CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Tebentafusp (Kimmtrak)

Indication: For the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma

Sponsor: Medison Pharma Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: December 2022
Report Length: 20 Pages

Single Technology

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

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that tebentafusp be reimbursed for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (mUM) in the first line setting only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, open-label, randomized controlled study (Study 202; N = 378) demonstrated that treatment with tebentafusp resulted in added clinical benefit for HLA-A*02:01-positive adult patients with mUM who had no prior systemic therapy in the advanced or metastatic setting. In the first overall survival (OS) interim analysis, Study 202 showed a statistically significant and clinically meaningful improvement in OS with tebentafusp compared to investigator's choice of either dacarbazine, pembrolizumab, or ipilimumab (hazard ratio [HR] = 0.51; 95% confidence interval [CI], 0.37 to 0.71; P <0.0001). Health-related quality of life (HRQoL) was assessed but not formally compared between the treatment groups in the trial; however, the available evidence suggested that there were no notable differences in HRQoL (measured using the EORTC QLQ-C30) observed between the tebentafusp and investigator's choice arms in Study 202. Tebentafusp was associated with a risk of cytokine release syndrome and dermatological adverse events. pERC acknowledged that while not insignificant, these adverse events are transient and manageable with monitoring in an inpatient setting for initial doses, supportive care, and dose adjustment. Tebentafusp addresses an unmet therapeutic need for this rare condition given the poor prognosis and high morbidity, and lack of standard of care or effective alternatives.

Patients expressed a need for treatment that can preserve vision, provide a good quality of life, and improve survival. Given the totality of the evidence, pERC concluded that tebentafusp met the unmet need for a treatment that prolonged survival, as identified by patients.

Using the sponsor submitted price for tebentafusp and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tebentafusp was $728,513 per quality-adjusted life-year (QALY) gained compared with investigator's choice of therapy. At this ICER, tebentafusp is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for previously untreated adults with HLA-A*02:01-positive advanced (metastatic or unresectable) uveal melanoma. A price reduction is required for tebentafusp to be considered cost-effective at this threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with tebentafusp should be reimbursed when initiated in adult patients who have HLA-A*02:01-positive unresectable or metastatic uveal melanoma in the first line setting	Evidence from Study 202 demonstrated that treatment with tebentafusp resulted in statistically significant and clinically meaningful improvement in OS, compared with investigator's choice of ipilimumab, pembrolizumab, or dacarbazine, in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma in the first-line setting.	It would be reasonable for jurisdictions to consider reimbursement of tebentafusp in a second- or later- line setting on a time-limited basis.
2. Patient must have: 2.1. good performance status 2.2. clinically stable CNS disease or no brain metastases	Patients with an ECOG performance status of 0 or 1 were included in Study 202. The clinical expert noted that with the use of stereotactic radiosurgery, which has shown to be an effective localized treatment for limited (≤ 10) metastatic lesions, there is no reason to withhold tebentafusp in patients with CNS metastases if CNS metastasis is controlled with radiation or surgery.	pERC acknowledged that clinicians may consider using tebentafusp for patients with an ECOG performance status ≥2 at their discretion.
Discontinuation		
3. Tebentafusp should be discontinued in patients who no longer derive clinical benefit or have intolerable toxicity: 3.1. assessment for clinical benefits should be assessed for treatment response every 3 to 4 months or as per physician discretion	In Study 202, patients receiving tebentafusp or immunotherapy were allowed to continue treatment beyond initial radiographic progression if there was evidence of clinical benefit, or in the absence of intolerable toxicity. The clinical expert noted there is generally a poor correlation between tumour response and survival in patients with metastatic uveal melanoma receiving systemic treatments and in clinical practice, patients would continue tebentafusp beyond initial radiographic progression unless there is clear evidence of significant progression. The clinical expert also noted that in a post-hoc exploratory analysis of Study 202 among patients who had disease progression as their best overall response, patients who received tebentafusp had longer OS than patients in the investigator's choice arm.	pERC agreed with the clinical experts that the decision to discontinue treatment should be left to the discretion of the treating clinician.
Prescribing		
4. Tebentafusp should only be prescribed by a clinician with expertise in the management of	To ensure that tebentafusp is prescribed only for appropriate patients and adverse	—

Reimbursement condition	Reason	Implementation guidance
UM and cytokine release syndrome	effects are managed in an optimized and timely manner. As per clinical expert input, the first 3 to 4 infusions of tebentafusp are associated with a risk of cytokine release syndrome which requires inpatient monitoring in an experienced institution and management by a specialist physician experienced in the use of tebentafusp. Subsequent infusions may be performed in community clinic setting. However, overall monitoring of UM should be supervised by a clinician with expertise in the management of UM.	
Pricing		
5. A reduction in price	The ICER for tebentafusp is $728,513 per QALY gained when compared with investigator's choice of therapy. A price reduction of 91% would be required for tebentafusp to achieve an ICER of $50,000 per QALY gained compared to investigator's choice of therapy. Given the high degree of uncertainty in the long-term efficacy of tebentafusp, a higher price reduction may be warranted.	—
Feasibility of adoption		
6. The feasibility of adoption of tebentafusp must be addressed	At the submitted price, 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(s).	—

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness; OS = overall survival; QALY= quality-adjusted life-year; UM = uveal melanoma

Discussion Points

- pERC discussed the current treatment options for patients in this setting. According to the clinical expert, while immunotherapy is a reasonable first line option, the response to immunotherapy is considered poor, and therefore clinical trials are preferred for patients in first line and beyond. pERC agreed with the clinical expert that there is an unmet need for effective treatment options in first line and beyond given the poor prognosis and high morbidity, and lack of standard of care or effective alternatives for this rare disease.
- pERC discussed the single-arm expansion cohort of Study 102 (a phase I/II multicentre, open-label study of patients who had 1 or 2 prior lines of therapy in the metastatic or advanced setting) to inform a recommendation in the second and later-line setting. While patients in the second and later-line setting appeared to benefit from tebentafusp, the non-comparative design was a key limitation and there was considerable uncertainty about the magnitude of clinical benefit of tebentafusp compared to currently available treatment options in second-line or beyond. pERC acknowledged the input from clinical expert who expressed that tebentafusp should not only be offered in first line, but also in second- or later-line settings based on clinical trial and anecdotal evidence. As a result, pERC noted that it would be reasonable for jurisdictions to consider

reimbursement of tebentafusp in a second- or later- line setting on a time-limited basis due to the rare nature of the cancer and paucity of effective therapeutic options.

