

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

Changes have been made to this item. Details of the corrigendum are at the end of this document.

## 5.01 TEBENTAFUSP, Solution concentrate for I.V. infusion 100 mcg in 0.5mL vial, Kimmtrak<sup>®</sup>, Synevi Pty Limited.

### 1 Purpose of submission

1.1 The Category 1 submission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required (telephone/online) listing for tebentafusp for the treatment of HLA-A\*02:01-positive adult patients with advanced (unresectable or metastatic) uveal melanoma (UM).

1.2 Listing was requested on the basis of a cost-utility analysis versus pembrolizumab.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults with advanced (unresectable or metastatic) HLA-A*02:01 positive uveal melanoma
Intervention	Tebentafusp IV 20 mcg on day 1, 30 mcg on day 8, 68 mcg on day 15, and 68 mcg once every week thereafter.
Comparator	Pembrolizumab 200 mg IV fixed dose given on day 1 of each 21-day cycle or 2 mg/kg up to a maximum of 200 mg.
Outcomes	OS, PFS, ORR, DOR, AEs and HRQoL
Clinical claim	In patients with advanced (unresectable or metastatic) uveal melanoma, tebentafusp is superior in terms of efficacy compared to pembrolizumab, with a non-inferior safety profile.

Source: Table 1.1.1, p2 of the submission.

AE = adverse event, DOR = duration of response, HLA = human leukocyte antigen, HRQoL = health-related quality of life, IV = intravenous, kg = kilograms, mcg = micrograms, mg = milligrams, PFS = progression-free survival, ORR = objective response rate, OS = overall survival.

### 2 Background

#### Registration status

2.1 Tebentafusp was TGA registered on 27th May 2022 for the treatment of HLA-A\*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

### 3 Requested listing

3.1 The submission proposed restriction is presented below. Secretariat suggested additions are in italics and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Max. Amount	DPMA	No. of Rpts
TEBENTAFUSP	300 mcg	Published Public: \$58,698.94 Private: \$59,561.14 Effective Public: \$ Private: \$	0
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)			
<b>Administrative Advice:</b> <i>No increase in the maximum number of repeats may be authorised.</i>			
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>			
<b>Administrative Advice:</b> <i>No increase in the maximum amount or number of units may be authorised</i>			
<b>Administrative Advice:</b> <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</i>			
<b>Episodicity:</b> [blank]			
<b>Severity:</b> <del>Advanced disease</del> (unresectable or metastatic)			
<b>Condition:</b> Uveal melanoma			
<b>Indication:</b> <del>KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01 positive adult patients with unresectable or metastatic uveal melanoma</del> <i>Advanced (unresectable or metastatic) uveal melanoma</i>			
<b>Treatment Phase:</b> Initial treatment			
<b>Clinical criteria:</b>			
The patient must <del>be</del> have HLA-A*02:01-positive disease			
<b>AND</b>			
<b>Clinical criteria:</b>			
The patient must have uveal melanoma that has been confirmed either (i) <del>H</del> histologically, <del>or</del> (ii) cytologically confirmed <del>metastatic UM or unresectable UM patients</del>			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be the sole PBS subsidised therapy for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
The patient must not have received prior systemic therapy for metastatic disease			

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	<b>Treatment criteria:</b>
	<p><b>For location:</b> The first three doses of KIMMTRAK must be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. After 68 mcg dose level is tolerated (i.e., absence of Grade <math>\geq</math> 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should then be observed for a minimum of 30 minutes following each infusion.</p> <p><b>For prescriber:</b> For the first three doses KIMMTRAK should be administered under the direction and supervision of a physician experienced in the use of anti-cancer agents and who is prepared to manage cytokine release syndrome in an environment where full resuscitation facilities are immediately available. Subsequent doses can be administered in appropriate outpatient setting by a trained healthcare professional.</p> <p><i>According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.</i></p>
	<b>AND</b>
	<b>Treatment criteria:</b>
	<i>Tebentafusp is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</i>
	<b>Population criteria:</b>
	<i>For pPatients must be aged at least 18 years and older</i>
	<b>Prescribing Instructions:</b>
	<i>Authority applications must have Positive HLA-A*02:01-positive assessment must be documented in the patient's medical records confirmed on the clinical file</i>
	<b>Administrative Advice:</b>
	<i>KIMMTRAK is for intravenous use. The recommended infusion period is 15 to 20 minutes. KIMMTRAK requires dilution with sodium chloride 9 mg/mL (0.9%) solution for injection containing human albumin for intravenous infusion.</i>
	<b>Caution:</b>
	<i>Cytokine Release Syndrome (CRS), which may be serious or life-threatening, can occur in patients receiving tebentafusp. Only administer in an appropriate hospital setting for the first three infusions. Monitor for at least 16 hours following each of the first three infusions, and then as clinically indicated. Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome.</i>

