100 kg) until disease progression or unacceptable toxicity. Weekly dosing is more labour-intensive and requires frequent patient visits for administration.	pERC noted that the dosing schedule should follow what is used the EV-301 study, although it may be burdensome.
Skin and soft tissue injury following administration has been observed when extravasation occurred. It is important to ensure good venous access prior to starting the infusion and the infusion site should be monitored for extravasation during administration. If extravasation occurs, it is recommended to stop the infusion and monitor for adverse reactions. Enfortumab vedotin should only be administered by staff trained to manage extravasations of vesicants/irritants in appropriate facilities.	pERC noted the importance of administering enfortumab vedotin in treatment centers where there is experience using a drug at risk for extravasation.
Generalizability	
The eligibility criteria in the EV-301 study included patients with an ECOG PS of 0 or 1. Should patients with an ECOG PS >1 be eligible for enfortumab vedotin?	pERC agreed with the clinical expert consulted by CADTH that selected patients with an ECOG PS of 2 could be considered for treatment with enfortumab vedotin, at the discretion of the treating physician.

Implementation Issues	Response
Patients currently receiving taxanes or alternate chemotherapy would have a time-limited opportunity to switch to enfortumab vedotin. Should patients receiving these treatments be switched to enfortumab vedotin at the time of public funding, or would they be eligible after disease progression on these treatments?	pERC agreed with the clinical expert that, in the absence of disease progression, the decision to switch therapies should be based on discussion with the patient and physician. However, after disease progression, the patient may be switched to enfortumab vedotin, if otherwise eligible.
Care provision issues	
PAG notes that enfortumab vedotin is available in single-use vials of 20 mg and 30 mg. Vial sharing is not expected due to the size of the patient population, and it is anticipated that drug wastage will occur, especially at the maximum dose of 125 mg. The vial sizes do not match the maximum dose at some dosing levels (1.25 mg/kg up to 125 mg; 1.0 mg/kg up to 100 mg; 0.75 mg/kg up to 75 mg; 0.5 mg/kg up to 50 mg) so there is wastage expected with doses. Also, the vial sizes are small relative to the usual starting dose, so there is a resource impact (e.g., 125 mg dose requires 3 x 30 mg + 2 x 20 mg to minimize wastage but requires 5 vials to reconstitute and dilute to final preparation, so there is an impact on Pharmacy resources). PAG also notes the chemical/physical stability of the final preparation is limited (16 hours - refrigerated), thus treatment will likely need to occur at facilities where sterile compounding pharmacies are nearby or on-site.	pERC agreed that vial sharing will not be an option, and that enfortumab vedotin will be limited to treatment centers where sterile compounding pharmacies are nearby or on-site.
The draft product monograph states that no dose adjustments are required for patients with mild hepatic impairment, mild to severe renal impairment or with concomitant use of strong inhibitors of CYP3A4. However, it is noted in drug information databases that strong inducers or inhibitors of CYP3A4 may decrease or increase the serum concentration of enfortumab vedotin. PAG notes there is the potential for clinically significant drug-drug interactions with strong CYP3A4 inducers/inhibitors, which may impact Pharmacy resources for identification, monitoring and resolution of these drug-drug interactions.	pERC noted that administering enfortumab vedotin and monitoring patients must be done in multidisciplinary treatment centers with adequate pharmacy facilities and resources.
System and economic issues	
The number of patients eligible for enfortumab vedotin in Canada (excluding Quebec) was estimated by the manufacturer at 388 for Year 1, 461 for Year 2 and 534 for Year 3, for a total of 1,382 patients over the three-year period. The manufacturer BIA estimates $5,950,573 in Year 1, $12,707,014 in Year 2, and $21,272,715 in Year 3, for a total of $39,930,302 over the 3-year projection period. The BIA predicts that funding of enfortumab vedotin for the treatment of la/mUC would result in incremental costs of $4,804,551 in Year 1, $11,347,174 in Year 2, $19,696,563 in Year 3, for a total incremental cost of $35,848,288 over the 3-year projection period. This is based on market share estimates of 15%, 30% and 45% for Years 1 to 3 in the second- line setting, and 25%, 40% and 55% for Years 1 to 3 in the third-line setting.	pERC considered the budget impact to be underestimated, anticipating enfortumab vedotin to become the standard of care in the third-line setting, and considers the CADTH reanalysis more appropriate. pERC noted that CADTH's estimate of the BIA is above a threshold identified by drug plans as presenting concerns for feasibility of adoption. pERC further noted the presence of meaningful uncertainty surrounding the estimated budget impact, given the difference between the sponsor's estimate ($39,930,302) and CADTH's estimate ($99,379,089).