- pERC discussed the indirect treatment comparison (ITC) submitted by the sponsor: an unanchored matching-adjusted indirect comparison (MAIC) of tebentafusp relative to ipilimumab plus nivolumab. pERC noted that while a statistically significant improvement in OS and PFS for tebentafusp was demonstrated, the results of the ITCs stem from highly uncertain evidence due to limitations that impact the internal and external validity, despite the various adjustments. The sponsor submitted a supplementary HLA analysis and propensity score analysis (inverse probability treatment weighting-based) but were unable to address the limitations of the MAIC. pERC acknowledged, however, that given the rarity of mUM and the high unmet need for patients, there should be greater allowance for uncertainty in the evidence.
- Patients expressed a need for treatment that can preserve vision. pERC discussed that while vision preservation is not an outcome measured in Study 202, according to the clinical expert, treatment with tebentafusp did not translate to vision preservation as vision loss may be due to local tumour or radiation. Patients also expressed a need for treatment that provides good quality of life. pERC noted that HRQoL was not formally compared between the treatment groups in the trial. While no clinically meaningful improvement in quality of life was observed, the available evidence suggested that no notable differences in HRQoL were observed between the tebentafusp and investigator's choice arms in Study 202.
- pERC discussed the care provision, and system and economic considerations noted by drug plans and acknowledged the extensive health system resources implications for the preparation, administration, and monitoring of therapy as well as the substantial degree of drug wastage. pERC noted similar considerations reflected in the patient input as the majority of patients who had experience with tebentafusp had reported that they had to travel long distances to access the drug, which led to financial difficulties and disruption to their lives.
- The estimated price reduction required to achieve cost-effectiveness is highly uncertain. The long-term efficacy of tebentafusp is uncertain, and is highly influenced by the estimated comparative effectiveness compared to investigator's choice of therapy. Additionally, there was no direct comparative evidence between tebentafusp and nivolumab and ipilimumab combination therapy, which clinical experts identified as the most common treatment approach for patients with unresectable or metastatic mUM. Finally, the sponsor's submitted evidence did not consider the full Health Canada indicated population (all adult (HLA)-A*02:01-positive, irrespective of prior treatment), and so the cost-effectiveness in this population remains unknown.
- The estimated budget impact of tebentafusp is uncertain. The CADTH base case estimate of the BIA includes both previously treated and previously untreated patients, based on the Health Canada indication. If a time-limited approach is chosen for previously treated patients, the budget impact will likely decrease. Jurisdictions considering such an approach will need to consider the effect that it will have on the overall budget impact.

Background

Uveal melanoma (UM) is a rare subset of melanoma that arises from the uveal tract (choroid, ciliary, iris) in the eye. It is estimated that 3.75 new cases of UM arose per million Canadians each year between 1992 and 2010, with an increase of 0.074 new cases per million individuals annually. At diagnosis, most patients have localized disease and approximately 50% of patients are symptomatic (vision loss or disturbances). About 50% of patients will progress to metastatic disease, with metastasis most commonly in the liver (93%). The survival of metastatic uveal melanoma (mUM) is unfavourable, with an estimated 1-year survival rate of 43% to 52% with first-line treatments, and about 37% in second-or-later line setting.

Systemic therapies are usually prescribed in patients with mUM who have a larger number of metastatic lesions and/or disease external to the liver. The most commonly prescribed systemic therapies in a first-line setting are immunotherapies (off-label), given as monotherapies (i.e., nivolumab, or pembrolizumab alone), or in combination (i.e., ipilimumab plus nivolumab). Ipilimumab monotherapy is generally given in later-line settings in Canada. Systemic chemotherapies have a limited role in the treatment of mUM in Canada, due to toxicity and a low response rate. Given that there are poor survival benefits and tumour response to all available systemic treatments, the standard of care for mUM is enrollment in a clinical trial if available. Of note, funding for systemic therapies for mUM is usually assessed on a case-by-case basis by the jurisdictions.

Tebentafusp has been approved by Health Canada for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma, Tebentafusp is a gp100 peptide-HLA-A*02:01 directed T cell receptor CD3 bispecific T cell engager and is supplied as a solution (100 mcg/0.5 mL) for intravenous infusion. The recommended dosage of

tebentafusp in the product monograph is 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, administered intravenously, until unacceptable toxicity or disease progression.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III randomized controlled trial (Study 202) and 1 phase I/II cohort study (Study 102)
- patient perspectives gathered by 2 patient groups, including Melanoma Canada (MC) and Save Your Skin Foundation (SYSF).
- input from public drug plans and cancer agencies that participate in the CADTH review process.
- Input from one clinical specialist with expertise diagnosing and treating patients with mUM.
- input from 1 clinician group, the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee.
- a review of the pharmacoeconomic model and report, match-adjusted indirect comparison (MAIC), and propensity score analysis (Inverse Probability Treatment Weighting [IPTW]-based) submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups provided input for this reimbursement review - MC and SYSF. MC gathered information from patients with UM and caregivers (N = 19) via an online survey. SYSF collected responses from patients with ocular melanoma (N = 38) via patient interviews, patient roundtables and online surveys. Most of the SYSF respondents (n = 33) resided in Canada. The majority of respondents were diagnosed with early-stage or primary disease in both patient group input.

Respondents from MC mentioned that the diagnosis of UM affects their day-to-day life and quality of life, with most common issues being loss of vision, vision impairment, fear or anxiety, depression, and fatigue. In addition, respondents from SYSF mentioned that their balance is affected which causes huge physical and psychological deterioration.