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MEDICINAL PRODUCT medicinal product pack	Max. Amount	DPMA	№. of Rpts
TEBENTAFUSP	400 mcg	Published Public: \$78,236.23 Private: \$79,371.95 Effective Public: \$ Private: \$	3
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
		<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals	
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
		<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]	
		<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.	
		<b>Administrative Advice:</b> Special Pricing Arrangements apply.	
		<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised	
		<b>Episodicity:</b> [blank]	
		<b>Severity:</b> Advanced disease (unresectable or metastatic)	
		<b>Condition:</b> Uveal melanoma	
		<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma	
		<b>Treatment Phase</b> Continuing treatment	
		<b>Treatment Clinical criteria:</b>	
		The treatment must be the sole PBS-subsidised therapy for this condition	
		<b>AND</b>	
		<b>Clinical criteria:</b>	
		Patient must have previously received PBS-subsidised <del>tebentafusp</del> <del>treatment with this drug</del> for this condition.	
		<b>AND</b>	
		<b>Clinical criteria:</b>	
		Patient must not develop disease progression as determined by the treating clinician while receiving PBS subsidised treatment with this drug for this condition. <del>Patients can continue to receive treatment beyond RESIST 1.1 classified disease progression occurs. Decisions on treatment discontinuation should be based on a fully integrated clinical evaluation by the treating clinician.</del>	
		<b>Population criteria:</b>	
		Patients must be aged 18 years or older	
		<b>Administrative Advice:</b>	
		KIMMTRAK is for intravenous use. The recommended infusion period is 15 to 20 minutes. KIMMTRAK requires dilution with sodium chloride 9 mg/mL (0.9%) solution for injection containing human albumin for intravenous infusion.	

	<p><b>For prescriber:</b> For the first three doses (in the initiating phase), KIMMTRACK must be administered under the direction and supervision of a physician experienced in the use of anti-cancer agents and who is prepared to manage cytokine release syndrome in an environment where full resuscitation facilities are immediately available.  <del>Subsequent doses can be administered in appropriate outpatient setting by a trained health care professional. Patients should then be observed for a minimum of 30 minutes following each infusion.</del></p>
	<p><b>Treatment criteria:</b></p>
	<p>According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.</p>
	<p><b>Caution:</b>  Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).</p>

- 3.2 The submission proposed a Special Pricing Agreement in which the ex-manufacturer price per 100 mcg vial was \$1. The pre-PBAC response proposed a revised ex-manufacturer price of \$1 per 100 mcg vial.
- 3.3 The proposed wording of the requested restriction was broader than the eligibility criteria in the key clinical trial (IMCgp100-202), in terms of Eastern Cooperative Oncology Group (ECOG) performance status and prior systemic therapies received by the patients as the requested restriction did not:
- specify the requirement of an ECOG performance status. Patients were eligible to enrol in the IMCgp100-202 trial if they had a ECOG performance status of 0 or 1.
  - restrict the use of tebentafusp in patients who have received prior systemic treatments for metastatic UM, indicating that tebentafusp could be used in subsequent lines of treatment (e.g., after pembrolizumab or other agents). Patients were eligible to enrol in the IMCgp100-202 trial if they had not received prior treatment in the metastatic or advanced setting. A single-arm phase 2 study in patients (n = 127) who had received prior treatment in the metastatic setting reported: response rate = 5%, stable disease = 45%, 12-month OS = 62%<sup>1</sup>.
- 3.4 The recommended dose of tebentafusp is 20 micrograms (mcg) on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg weekly thereafter. The first three doses of tebentafusp require administration as an inpatient to allow for monitoring for signs

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<sup>1</sup> Sacco JJ, et al. 64MO: A phase (ph) II, multi-center study of the safety and efficacy of tebentafusp (tebe)(IMCgp100) in patients (pts) with metastatic uveal melanoma (mUM). *Annals of Oncology* 31 (2020): S1442-S1443

and symptoms of cytokine release syndrome (CRS) during infusion and for 16 hours after infusion is complete.

- 3.5 There is a potential for wastage of tebentafusp. Although the maximum dose is 68 mcg every week, tebentafusp is only available as single-use, 100 mcg vial. The Pre-Sub-Committee Response (PSCR) stated that the volume in excess of 68 mcg is required to account for the 'dead-volume' in standard syringes. The ESC noted that although the explanation relating to wastage was reasonable for a 68 mcg dose, there would be wastage associated with the first two induction doses (20 mcg on Day 1 and 30 mcg on Day 8).
- 3.6 The proposed wording of the continuation restriction allowed for treatment to continue beyond initial disease progression. In the IMCgp100-202 trial, patients who were treated beyond the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 for progressive disease had to permanently discontinue treatment if they experienced further progression, defined as any one of the following observed at least four weeks after the initial progressed disease (PD) assessment per RECIST v1.1: (1) an additional  $\geq 20\%$  increase in tumour burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of  $\geq 5$  mm; (2) unequivocal PD of non-target lesions; or (3) new non-measurable lesions.
- 3.7 The submission did not request listing for grandfathered patients. The submission stated that any existing early access programme (EAP) patients will remain on the programme.