Implementation Issues	Response
PAG is concerned that the market share and BIA may be underestimated, resulting in a substantially higher budget impact.	

BIA = budget impact analysis; ECOG = Eastern Cooperative Oncology Group; la/mUC = locally advanced/metastatic urothelial carcinoma; PAG = Provincial Advisory Group; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; PS = performance status.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Study EV-301 was a global, open-label, phase III randomized controlled trial (RCT) comparing enfortumab vedotin to standard salvage chemotherapy regimens in adults with locally advanced or metastatic UC who had received a platinum-containing chemotherapy and who had experienced disease progression or relapse during or following treatment with PD-1 or PD-L1 inhibitors. Patients were randomized 1:1 to receive enfortumab vedotin (n = 301) 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle, or standard chemotherapy consisting of paclitaxel, docetaxel, or vinflunine (n = 307) on day 1 of each 21-day cycle until disease progression. The primary endpoint of the EV-301 study was OS, with secondary endpoints of progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and health-related quality of life (HRQoL).

Baseline characteristics of the EV-301 trial were well balanced between treatment groups, however, may have enrolled a healthier group of patients with a younger median age and lower Eastern Cooperative Oncology Group (ECOG) performance status (PS) compared to the Canadian population. In Study EV-301, patients were mostly white (51.6%), male (77.3%), with a median age of 68 years. Most patients were ECOG 1 (59.9%) and had metastatic disease (95.2%).

Efficacy Results

In the final primary efficacy analysis of Study EV-301, the median OS was 12.88 months (95% CI: 10.58, 15.21) in the enfortumab vedotin arm, and 8.97 months (95% CI: 8.05, 10.74) in the chemotherapy arm. Enfortumab vedotin was associated with a statistically significantly prolonged OS compared to chemotherapy (HR: 0.702 [95% CI: 0.556, 0.886]; P = 0.00142). Results for all sensitivity and subgroup analyses were consistent with the primary analysis.

The secondary endpoint of PFS was in line with the primary endpoint. Enfortumab vedotin was associated with a statistically significantly prolonged PFS compared to chemotherapy (HR = 0.615, 95% CI: 0.505, 0.748; P < 0.00001), with a median PFS of 5.55 months (95% CI: 5.32, 5.82) in the enfortumab vedotin arm, and 3.71 months (95% CI: 3.52, 3.94) in the chemotherapy arm. Sensitivity and subgroup analyses for PFS were consistent with the overall analysis.

Health-related quality of life was assessed by the EORTC QLQ-C30 and EQ-5D and was a secondary outcome of Study EV-301. In the enfortumab vedotin arm, change in scores from baseline to week 12 for functional scales of the EORTC QLQ-C30 ranged from 2.17 (SD: 16.20) for emotional functioning to -5.12 (SD: 23.80) for social functioning. In the chemotherapy arm, change from baseline scores at week 12 ranged from 3.27 (SD: 18.06) in emotional functioning to -9.15 (SD: 26.29) in role functioning. For symptom scores in the enfortumab vedotin arm, the change from baseline at week 12 ranged from 5.77 (SD: 32.56) for appetite loss to -6.96 (SD: 26.26) for pain, while in the chemotherapy arm, scores ranged from -1.63 (SD: 27.90) for insomnia to 6.64 (SD: 22.56) for fatigue. For the EQ-5D, the mean change from baseline to week 12 for the visual analog scale (VAS) was -1.8 (SD: 16.6) for enfortumab vedotin, and -5.3 (14.5) for the chemotherapy arm.

Overall response rate was a secondary outcome of Study EV-301. The confirmed ORR was statistically significant in favour of enfortumab vedotin with an ORR of 40.6% compared to 17.9% for the chemotherapy arm (P < 0.001). A total of 4.9% and 35.8% of patients achieved confirmed complete response (CR) and partial response (PR) in the enfortumab vedotin arm, respectively compared to 2.7% and 15.2% in the chemotherapy arm. Results for sensitivity and subgroup analyses for ORR were comparable to the primary analysis.