There were 5 patients from MC and 10 patients from SYSF who indicated that they had experience with tebentafusp treatment through clinical trials or Health Canada compassionate access. According to the submissions by MC and SYSF, three patients (2 from MC and 1 from SYSF) who had access to tebentafusp indicated that the drug has shown effectiveness in slowing down the disease progression and another two patients could not comment on the effectiveness as it was too early for them to tell. The frequently reported side effects by patients from both groups were skin rash, fever, fatigue, cognitive impairment, gastro issues, nausea, muscle, joint pain, and headaches. Most patients described the side effects as short term, tolerable, and manageable and that the benefits of the treatments outweighed the negative side effects based on their experience. Only 1 patient from SYSF said the side effects were not manageable. In addition, patients from both groups also reported that they had to travel long distances to access the drug and had financially difficulties.

Patients from both groups expressed their desire to have an effective treatment that can preserve vision, provide a good quality of life and longer survival. In addition, patients interview by MC indicated that they would like to have improvements in earlier diagnosis and detection of metastasis. Patient respondents highlighted their preference for HLA testing to be done as soon as possible following UM diagnosis.

Clinician input

Input from clinical expert consulted by CADTH

The clinical expert highlighted that mUM is an aggressive disease associated with a poor survival and there are no current available therapies that predictably improve outcomes. The clinical expert expressed that a shift in current treatment paradigm is anticipated where tebentafusp is used in a first- or later-line setting, as supported by clinical trial and anecdotal evidence.

The clinical expert indicated that only patients with HLA-A*02:01-positive mUM are expected to benefit from tebentafusp owing to its unique mechanism of action. The clinical expert was unable to identify which HLA-A*02:01-positive patients are most likely to benefit from tebentafusp, noting that there is currently no good clinical or biological predictor of response to tebentafusp. The clinical expert indicated that patients with a poor performance status (i.e., Eastern Cooperative Oncology Group [ECOG] of 3 or above) are generally not eligible for treatment in clinical practice as they are less likely to benefit.

The clinical expert strongly suggested that patients be allowed to continue treatment as long as they continue to derive clinical benefits from tebentafusp, noting that there was some evidence from a post-hoc analysis of Study 202 that patients with radiographic progression on tebentafusp can continue to benefit from treatment beyond progression.[10] The clinical expert highlighted that, given the complexity of the clinical considerations involved, treatment response and the decision to discontinue treatment should be left to the discretion of the attending oncologist based on assessments of history and physical examinations (every 3 to 4 weeks), laboratory tests (weekly) and imaging (every 12 to 16 weeks) findings. According to the clinical expert, treatment discontinuation is generally considered in clinical practice in the presence of intolerable toxicities, or clear evidence of significant progression, which is indicated by a decline in performance status, increased pain, rising LDH levels, and marked radiographic progression.

The clinical expert recommended that tebentafusp initially should only be prescribed by specialist physicians experienced in the use of tebentafusp and familiar with the management of CRS, noting that the risk of CRS is the highest with the first 3 to 4 doses, and substantially lower with subsequent doses. The clinical expert noted that once a pattern of use is established and when the risk of CRS is absent, subsequent infusions can be performed in a community clinic setting.

Clinician group input

CADTH received input from one clinician group, Ontario Health (Cancer Care Ontario) (OH-CCO) Skin Cancer Drug Advisory Committee, based on responses from 6 clinicians. OH-CCO's Skin Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. No major contrary views from those provided by the clinical expert consulted by CADTH for this review were presented.

The clinician group stated that UM is a disease that has a low tumour mutational burden and a low 1-year survival rate of 50% in the metastatic setting, which is distinct from cutaneous melanoma. None of the current systemic treatments for UM have been proven to have OS benefit, which represents a major unmet need in patients with mUM. The clinician group noted that tebentafusp has demonstrated an improvement in OS in clinical trials. The clinician group highlighted that the treatment goal is to improve OS and quality of life. The clinician group expressed that tebentafusp would be the first-line treatment of choice for HLA-A*0201 positive patients with mUM, although they did not comment on the use of tebentafusp in second- or later-line settings. The clinician group stated that HLA-A*0201 positive patients with mUM who do not meet the exclusion criteria of Study 202 would be suitable for tebentafusp. They noted that ongoing performance status, tumour size, and Response Evaluation Criteria in Solid Tumours (RECIST) progression requirements are the clinical outcomes used to determine whether a patient is responding. They indicated that treatment response is considered clinically meaningful in the presence of at least 20% reduction in tumour size and improved performance status, while noting that treatment may be continued in some patients with radiographic progression (new and/or increasing target lesions) if clinical benefits are observed. The clinician group highlighted that toxicity or symptomatic disease progression without clinical benefit would be considered when deciding to discontinue tebentafusp. The clinician group indicated that oncologists with experience in the inpatient management of side effects of tebentafusp are required due to the known toxicities that commonly occur following the first three doses.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for tebentafusp

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy

- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

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

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The IMCgp100-202 trial ("202 trial") compared tebentafusp against investigator's choice of pembrolizumab, ipilimumab, or dacarbazine. Immunotherapy (e.g., pembrolizumab, nivolumab, ipilimumab) and chemotherapy (e.g., dacarbazine, temozolomide, paclitaxel-carboplatin) are funded for cutaneous melanoma in most jurisdictions. Funding for systemic therapies for UM is usually assessed on a case-by-case basis and would usually include therapies used for cutaneous melanoma. Other comparators for UM include enrollment onto clinical trials, where available.	*Comment from the drug programs to inform pERC deliberations.*
Considerations for initiation of therapy	
Patients require confirmation of HLA-A*02-01 positive status to be eligible for tebentafusp. HLA typing would be required for all patients diagnosed with UM. Access to HLA typing may differ by jurisdiction. The 202 trial required HLA testing by "central assay."	*Comment from the drug programs to inform pERC deliberations.*
The 202 trial included patients who had not received any prior therapy for advanced/metastatic disease but were permitted to have received prior (neo)adjuvant therapy. The funding request is not specific to use of tebentafusp in the 1st line setting Should patients who received prior therapies in the advanced/metastatic setting be eligible for tebentafusp? Is there clinical evidence to inform the efficacy/safety of tebentafusp in this patient population?	It would be reasonable for jurisdictions to consider reimbursement of tebentafusp in a second- or later- line setting for patients who received prior therapies in the advanced or metastatic setting on a time-limited basis. The clinical expert highlighted that treatment options are limited. Whilst immunotherapy is a reasonable first option, the response to immunotherapy is poor, so clinical trials are preferred for patients in first line and beyond, according to the clinical expert. The clinical expert concluded that there is an unmet need for effective treatment options in first line and beyond. The clinical expert noted if tebentafusp is available first line and beyond, clinicians would prescribe this drug. The clinical expert noted that in the phase II Study 102 where tebentafusp was used as a second- or later-line treatment in patients with mUM, patients appeared to benefit from tebentafusp, although the clinical expert acknowledged that this is a phase II trial which is subject to limitations. The clinical expert also noted that in their clinical experience, patients receiving tebentafusp via compassionate drug programs in a second-line setting also benefit, therefore, the clinical expert felt that there is no justification to exclude patients who had prior therapies from receiving tebentafusp. The clinical expert expressed that access to tebentafusp is particularly important in