*For more detail in PBAC's view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 UMs are the most common eye-related malignancies in adults. In Australia, the average age-standardised incidence rate of UM was 7.6 (95% CI: 7.3, 7.9) per million between 1982-2014<sup>2</sup>. Based on 1982-2014 data, the overall 5-year survival rate of patients diagnosed with primary UM was around 81% (95% CI: 80%, 82%), with a non-significant average annual percentage change of 0.1%<sup>1</sup>. Approximately, 50% of patients with primary UM develop metastatic disease<sup>3</sup>. Of those with metastatic UM, approximately 47% of patients are HLA-A\*02:01 positive.
- 4.2 Currently, there are no PBS approved treatments for patients diagnosed with metastatic UM in Australia. Cancer Council Australia clinical guidelines for metastatic melanoma (any type) recommend the use of immunotherapies, such as anti-

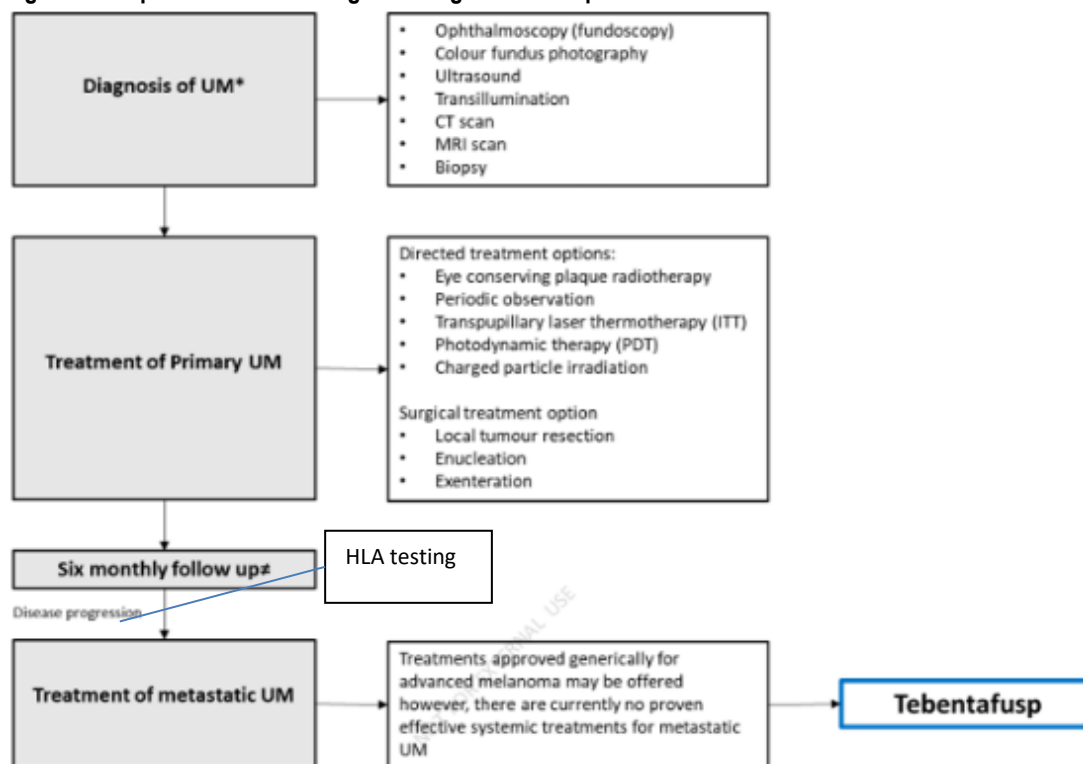
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<sup>2</sup> Beasley A, Preen D et al., (2021), 'Incidence and mortality of uveal melanoma in Australia (1982–2014)', British Journal of Ophthalmology, 0:1-6.

<sup>3</sup> Kolandjian N, Wei C et al., (2013), 'Delayed systemic recurrence of uveal melanoma', American Journal of Clinical Oncology, 36(5):443-449.

programmed death-1 (PD-1) monotherapy (e.g., pembrolizumab or nivolumab) or nivolumab plus ipilimumab (NIVO+IPI) combination therapy. The submission’s proposed place in therapy for tebentafusp is presented in Figure 1.

Figure 1: Proposed clinical management algorithms for patients with uveal melanoma.



Source: Figure 1.1-5, p16 of the submission.

CT = Computerised Tomography scan, MRI = Magnetic Imaging Resonance scan, UM = uveal melanoma.

\*If ocular melanoma is suspected, patient will be referred by their doctor/optometrist to an ophthalmologist specialising in ocular oncology (Cancer Council Australia, 2021)

≠There is currently no consensus on the ideal protocol for follow up and screening for metastatic UM and may vary between centres. A six monthly observation period was suggested for monitoring the growth of lesions in the published literature (Skalicky et al., 2008).