Harms Results

The overall incidence of treatment-emergent adverse events (TEAEs) was consistent between enfortumab vedotin (98.0%) and taxane chemotherapy arms [redacted], however, there were imbalances in the specific TEAEs experienced in either arm, with differences ≥5% for enfortumab vedotin in 15 preferred term TEAEs. The incidence of serious adverse events (SAEs) was higher in the enfortumab vedotin arm compared to taxane chemotherapy (46.6% vs. [redacted]), with acute kidney injury occurring most frequently in the enfortumab vedotin arm (6.4% vs. [redacted]), and febrile neutropenia occurring most frequently with taxane chemotherapy (1.4% vs. [redacted]). Withdrawals due to adverse events (WDAEs) and TEAEs resulting in death were similar between enfortumab vedotin and taxane chemotherapy group (17.2% vs. [redacted], and 7.1% vs. [redacted], respectively). The most common reason for WDAE was peripheral sensory neuropathy occurring in 2.4% and [redacted] of patients in the enfortumab vedotin and taxane chemotherapy groups.

The incidence of notable harms including infusion-related reactions (IRR), ocular disorders, skin reactions, and peripheral neuropathy was generally more frequent in the enfortumab vedotin arm than chemotherapy arm. Infusion-related reactions were the least frequently occurring group of notable harms in 9.1% vs. [redacted] of patients in the enfortumab vedotin and taxane chemotherapy group, respectively. Drug eruption was the most common IRR with enfortumab vedotin (5.7% vs. [redacted]), while general systemic IRR was most frequent in the taxane chemotherapy arm (1.4% vs. [redacted]). Incidence of treatment-emergent ocular disorders was higher in the enfortumab vedotin arm compared to the taxane chemotherapy group (28.0% vs. [redacted]), the most frequent being increased lacrimation (10.1% vs. [redacted]), dry eye (6.4% vs. [redacted]), and conjunctivitis (6.4% vs. [redacted]). Skin reactions were more frequent in the enfortumab vedotin arm (53.7%) compared to the taxane chemotherapy group ([redacted]). The most frequently occurring skin reactions were rash (16.9% vs. [redacted]), maculopapular rash (16.9% vs.[redacted]), stomatitis (9.1% vs. [redacted]), and drug eruption (8.8% vs. [redacted]). Peripheral neuropathy events occurred in 50.3% and [redacted] of patients in the enfortumab vedotin and taxane chemotherapy group, respectively. The majority of notable harms were of mild to moderate severity.

Critical Appraisal

Study EV-301 was a phase III, open-label RCT. In general, patients in the two treatment arms did not differ with regards to baseline disease or treatment characteristics, indicating that randomization was successful. The reviewers and the clinical expert consulted by CADTH agreed that the open-label design used was appropriate; however, noted that this could potentially increase the risk of bias in the reporting of outcomes that are subjective in measurement and interpretation such as response, HRQoL, and adverse events (AEs). The primary endpoint of OS is an objective endpoint, and unlikely to be affected by biases of open-label study designs. Secondary endpoints of PFS and ORR are subjective, and therefore subject to potential bias. Reporting of patient-rated outcomes, such as symptom reduction and HRQoL, and some of the harms outcomes may have been biased or influenced by the patient or investigators' knowledge of treatment assignment. All study outcomes were investigator-assessed and did not include full evaluation via an independent review committee to mitigate the biases associated with the open-label study design. Discontinuation rates were higher in the chemotherapy arm (81.4% vs. 92.8%), while the rate of discontinuation due to disease progression was nearly identical (58.8% vs. 58.6%), which may reflect the open-label design, given that the reason for discontinuation due to patient and physician decision were higher in the chemotherapy arm. The study was stopped early for efficacy based on a statistically significant result for OS in favour of enfortumab vedotin. Trials that stop early for benefit may typically show a higher/better treatment effect estimate in the intervention group; however, given that the primary endpoint of the study, OS, was not subjective, the review teams' concerns were minor. That said, the primary analysis was conducted early based on the information fraction (68.6%) suggesting an increased, and notable risk of over-estimation.