Implementation issues	Response
	patients who did not have access to compassionate supplies of tebentafusp in the past and perforce, had to receive other therapies.
The 202 trial excluded patients with "symptomatic CNS metastases". Should patients with CNS involvement be eligible for tebentafusp? Is there clinical evidence to inform the efficacy/safety of tebentafusp in this patient population?	The clinical expert noted that CNS metastases are rare in UM and tend to occur only after a prolonged period of existing metastatic disease. The clinical expert highlighted that historically, patients with CNS metastasis would have been excluded from systemic therapy. However, now with the use of stereotactic radiosurgery, which has shown to be an effective localized treatment for limited (≤ 10) metastatic lesions, there is no reason to withhold tebentafusp in patients with CNS metastases if CNS metastasis is controlled with radiation or surgery. pERC agreed with the clinical expert.
Considerations for discontinuation of therapy	
It is uncertain how long patients can be treated since the response evaluation may not follow the RECIST-based assessment. What discontinuation criteria should be applied for tebentafusp?	The clinical expert noted that in a post-hoc exploratory analysis of Study 202 among patients who had disease progression as their best overall response, patients who received tebentafusp had longer OS than patients in the investigator's choice arm, suggesting that patients with evidence of progression on tebentafusp may still benefit from treatment beyond progression. The clinical expert, therefore, felt that the decision to discontinue treatment should be left to the discretion of the attending oncologist. The clinical expert indicated that in clinical practice, treatment discontinuation is generally considered in patients with clear evidence of significant progression, as suggested by a decline in performance status, increasing pain, rising LDH levels, and marked progression on imaging.
Considerations for prescribing of therapy	
Tebentafusp is available as a 100 mcg/0.5 mL vial. Doses are administered weekly via intravenous infusion over 15-20 minutes. Doses follow an escalation dosing schedule: Dose 1: 20 mcg, Dose 2: 30 mcg, Dose 3 and beyond: 68 mcg. Weekly treatment continues until disease progression or unacceptable toxicity.	*Comment from the drug programs to inform pERC deliberations.*
The first three infusions of tebentafusp should be administered in an appropriate healthcare setting by intravenous infusion over 15 to 20 minutes, per manufacturer's product monograph.[9] Observation period of up to 16 hours is required after the first 3 doses to provide monitoring/management for potential cytokine release syndrome.[9] If no grade 2 or greater cytokine release after 3 doses, further doses can be administered on an outpatient basis, with observation period reduced to 30 minutes.[9] Administration of tebentafusp, in particular the first 3 doses in an inpatient setting, would represent a significant increase in health system resources versus other comparators. It is noted that the patient population eligible for tebentafusp is a small number of patients.	*Comment from the drug programs to inform pERC deliberations.*
Clinicians/facilities with experience monitoring/managing cytokine release syndrome are required for administration of tebentafusp.	*Comment from the drug programs to inform pERC deliberations.*

Implementation issues	Response
In some jurisdictions, systemic treatments administered in the inpatient setting are outside the scope of the drug plan budgets. Coverage of the inpatient treatment would need to be addressed.	
Generalizability	
The "202" trial only enrolled patients with ECOG of 0, 1. Should patients with ECOG performance status of 2 or greater be eligible for tebentafusp?	pERC acknowledged that clinicians may consider using tebentafusp for patients with an ECOG performance status ≥2 at their discretion. The clinical expert noted that patients with ECOG performance status of 2 or greater may benefit from tebentafusp in clinical practice, but in general patients with a very poor performance status are less likely to benefit from systemic treatments. Clinicians generally do not treat a patient with ECOG performance status of 3 or worse, according to the clinical expert.
Care provision issues	
The preparation of tebentafusp is complex and intense and will require considerable Pharmacy resources to prepare each dose. Preparations use very small volumes from each drug vial (Dose 1 uses 20 mcg from the 100 mcg vial); drug wastage will occur with each weekly dose. The manufacturer's monograph specifies "do not prepare more than one dose from the vial" thus vial sharing will not be possible. Preparations require integration of human albumin, which will not be readily available in most sterile compounding Pharmacy facilities (would usually be requested from the blood bank, introducing an additional step to this preparation). Volume required of human albumin is small, thus wastage is expected to occur. Use of human albumin, as a biologic agent, requires additional decontamination of the biologic safety cabinet during the preparation process. Because the human albumin volume and drug volume are so low, each time the drug is prepared, there are dozens of steps to ensure appropriate mixing. The manufacturer outlines the recommended methodological preparation process, which will require considerable Pharmacy resources for each weekly dose. While administration time of each dose is short (15-20 minutes), required observation time after doses 1-3 is considerable (16 hours). Doses 1-3 are required to be administered in an inpatient setting. Therefore, use of health system resources for the preparation, administration, and monitoring of tebentafusp is significant.	*Comment from the drug programs to inform pERC deliberations.*
Potential for cytokine release syndrome requires monitoring and management on an inpatient basis for doses 1-3.	*Comment from the drug programs to inform pERC deliberations.*
For patients diagnosed with non-metastatic UM, should HLA typing be evaluated at diagnosis?	The clinical expert noted that, in patients with non-metastatic UM, initial HLA testing is not usually done in major treatment centers,