4.3 Tebentafusp, the first in the ImmTACs® class, is a bispecific fusion protein, comprised of a T-cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a glycoprotein 100 (gp100) peptide presented by HLA-A\*02:01 on the cell surface of UM tumour cells, and the effector domain binds to the CD3 receptor on polyclonal T cells. An immune synapse is formed and tebentafusp-activated polyclonal T-cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumour cells.

For more detail in PBAC’s view, see section 7 PBAC outcome.

## 5 Comparator

- 5.1 The submission nominated pembrolizumab as the main comparator. The main arguments provided in support of this nomination were:

Currently, there are no standard treatment for patients with metastatic UM.

Cancer Council Australia clinical guidelines for metastatic melanoma recommend the use of either anti-programmed death-1 (PD-1) monotherapy (e.g., pembrolizumab or nivolumab) or nivolumab plus ipilimumab (NIVO+IPI) combination therapy.

The PBS listing for NIVO+IPI prevents the use of the combination therapy in patients with ocular or UM due to lack of clinical evidence (paragraph 7.2, nivolumab and ipilimumab, Public Summary Document, July 2018 PBAC meeting).

The PBAC previously considered that “nivolumab was non-inferior in terms of both comparative effectiveness and safety to pembrolizumab for the treatment of unresectable Stage III or Stage IV malignant melanoma” (paragraph 7.5, nivolumab, Public Summary Document, November 2015 PBAC meeting).

- 5.2 The ESC considered that the nomination of pembrolizumab monotherapy was appropriate as this represented the most consistently available treatment in Australia.

- 5.3 The evaluation noted that the National Comprehensive Cancer Network (NCCN) guidelines suggest that a combination of treatment options may be needed depending on the location and extent of disease. The NCCN guidelines recommend that metastatic UM patients with symptomatic liver metastases could benefit from liver-directed therapies (e.g., percutaneous hepatic perfusion (PHP) and embolization techniques) or NIVO+IPI<sup>4</sup>. The PSCR noted that the use of liver directed therapies is low (data from the UK indicated that approximately 1% of patients receive live directed therapies). The ESC considered that this may not be reflective of clinical practice in Australia where liver directed therapies are available at larger treatment centres. However, the ESC noted that the rate of liver directed therapy use in Australia was unknown and inconsistently accessible.

- 5.4 Two clinical trials were identified during evaluation which aimed to assess the efficacy of NIVO+IPI as a first-line therapy in patients with metastatic UM, (i) a single arm, phase II study conducted in the USA, which estimated an ORR of 18%, with median OS of 19.1 months and median PFS of 5.5 months for NIVO+IPI<sup>5</sup>, and (ii) a single-arm, phase II trial led by the Spanish Multidisciplinary Melanoma Group (GEM), which estimated median OS and PFS of 12.7 months and 3.0 months respectively for those

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<sup>4</sup> National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology, Melanoma: Uveal, Version 2.2022

<sup>5</sup> Pelster M, Gruschkus S, et al., (2020), ‘Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study’, *Journal of Clinical Oncology* 39, 6:599-607.

treated with NIVO+IPI<sup>6</sup>. Therefore, it may have been useful for the submission to have presented a matching-adjusted indirect comparison (MAIC) comparing tebentafusp with NIVO+IPI using the two published clinical trials of NIVO+IPI in metastatic UM setting. The PSCR compared the individual patient data from the GEM study (NIVO+IPI) with the pembrolizumab subgroup from the April 2022 data cut of Study IMCgp100-202 via a propensity score analysis. The PSCR reported that this resulted in no significant difference in terms of OS (HR = 0.76; 95% CI: 0.49, 1.16). Similarly, a propensity score analysis was conducted comparing tebentafusp with NIVO+IPI, with the adjusted OS favouring tebentafusp (HR = 0.43; 95% CI: 0.29, 0.64). The ESC noted that the methodology used in the propensity score analysis was not presented.

*For more detail in PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### ***Sponsor hearing***

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and the high unmet clinical need for new UM treatments. They also outlined the mechanism of action of tebentafusp and described the potential longer-term benefits of treatment and the management of adverse events. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from individuals (10), health care professionals (7) and organisations (6) via the Consumer Comments facility on the PBS website. The comments from individuals and health care professionals described the high clinical need for new UM treatments and the potential benefits of treatment with tebentafusp including an increased overall survival and improved quality of life.

6.3 The PBAC noted the advice received from the Melanoma and Skin Cancer Advocacy Network (MSCAN), Rare Cancers Australia, Australasian Ocular Melanoma Alliance (AOMA), Melanoma Patients Australia (MPA) and Ocumel Australia and New Zealand Support Group which outlined the high unmet clinical need for new UM treatments and stated that tebentafusp is a well tolerated treatment that improves prognosis and quality of life for patients.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the tebentafusp submission, categorising it as one of the therapies of “highest

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<sup>6</sup> Piulats J, Espinos E, et al., (2021), ‘Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402)’, *Journal of Clinical Oncology* 39, 6:586-598.

priority for PBS listing” on the basis of the IMCgp100-202 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for tebentafusp, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>7</sup>, based on a comparison with investigators choice.