In discussion with the clinical expert consulted by CADTH, the inclusion and exclusion criteria for Study EV-301 were generally as expected for patients with locally advanced/metastatic UC, however it was hypothesized that the patients included in the trial may reflect a 'less sick' population than would be seen in the real world. The median age of 68 years as noted by the clinical expert to represent a younger population than expected. Additionally, the clinical expert also considered the ECOG PS of patients to be unreflective of patients at this stage of disease, as most patients would not be ECOG 0 or 1 (ECOG 0: 40.1%, ECOG 1: 59.9%). The chosen comparator of standard chemotherapy generally aligns with the recommended standard of care guidelines in Canada, however, vinflunine is not a treatment option available in Canadian clinical practice, and therefore any aggregate results for the chemotherapy arm need to consider the proportion of patients that may have received this treatment. In discussion with the clinical expert, it was noted that this may not affect efficacy outcomes but would impact the results for safety. Given the known differences in safety profiles of enfortumab vedotin, taxanes, and vinflunine, safety results must be interpreted with caution, and may not be

generalizable. The high rate of dropouts in completion of the patient-reported outcome measures should also be taken into account when interpreting the results.

Indirect Comparisons

No indirect evidence was included in the sponsor's submission to CADTH or identified in the literature search that matched the inclusion and exclusion criteria of this review.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Adult patients with mUC previously treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor, which is consistent with the reimbursement request
Treatment	Enfortumab vedotin
Submitted price	Enfortumab vedotin, 20 mg vial: $1,181.00 Enfortumab vedotin, 30 mg vial: $1,772.00
Treatment cost	28-day cost of $19,491
Comparator	A combined taxane comparator consisting of docetaxel and paclitaxel (DP)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	Clinical efficacy was modelled using the overall survival (OS), progression-free survival (PFS), and duration of treatment (DoT) observed in the EV-301 trial. This trial was also used to generate health state utility values based on the EQ-5D and to estimate the incidence of relevant adverse events (AEs).
Key limitations	• The sponsor's choice of parametric survival function overestimated the survival of patients with mUC with their parametric OS extrapolation. • The sponsor's use of treatment-specific utilities is inappropriate and fails to explicitly model disutilities due to AEs. • The use of a relative dose intensity (RDI) potentially underestimates drug costs as RDI considers dose delays, reductions, escalations, and other factors which may not correlate directly with drug costs. Furthermore, there is uncertainty surrounding how wastage considerations might affect the calculation of RDI.
CADTH reanalysis results	• CADTH made several changes to derive the base case including using a Gompertz parametric function to estimate OS, shortening the time horizon to 5 years, using health state utilities, and excluding consideration of RDI. • Based on the CADTH base case, enfortumab vedotin was associated with an ICER of $506,439 per QALY, and the probability of cost-effectiveness at a $50,000 per QALY threshold was 0%. A price reduction of 93% would be required to achieve cost-effectiveness at this threshold. • Scenario analyses were performed to assess other aspects of uncertainty surrounding RDI assumptions, taxane prices, and treatment-specific utilities. When considering the sponsor's RDI assumptions, this resulted in an ICER of $412,286 per QALY. The analysis in which OS was modelled using independent Gompertz functions resulted in an ICER of $687,056. Other analyses had limited impact on the ICER.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the market shares for enfortumab vedotin were underestimated, median treatment durations were used rather than mean, and RDIs were included for all drugs which are associated with uncertainty. CADTH reanalysis increased the market shares for enfortumab vedotin, used mean treatment duration, and assumed RDIs of 100%. In the CADTH base case, the budget impact is expected to be $20,806,133 in year 1, $32,299,559 in year 2, and $46,273,397 in year 3, with a three-year total of $99,379,089. CADTH found the budget impact to be sensitive to market share and RDI assumptions. Moreover, the eligible patient population size in this analysis is dependent on the number of patients progressing on avelumab maintenance therapy. As avelumab is not yet funded and the optimal maintenance duration is unknown, it is unclear how many patients would be eligible for treatment post-avelumab maintenance within the time horizon of this BIA.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan, Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: November 10, 2021

Regrets

None

Conflicts of Interest

None