Implementation issues	Response
What is the anticipated turnaround time for HLA testing results?	since the turnaround is about one week; while in a peripheral center, testing might be advisable to pre-screen patients.
Careful coordination and transfer of care between inpatient and outpatient care teams and facilities will be required in order to ensure continuity of weekly treatments for each patient. As a rarely used agent, it is not anticipated that many facilities would have this drug in regular stock, thus adequate communication and preparation time will be required to coordinate appropriate care for each patient.	*Comment from the drug programs to inform pERC deliberations.*
System and economic issues	
The potential drug acquisition cost per patient is high. The health system resource use for tebentafusp is considerable relative to comparators.	*Comment from the drug programs to inform pERC deliberations.*
Tebentafusp requires specialized clinicians for administration/preparation/monitoring, thus treatment is likely to be limited to larger centres. This introduces potential need for travel, additional impact to daily life, and potential for increased expenses for eligible patients. Drug wastage is quite significant as the standard dose is considerably less than the vial size (68 mcg vs 100 mcg) and single vial use is recommended. In some jurisdictions, wastage is not reimbursed by the drug plan and so hospitals may not be able to absorb the wastage cost.	*Comment from the drug programs to inform pERC deliberations.*

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; mUM = metastatic uveal melanoma; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumours; UM = uveal melanoma.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of study

Study 202 met the inclusion criteria for the CADTH systematic review. Study 202 was a phase III, open-label, randomized, active-controlled study that aimed to compare the efficacy and safety of tebentafusp and investigator's choice (either pembrolizumab, ipilimumab, or dacarbazine) in HLA-A*02:01-positive adult patients with mUM who had no prior therapy in the metastatic setting (N = 378). Patients were randomized in a 2:1 ratio to receive either tebentafusp (20 mcg on day 1, 30 mcg on day 8, and 68 mcg on day 15 and weekly thereafter via IV infusion), or investigator's choice of either: dacarbazine (1000 mg/m^2), ipilimumab (3 mg/kg), or pembrolizumab (2 mg/kg/dose - up to 200 mg/dose, or 200 mg flat dose), via intravenous infusion (IV) every 3 weeks. Treatments were continued until disease progression per RECIST v1.1, unacceptable toxicity, or completion of a maximum of 4 doses for ipilimumab. Patients receiving tebentafusp, pembrolizumab, and ipilimumab were permitted to continue treatment beyond initial disease progression if pre-specified criteria were met indicating clinical benefit and tolerance of the study drugs.

Study 202 aimed to establish the superiority of tebentafusp to investigator's choice of therapy through the co-primary endpoints of OS in the Rash Analysis Set (RAS), which consisted of patients receiving tebentafusp who developed a rash within the first week of treatment and all patients in the investigator's choice arm, and OS in the intention-to-treat (ITT) analysis set. The key secondary endpoints were progression-free survival (PFS) and best overall response (BOR) (evaluated statistically as objective response rate [ORR]). Other secondary outcomes included health-related quality of life (EQ-5D-5L and European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 [EORTC QLQ-C30]), disease control rate (DCR), duration of response (DOR), and safety, all of which were measured without control for multiplicity. The first interim OS analysis and the final PFS were performed based on the data cut-off on October 13, 2020. An informal updated OS analysis and the primary ORR analysis were performed based on the data cut-off on August 12, 2021 to fulfil the regulatory requirements in Europe.

The baseline patient characteristics were balanced between treatment arms. Overall, the mean age of patients was 62.1 (SD: 11.6) years. Approximately half of the patients were female. The majority of patients were White, had an ECOG performance status of 0, and had liver metastases. In most patients, there was no prior surgery for metastatic disease (91.3%). A small proportion of patients (3.7%) had prior antineoplastic systemic treatments (in any setting) and 40.2% of patients had prior local radiotherapy. In the investigator's choice arm, the majority of patients were assigned pembrolizumab (81.7%), while others received ipilimumab (12.7%) and dacarbazine (5.6%).

Efficacy Results

Overall survival

In the first interim OS analysis (median duration of follow-up 14.1 months), the median OS in the RAS was 27.4 (95% confidence interval [CI], 20.2 to not reported [NR]) months in the tebentafusp arm, and 16.0 (95% CI, 9.7 to 18.4) months in the investigator's choice arm, with a HR of 0.38 (95% CI, 0.25 to 0.56) and a P value of < 0.0001, in favour of tebentafusp. The median OS in the ITT analysis set was 21.7 (95% CI, 18.6 to 28.6) months in the tebentafusp arm, and 16.0 (95% CI, 9.7 to 18.4) months in the investigator's choice arm, with a hazard ratio (HR) of 0.51 (95% CI, 0.37 to 0.71) and a P value of <0.0001, in favour of tebentafusp. The results of the informal updated OS analysis were consistent with the first interim analysis.

Progression-free Survival

In the final PFS analysis (median follow-up duration of 11.4 months), the median PFS in the ITT analysis set was 3.3 months (95% CI, 3.0 to 5.0) in the tebentafusp arm, and 2.9 months (95% CI, 2.8 to 3.0) in the investigator's choice arm, with a HR of 0.73 (95% CI, 0.58 to 0.94) and a P value of 0.0139, in favour of tebentafusp.

Health-related Quality of Life

As of the data cut-off on October 13, 2020, the change in score from baseline in EORTC QLQ-C30 was generally stable and similar between treatment arms at most timepoints for almost all domains. With respect to the fatigue scale (higher scores indicate worse

symptoms), the difference in least square (LS) mean change in score from baseline at end of treatment between tebentafusp versus investigator's choice was -9.259. This analysis was not adjusted for multiplicity.

The baseline mean EQ visual analogue scale (VAS) (higher scores indicate better HRQoL) was 81.0 (SD: 16.4) in the tebentafusp arm, and 80.4 (SD: 18.3) in the investigator's choice arm. The mean change from baseline at end of treatment was -10.1 (SD: 22.53) in the tebentafusp arm, and -11.7 (SD: 21.40) in the investigator's choice arm. The difference between arms was not tested statistically.