### ***Clinical trials***

- 6.5 The submission was based on one head-to-head randomised trial comparing tebentafusp to investigator’s choice of therapy (pembrolizumab, dacarbazine, or ipilimumab) in previously untreated patients with metastatic UM, IMCgp100-202 (NCT03070392). A claim of superiority was made on the outcome of overall survival.
- 6.6 Additionally, the submission presented results from IMCgp100-102 (NCT02570308), a single-arm study to inform tolerability and safety of tebentafusp in patients with metastatic UM previously treated with one or more lines of therapy. This study was not included in the economic model.
- 6.7 Details of the trials presented in the submission are provided in Table 2.

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<sup>7</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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**Table 2: Trials presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
IMCgp100-202 (NCT03070392)	<p>Immunocore Ltd. Safety and Efficacy of IMCgp100 Versus Investigator Choice in Advanced Uveal Melanoma.</p> <p>Nathan P, Hassel J, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma.</p> <p>Salama A, Cheshuk V, et al. Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in previously untreated patients with metastatic uveal melanoma.</p> <p>Chmielowski B, Kapiteijn E, et al. Characterization of liver function tests following tebentafusp in phase III randomized trial comparing tebentafusp with investigator's choice in first line metastatic uveal melanoma (mUM)</p> <p>Piperno-Neumann S, Hassel J, et al. Phase 3 randomized trial comparing tebentafusp with investigator's choice in first line metastatic uveal melanoma.</p> <p>Hassel J, Rutkowski P, et al. Co-primary endpoint of overall survival for tebentafusp (tebe) - induced rash in a phase 3 randomized trial comparing tebe versus investigator's choice (IC) in first-line metastatic uveal melanoma.</p>	<p>2017</p> <p><i>New England Journal of Medicine</i> 2021; 385, 1196-206</p> <p><i>Annals of Oncology</i> 2021; 32,5</p> <p><i>Annals of Oncology</i> 2021, 32, S856-S857</p> <p><i>Cancer Research</i> 2021, 18, 13_supplement</p> <p><i>Journal of Clinical Oncology</i> 2021, 39, 15_supplement</p>
IMCgp100-102 (NCT02570308)	<p>Immunocore Ltd. A Study of the Intra-Patient Escalation Dosing Regimen With IMCgp100 in Patients With Advanced Uveal Melanoma.</p> <p>Carvajal R, Sacco J, et al. Phase I Study of Safety, Tolerability, and Efficacy of Tebentafusp Using a Step-Up Dosing Regimen and Expansion in Patients With Metastatic Uveal Melanoma.</p> <p>Sacco J, Carvajal R, et al. Updated survival of patients with previously treated metastatic uveal melanoma who received tebentafusp.</p> <p>Piulats J, Sato T, et al. Similar overall survival in tebentafusp-treated 2L+ metastatic uveal melanoma regardless of prior immunotherapy.</p> <p>Piperno-Neumann S, Hassel J, et al. Kinetics of radiographic response for tebentafusp (tebe) in previously treated metastatic uveal melanoma (mUM) patients (pts) achieving prolonged survival.</p> <p>Sato T, Carvajal R, et al. Characterization of liver function tests (LFTs) following tebentafusp (tebe) in previously treated (2L+) metastatic uveal melanoma (mUM) patients (pts).</p> <p>Carvajal R, Sato T, et al. Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in patients (pts) with previously treated (2L+) metastatic uveal melanoma (mUM).</p> <p>Sacco J, Carvajal R, et al. A phase (ph) II, multi-center study of the safety and efficacy of tebentafusp (tebe) (IMCgp100) in patients (pts) with metastatic uveal melanoma (mUM).</p> <p>Dato T, Nathan P, et al. Intra-patient escalation dosing strategy with IMCgp100 results in mitigation of T-cell based toxicity and preliminary efficacy in advanced uveal melanoma.</p>	<p>2016</p> <p><i>Journal of Clinical Oncology</i> 2022, 40, 17</p> <p><i>Journal for ImmunoTherapy of Cancer</i> 2021, 9</p> <p><i>Annals of Oncology</i> 2021; 32,5, S854</p> <p><i>Cancer Research</i> 2021, 18, 13_supplement</p> <p><i>Journal of Clinical Oncology</i> 2021, 35, 15_supplement</p> <p><i>Journal of Clinical Oncology</i> 2021, 39, 15_supplement</p> <p><i>Annals of Oncology</i> 2020, 31, Supplement 7</p> <p><i>Journal of Clinical Oncology</i> 2017, 35, 15_supplement</p>

Source: e A3.1 of Appendix 3 to the submission.