Duration of Response

As of the data cut-off on August 12, 2021, 26 (10.3%) patients receiving tebentafusp and 6 (4.76%) patients receiving investigator's choice of therapy had complete or partial response. Among these patients, the median DOR was 9.9 months (95% CI, 5.6 to 22.1) in the tebentafusp arm, and 9.7 months (95% CI, 2.7 to NR) in the investigator's choice arm. The difference between arms was not tested statistically.

Objective Response Rate

In the primary ORR analysis (data cut-off on August 12, 2021), the ORR in the ITT analysis set was 10.3% (95% CI, 6.9% to 14.8%) in the tebentafusp arm, and 4.8% (95% CI, 1.8% to 10.1%) in the investigator's choice arm, corresponding to an odds ratio of 2.26 (95% CI, 0.91 to 5.61) and a P value of 0.684. Due to imprecision, the results for ORR are inconclusive.

Disease Control Rate

As of the data cut-off on August 12, 2021, the DCR in the ITT analysis set was 45.6% (95% CI, 39.4% to 52.0%) in the tebentafusp arm, and 27.0% (95% CI, 19.5% to 35.6%) in the investigator's choice arm, corresponding to an odds ratio of 2.34 (95% CI, 1.45 to 3.76). This analysis was not adjusted for multiplicity.

Harms Results

As of data cut-off on October 13, 2020, treatment-emergent adverse events (TEAE) were reported in all patients in the tebentafusp arm, and 94.6% of patients in the investigator's choice arm. The most common TEAE were pyrexia (tebentafusp [76%] versus investigator's choice [7.2%]), pruritus (69.0% versus 23.4%), rash (55.1% versus 16.2%), and fatigue (51.0% versus 35.1%). Serious TEAE were reported in 28.2% of patients in the tebentafusp and 23.1% of patients in the investigator's choice arm. The most common serious TEAE in the tebentafusp arm was CRS (9.8% for tebentafusp; 0% in the investigator's choice arm). The proportion of patients who discontinued treatment due to TEAE were 3.3% and 6.6 % in the tebentafusp arm and the investigator's choice arm, respectively. Eighty-four deaths (34.3%) and 57 deaths (51.4%) were reported in the tebentafusp arm and the investigator's choice arm, respectively. The majority of deaths in both arms were attributed to disease progression.

The proportion of patients who reported CRS (or presentations related to CRS), and dermatological adverse events (AE) was notably higher in the tebentafusp arm than in the investigator's choice arm. The most common notable harm of any grade (30% or greater) being pyrexia, pruritus, rash, fatigue, nausea, chills, hypotension, dry skin, headache, and maculopapular rash, all of which were mostly grade 1 or 2.

Critical Appraisal

The overall study design of Study 202 was appropriate for the objectives of the study. There was no particular concern with the methods of randomization and allocation concealment. In consultation with the clinical expert, the open-label design was considered reasonable. However, there is potential for reporting bias on tumour response (ORR, DCR, BOR, DOR) and subjective harms outcomes since these outcomes were based on investigator's assessment, although the extent and direction of bias are unclear. The statistical analyses were generally appropriate, with proper processes in place to preserve power in the interim and final OS analyses, and to account for multiplicity for the co-primary endpoints and key secondary endpoints using a hierarchal approach. DCR, DOR, and HRQoL outcomes however were not adjusted for multiplicity and were considered exploratory due to increased risk of type 1 error. It should be noted that the OS analyses were interim, and interim analyses are typically associated with a risk of over-estimating the treatment effects in favour of the experimental intervention (i.e., tebentafusp).[13] Considering that the OS analyses were based on a relatively small number of events, the OS results are prone to imprecision. OS analysis in the RAS should also be

interpreted with caution, due to the risk of confounding resulting from the absence of randomization in the comparison, although the direction of bias could not be determined. There is also uncertainty in the HRQoL outcomes, due to potential reporting and attrition bias, and also considering the instruments used (EORTC QLQ-C30 and EQ-5D-5L) had not been validated in patients with mUM.

In terms of generalizability, a limitation to note is that the studies included patients who had no prior therapies in the metastatic setting, therefore the applicability of trials results to patients who had prior therapies in the metastatic setting is unclear. The treatments included in the comparator arm accounts for a small proportion of systemic treatments prescribed for mUM in Canada which increases uncertainty in the generalizability of study results. The clinical expert consulted by CADTH commented that the impact on generalizability is likely to be small since the efficacy of immunotherapies is considered similar by clinicians. However, this opinion was formed based on a small retrospective cohort study and is associated with some uncertainties. The OS benefits of tebentafusp was considered clinically meaningful by the clinical expert, while PFS and tumour response outcomes were noted to have limited clinical relevance by the clinical expert since tumour response is poorly correlated with overall survival in patients with mUM receiving systemic therapy in general, according to the clinical expert. The clinical relevance of the HRQoL outcomes was also uncertain since the instruments used were not routinely administered in clinical practice, although they have captured some of the most common HRQoL concerns (e.g., anxiety, depression, fatigue) reported by patients. With respect to the safety, specifically CRS, the clinical expert expected the study findings to be generalizable to clinical practice provided that tebentafusp is administered in appropriate treatment settings as specified in the product monograph, noting that that in their clinical experience, CRS generally occurs following the first 3 to 4 infusions and is manageable if proper supportive care is provided.

Indirect Comparisons

Description of study

One indirect treatment comparison (ITC) was submitted by the sponsor and included in this review. No additional ITCs were identified in the literature. The sponsor performed an unanchored match-adjusted indirect comparison (MAIC) to estimate the comparative OS and PFS of tebentafusp compared with ipilimumab plus nivolumab in patients with mUM who had no prior therapy in the metastatic setting, based on data from the GEM-1402 comparator trial,[15] which was identified in a systematic literature review (SLR), and the index trial Study 202. Of note, the GEM-1402 trial enrolled patients with mUM regardless of HLA status and Study 202 enrolled HLA-A*02:01 positive patients with mUM. The sponsor submitted a supplementary analysis of the prognostic value of HLA-A*02:01 for OS to support the MAIC analyses.