6.8 The key features of the direct randomised trial are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Tebentafusp versus Investigator's Choice arm</b>						
IMCgp100-202	Total = 378 Tebentafusp, n = 252 Investigator choice, n = 126 (Pembrolizumab, n = 103; Dacarbazine, n = 7; and Ipilimumab, n = 16)	R, OL, MC Median duration of follow-up of 29.6 months	Low	Previously untreated patients with metastatic UM	OS, PFS, ORR, DOR, AEs, HRQoL	OS, PFS, TTD, AE and HRQoL

Source: Section 2.4, pp39-62

AE = adverse event, DOR = duration of response, HRQoL = health-related quality of life, MC = multi-centre, N = total participants in group, n = number of participants reporting data, OL = open label, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, R = randomised, TTD = time-to-treatment discontinuation, UM = uveal melanoma.

6.9 The submission presented key primary outcomes for the Intention-to-treat (ITT) population, which included all randomised patients in the IMCgp100-202 trial.

6.10 The submission also presented a post-hoc subgroup analysis to inform efficacy and safety of tebentafusp compared to the main comparator, pembrolizumab. The comparison was between a subgroup of patients in the tebentafusp intervention arm pre-selected to receive pembrolizumab prior to randomisation, termed “pre-choice pembrolizumab” (PCP) and patients who received pembrolizumab in the investigator’s choice arm. The prognostic variables for patients preselected for dacarbazine or ipilimumab (e.g., lactate dehydrogenase (LDH) levels) were different to patients pre-selected for pembrolizumab prior to randomisation; however, the impact of the difference in prognostic variables on the relative effectiveness of tebentafusp compared to pembrolizumab is not clear.

6.11 For the IMCgp100-202 trial, the submission presented results based on first interim analyses in October 2020 and an updated data sweep in April 2022. Following the first interim analysis, a subsequent amendment was made to the protocol which allowed patients randomised to in the investigator’s choice treatment arm to switch to tebentafusp arm in a crossover extension (see paragraph 6.17).

## **Comparative effectiveness**

### **IMCgp100-202 trial**

#### **Overall Survival (OS) and Progression-Free Survival (PFS)**

6.12 Table 4 summarises the OS and PFS results from the IMCgp100-202 trial for the ITT population as well as the subgroup population (data sweep: April 2022).

**Table 4: Summary of OS and PFS outcomes in IMCgp100-202 trial (Data sweep: April 2022a, median duration of follow up = 29.6 months)**

ITT Population	Tebentafusp n/N (%)	Investigator choice n/N (%)	Absolute difference	HR (95% CI)
<b>OS</b>				
Deaths, n/N (%)	162/252 (64%)	91/126 (72%)	-	-
Median months OS (95% CI)	21.6 (19.1, 24.3)	16.9 (13.1, 20.5)	4.8	<b>0.63 (0.49, 0.82)</b>
<b>PFS</b>				
Patients with event	231/252 (92%)	102/126 (81%)	-	-
Median months PFS (95% CI)	3.4 (3.0, 5.5)	2.9 (2.8, 3.0)	0.5	<b>0.76 (0.60, 0.96)</b>
Subgroup Population	Tebentafusp PCP n/N (%)	Pembrolizumab n/N (%)	Absolute difference	HR (95% CI)
<b>OS</b>				
Deaths, n/N (%)	126/199 (63%)	70/103 (68%)	-	-
Median months OS (95% CI)	21.7 (19.1, 24.3)	16.9 (12.9, 20.6)	4.8	<b>0.66 (0.49, 0.89)</b>
<b>PFS</b>				
Patients with event	183/199 (92%)	82/103 (80%)	-	-
Median months PFS (95% CI)	3.5 (3.0, 5.5)	2.9 (2.8, 3.6)	0.6	0.82 (0.63, 1.1)

Source: Table 5, p8 of the Executive Summary.

CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, n = number of participants reporting data, N = total participants in group, OS = overall survival, PCP = pre-choice pembrolizumab, PFS = progression-free survival.

<sup>a</sup> The data includes cross overs from the Investigator's Choice to tebentafusp arm between October 2020 and April 2022

**Bold** indicates statistically significant results.

*Italics* corrected during evaluation.

- 6.13 In IMCgp100-202, at the first interim analysis (data cut-off: October 2020; median duration of follow-up of 14.1 months), tebentafusp was associated with statistically significantly improvement in OS compared to the investigator's choice arm (HR: 0.51; 95% CI: 0.37, 0.71). Updated data from April 2022 data sweep (median duration of follow-up of 29.6 months) showed that OS remained superior in the tebentafusp arm when compared to the investigator's choice arm, with an HR of 0.63 (95% CI: 0.49, 0.82).
- 6.14 For the subgroup analysis, OS was statistically significantly longer in the tebentafusp PCP arm compared to the pembrolizumab arm (median OS of 21.7 months for tebentafusp PCP versus 16.9 months for pembrolizumab), with a hazard ratio of 0.66 (95% CI: 0.49, 0.89).
- 6.15 In IMCgp100-202, at the first interim analysis (data cut-off: October 2020), tebentafusp was associated with a statistically significant improvement in PFS compared with investigator's choice (HR = 0.73; 95% CI: 0.58, 0.94). The improvement in PFS associated with tebentafusp from the April 2022 data sweep analysis was consistent with the interim analysis, with an absolute difference of 0.5 months.
- 6.16 For the subgroup analysis, PFS was longer in the tebentafusp PCP arm compared to the pembrolizumab arm, with an absolute difference of 0.6 months. The extent of benefit with tebentafusp on PFS was relatively low compared to the magnitude of improvement in OS.