Efficacy Results

The ITC included 237 patients in the tebentafusp arm from Study 202 and the effective sample size (ESS) of the ipilimumab plus nivolumab arm from the GEM-1402 trial was 115.9. The MAIC analysis between tebentafusp versus ipilimumab plus nivolumab showed results in favour of tebentafusp with respect to both OS (HR 0.507; 95% CI, 0.324 to 0.793), and PFS (HR 0.647; 95% CI, 0.445 to 0.941).

Eighty patients were included in the supplementary HLA status analysis (HLA-A*02:01-positive, N = 43; HLA-A*02:01-negative, N = 37). The median OS was 45.9 months (range = NR) in HLA-A*02:01-positive patients and 45.2 months (range = NR) in HLA-A*02:01-negative patients, with a HR of 0.82 (95% CI, 0.36 to 1.88).

Harms Results

The ITC did not assess safety outcomes.

Critical Appraisal

A key limitation of the ITC was that the selection criteria for the SLR were not determined a priori, increasing the risk of selection bias for comparator trial included in the MAIC analysis. In addition, patient population heterogeneity, specifically with respect to HLA-A*02:01 status, could be a potential source of confounding given that the comparator trial included patients regardless of HLA-A*02:01 status. Based on the sponsor-submitted supplementary HLA analysis, the CADTH review team was unable to rule out the possible confounding effect of HLA status on OS given the study was based on a small observational cohort and results are subject to imprecision (wide 95% CI for HR with respect to OS). Further, time since primary diagnosis, a covariate identified in the multivariate analysis, was excluded from adjustment since it was not reported in the comparator trial, which may contribute to the

uncertainty of the results. There is also concern with a loss of precision in the results given a significant reduction in the ESS. Overall, the direction of bias of the limitations noted could not be determined and the results of the MAIC should be interpreted with caution due to the potential biases. There is also an evidence gap in that HRQoL and harms outcomes, as well as the efficacy of tebentafusp in treatment-experienced patients were not addressed in this analysis.

Other Relevant Evidence

This section includes 2 additional studies from the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review. The first study was a phase I/II, multicentre, open-label study (Study 102) which analyzed the efficacy and safety of tebentafusp in HLA-A*02:01 positive patients with mUM who had 1 or 2 prior lines of therapy in the metastatic or advanced setting.[17] The second study was an observational study that compared patients receiving tebentafusp from Study 202 versus patients receiving ipilimumab plus nivolumab from the GEM-1402 trial in a first-line mUM setting following propensity score weighting.[18] The analysis was based on the same studies that informed the sponsor-submitted MAIC and was submitted to CADTH after the sponsor had obtained IPD from the GEM-1402 trial. The study aimed to address the limitations of the MAIC analysis due to the use of aggregate data from the GEM-1402 trial.

Study 102

The Study 102 was *a* Phase I/II study, which analyzed the efficacy and safety of tebentafusp in HLA-A*02:01-positive patients with mUM who had 1 or 2 prior lines of therapy in the advanced or metastatic setting. The primary end point for Phase I was the incidence (number) of Dose Limiting Toxicity (DLT) whereas ORR was the primary end point for the Phase II single arm dose expansion. The secondary end points for Phase II were OS, PFS, DOR, DCR, and BOR.

Efficacy Results

In the phase II expansion cohort (N =127) (data cut-off on March 20, 2020), the ORR was 4.7% (95% CI, 1.8% to 10.0%) based on 6 of 127 patients receiving tebentafusp who achieved a partial response (PR); no patients achieved a complete response (CR). After a median duration of follow-up of 19.6 months (95% CI: 16.0 to 22.2 months), the median overall survival was 16.8 months (95% CI, 12.9 to 21.3 months). The median PFS was 2.8 months (95% CI, 2.0 to 3.7 months) as per the assessed by RECIST v1.1 by independent central review. The median DOR (CR or PR) by RECIST v1.1 assessed by independent central review (ICR) was 8.7 months (95% CI: 5.6 to 24.5 months). The DCR (CR, PR, or stable disease [SD]) was 22.8% (95% CI, 15.7% to 31.2%) at ≥ 24 weeks. The most frequently observed BOR was disease progression (47.2%), followed by SD (44.9%), and PR (4.7%).

Harms Results

Similar to in Study 202, all patients in Study 102 experienced any grade AEs. In addition, Study 102 Phase II expansion and Study 202 had comparable rates of grade ≥ 3 treatment emergent adverse events (TEAEs) (59.1% vs. 54.3%). In Study 102 Phase II expansion,
9 patients (7.1%) experienced TEAEs leading to tebentafusp discontinuation, and the proportion was comparable to that of Study 202 (6.6%). The most frequently reported any grade TEAEs were pyrexia (81.1%), pruritus (68.5%), nausea (67.7%), chills (66.1%) and hypotension (41.7%). These TEAEs were also observed in the tebentafusp arm in Study 202. A total of 86 serious TEAEs were reported in 42 (33.1%) patients. The proportion was comparable to that of Study 202 (28.2%). The serious TEAEs were cytokine release syndrome in 4 (3.1%) patients; and sepsis, alanine transaminase increased, rash maculo-papular, and hypotension in 3 (2.4%) patients each. No deaths related to TEAEs or caused by the study drug were observed.

Critical Appraisal

The non-comparative design of the Study 102, with no statistical testing, is the key limitation. The lack of direct comparative data means there is uncertainty regarding the magnitude of effects obtained for the efficacy outcomes. Although the clinician expert consulted highlighted that the efficacy outcomes of tebentafusp in Study 102 were clinically meaningful and demonstrated the activity of the drug and were compatible to the Phase III Study 202, CADTH review team notes that in the absence of a comparative arm, the findings obtained from the efficacy and safety analysis are uncertain as the single-arm design does not allow for drawing conclusions about the comparative efficacy for tebentafusp and differentiating of the symptoms of underlying mUM disease from treatment-related adverse events.

Propensity Score Analysis (Inverse Probability of Treatment Weighting [IPTW] Approach)

The sponsor-submitted observational study compared patients in the tebentafusp arm from Study 202 with patients receiving ipilimumab plus nivolumab from the GEM-1402 trial in a first-line metastatic setting. The study was not randomized, and propensity score weighting using the IPTW approach was used in an attempt to adjust for confounding.

Efficacy

The ESS of the GEM-1402 trial was 34.4 after weighting, compared to a sample size of 45 before weighting. The patient characteristics were generally balanced between the tebentafusp and ipilimumab plus nivolumab cohorts after weighting.

In the primary analysis, the median OS of the tebentafusp cohort was 21.7 months (SD = not reported [NR]), and the weighted median OS of the ipilimumab plus nivolumab cohort was 12.6 months (SD = NR). The HR between tebentafusp and ipilimumab plus nivolumab with respect to OS was 0.430 (95% CI, 0.287 to 0.643), in favour of tebentafusp.

Harms Results

The study did not assess safety outcomes.

Critical Appraisal

The IPTW approach improved upon the MAIC by leveraging IPD from the GEM-1402 trial; however, many of the limitations of the MAIC analysis also apply to the current analysis. Specifically, the lack of a priori selection criteria for the SLR is a potential source of selection bias for comparator studies. It is also unclear if all known or unknown confounding factors have been adequately adjusted for. Heterogeneity in HLA status was noted in the comparator groups and considering the supplementary analysis submitted by the sponsor that assessed the impact of HLA status on OS, the CADTH review was unable to confidently rule out confounding effects by the difference in HLA status between the cohorts. Lastly, outcomes that are of interest to stakeholders such as HRQoL and harms, and the efficacy of tebentafusp in patients with prior systemic therapy in the metastatic setting were not addressed in this analysis.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned Survival Model
Target population	Adults with HLA-A*02:01-positive advanced (metastatic or unresectable) uveal melanoma (UM) *Base case*: previously untreated patients *Scenario*: previously untreated and treated patients
Treatment	Tebentafusp
Dose regimen	The recommended dose is escalated from 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15 to a maintenance dose of 68 mcg once every week.
Submitted Price	$18,565 per 100 mcg/0.5 mL vial
Treatment Cost	$18,565 per week
Comparators	*Base case*: Investigator's choice (a basket of comparators consisting of ipilimumab, pembrolizumab or chemotherapy with dacarbazine) *Scenario*: Nivolumab-ipilimumab combination therapy and ipilimumab/pembrolizumab monotherapy
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (38 years)
Key data source	*Base case*: A phase III randomized, open-label, multi-center IMCgp100-202 clinical trial assessing the safety and efficacy of tebentafusp compared with investigator's choice of therapy in HLA-A*0201 positive patients with previously untreated advanced metastatic or unresectable UM *Scenario*: A match-adjusted indirect comparison (MAIC) of tebentafusp relative to nivolumab-ipilimumab combination therapy in previously untreated patients, a single arm phase I/II, open-label, multi-center trial, IMCgp100-102, and single-arm studies evaluating the safety of ipilimumab or pembrolizumab in previously treated patients with UM
Key limitations	• There was uncertainty in the long-term clinical effectiveness of tebentafusp. Approximately 72% of OS and 92% of PFS associated with tebentafusp treatment were accrued after the trial period and based on extrapolation of the OS and PFS curves. Approximately 72% of incremental QALYs were obtained in the post-progression health state, for which the evidence is uncertain. • In the absence of direct comparative evidence between nivolumab-ipilimumab combination therapy and tebentafusp, the sponsor submitted a MAIC, which had several methodological limitations. As such, no conclusions on the comparable clinical efficacy could be drawn. The cost-effectiveness of tebentafusp compared to the most frequently prescribed treatment at the time of this review is unknown. • The sponsor inappropriately imposed a cap on the treatment cost of tebentafusp in the Progression-Free health state, resulting in an underestimation of treatment cost associated with tebentafusp. • The sponsor assumed a compliance rate of 95% to account for missed doses or treatment interruptions in estimating drug costs, which is unlikely to reflect clinical practice. • The sponsor used inaccurate weighting of treatments to estimate cost of dose 5 and subsequent doses associated with the investigator's choice of therapy. • The sponsor's approach to model utilities based on time-to-discontinuation curves lacked face validity and do not align with CADTH guidelines.
CADTH reanalysis results	• CADTH made the following revisions to the sponsor's pharmacoeconomic model: corrected treatment weighting such that cost of ipilimumab is not included in dose 5 and subsequent doses in the comparator arm; assumed a compliance rate of 100% for all treatments; and removed cap on tebentafusp costs. • Based on CADTH's base case, compared with investigator's choice of therapy, tebentafusp was associated with an ICER of $728,513 per QALY gained in the previously untreated population with metastatic UM.

Component	Description
	• A price reduction of at least 91% would be needed for tebentafusp to be cost-effective at a WTP threshold of $50,000 per QALY gained.
Key scenario analyses	• CADTH conducted an additional scenario analysis in the previously treated population. In this analysis, tebentafusp was associated with an ICER of $1,054,187 per QALY gained compared with ipilimumab or pembrolizumab monotherapy. The cost-effectiveness of tebentafusp in the previously treated population could not be validated due to the lack of direct and indirect comparative evidence in this population.

ICER = incremental cost-effectiveness; OS = overall survival; PFS = progression-free survival; QALY= quality-adjusted life-year; WTP = willingness to pay

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. The budget impact estimated on the sponsor's assumptions regarding compassionate access of tebentafusp does not represent likely use of tebentafusp. The drug acquisition costs are underestimated because drug wastage was not included. The market share of tebentafusp was underestimated and treatment duration was uncertain.

CADTH reanalysis included: excluding the sponsor's assumption on compassionate access, including drug wastage and increasing the market share of tebentafusp. Based on the CADTH reanalysis, the three-year budget impact to the public healthcare payer of introducing tebentafusp was $54,017,379 (Year 1: $20,229,773; Year 2: $17,499,596; Year 3: $16,288,010). The estimated budget impact was sensitive to treatment duration of tebentafusp.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), 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, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: November 9, 2022

Regrets:

2 expert committee members did not attend

Conflicts of interest:

None