6.17 Patients from the investigator’s choice arm were allowed to cross over to tebentafusp arm between October 2020 and April 2022. The submission did not adjust the survival data for patients switching treatment due to following reasons:

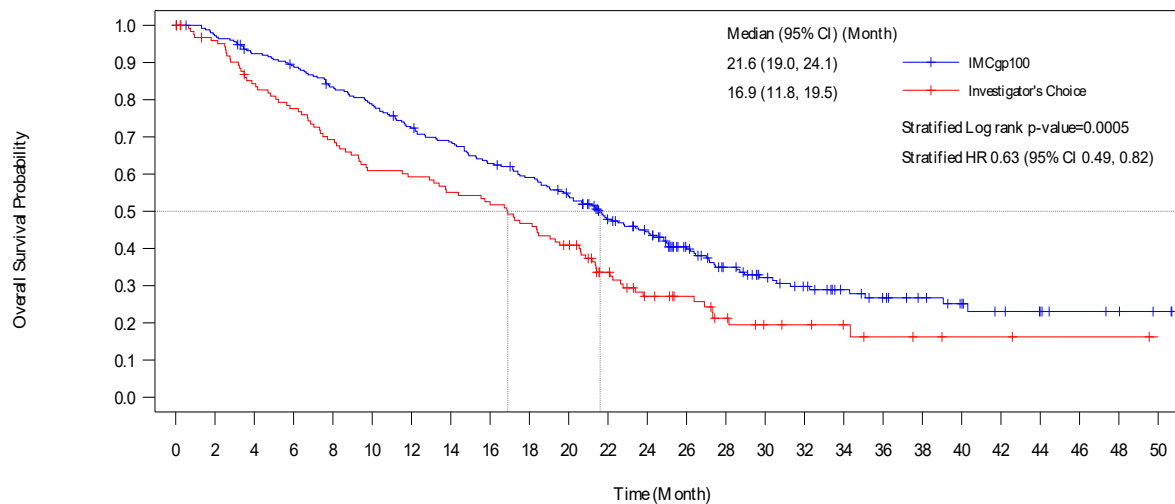
There were too few patients (n=14) who crossed over to tebentafusp to support a statistical analysis and adjustment for differences.

Cross-over was not mandated in the protocol so there was no clinical rule for determining the time of cross-over, which would have produced significant additional uncertainty in an adjustment for cross-over, as stated above.

All patients who crossed over from the investigator’s choice treatment to tebentafusp had confirmed disease progression and discontinued treatment at the time of cross-over.

6.18 Figure 2 and Figure 3 present the Kaplan-Meier (KM) OS and PFS plots for the ITT population in IMCgp100-202 trial (data sweep: April 2022).

Figure 2: KM analysis of OS in IMCgp100-202 trial (Data sweep: April 2022)



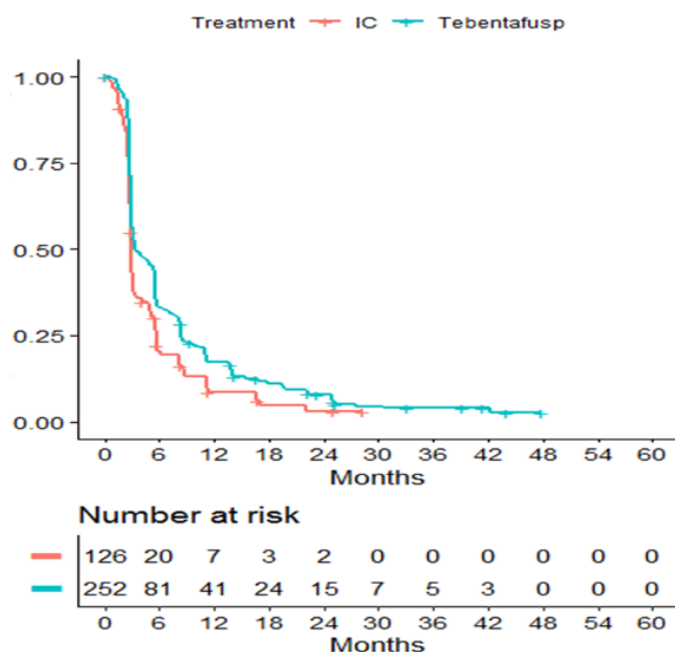
Number of subjects at risk

IM Cgp100	252	243	228	219	204	192	176	166	152	141	127	103	91	68	53	42	35	27	22	18	14	10	7	5	4	2
Investigator's Choice	126	116	101	93	83	73	71	66	63	56	48	33	23	19	13	9	8	6	4	3	2	2	1	1	1	0

Source: Figure 2.5-1 B, p64 of the submission.

CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, OS = overall survival.

Figure 3: KM analysis of PFS for ITT population in IMCgp100-202 trial (Data sweep: April 2022)



Source: Figure 2.5-8 B, p73 of the submission.

IC = investigator's choice, ITT = intention-to-treat, KM = Kaplan-Meier, PFS = progression-free survival.

### Objective Response Rate (ORR)

6.19 Table 5 summarises the results for ORR, best overall response and disease control rate in IMCgp100-202 trial for the ITT population (data cut-off: October 2020).

Table 5: Summary of ORR, BOR, DCR in IMCgp100-202 trial (data cut-off: October 2020; median duration of follow up = 14.1 months)

	Tebentafusp	Investigator choice
<b>Objective response rate (CR or PR)</b>		
n (%)	23 (9.1%)	6 (4.8%)
95% CI	5.9, 13.4	1.8, 10.1
Stratified odds ratio (95% CI of odds ratio)	1.98 (0.79, 4.97)	
<b>Best overall response</b>		
CR, n (%)	1 (0.4%)	0 (0.0%)
PR, n (%)	22 (8.7%)	6 (4.8%)
PD, n (%)	131 (52.0%)	78 (61.9%)
SD ≥ 12 weeks, n (%)	92 (36.5%)	28 (22.2%)
Not evaluable	6 (2.4%)	14 (11.1%)
<b>Disease control rate (CR or PR or SD ≥ 12 weeks)</b>		
n (%)	115 (45.6%)	34 (27.0%)
95% CI	39.4, 52.0	19.5, 35.6
Stratified odds ratio (95% CI of odds ratio)	2.33 (1.45, 3.75)	

Source: Table 2.5.4, p75 of the submission.

BOR = best overall response, CI = confidence interval, CR = complete response, DCR = disease control rate, n = number of participants reporting data, N = total participants in group, PD = progressive disease, PR = partial response, SD = stable disease.

- 6.20 At the first interim analysis (data cut-off: October 2020), the ORR was higher in the tebentafusp arm compared with investigator’s choice arm (9.1% compared with 4.8%).

**Duration of Response (DOR)**

- 6.21 Table 6 summarises the results for duration of response in IMCgp100-202 trial (data cut-off: October 2020).

**Table 6: Summary of DOR in IMCgp100-202 trial (data cut-off: October 2020; median duration of follow up = 14.1 months)**

	<b>Tebentafusp</b>	<b>Investigator choice</b>
Patients achieving ORR (N)	23	6
Median follow-up, months (95% CI)	10.8 (2.8, 13.8)	9.3 (2.8, NE)
<b>Duration of Response</b>		
PFS events, n (%)	9 (39.1%)	4 (66.7%)
PD	9 (39.1%)	4 (66.7%)
Death	0 (0.0%)	0 (0.0%)
Median (95% CI), months	9.9 (5.4, NE)	9.7 (2.7, NE)
<b>Kaplan Meier estimates for DOR (95% CI) [No. at risk]</b>		
3 months	84.8 (59.5, 94.9) [n = 14]	50.0 (11.1, 80.4) [n = 2]
6 months	60.6 (34.2, 7.2 <sup>a</sup> ) [n = 10]	50.0 (11.1, 80.4) [n = 2]
9 months	54.5 (28.9, 74.4) [n = 7]	50.0 (11.1, 80.4) [n = 2]
12 months	46.8 (21.8, 68.4) [n = 4]	50.0 (11.1, 80.4) [n = 2]

Source: Table 2.5.6, p77 of the submission.

DOR = duration of response, CI = confidence interval, n = number of participants reporting data, N = total participants in group, NE = not estimated, ORR = overall response rate, PD = progressive disease, PFS = progression-free survival.

<sup>a</sup> There was an error in reporting the Kaplan-Meier estimated for DOR at 6 months.

- 6.22 At the first interim analysis (data cut-off: October 2020), median duration of response was 9.9 months for tebentafusp compared to 9.7 months for investigator’s choice. However, the results were uncertain given the low number of patients achieving ORR (23 in the tebentafusp arm and 6 in the investigator’s choice arm).

**IMCgp100-102 study**

- 6.23 The submission presented data from the single-arm IMCgp100-102 study to inform the tolerability and safety of tebentafusp. The results from the IMCgp100-102 study (median duration of follow-up of 19.6 months) are summarised below:

the median OS was 16.8 months (95% CI: 12.9, 21.3). The OS rate at 12 months was 61.8% (95% CI: 52.6%, 69.8%) and at 24 months it was 37.0% (95% CI: 26.5%, 47.5%).

The median PFS (assessed by RECIST v1.1 by the investigator) was 2.3 months (95% CI: 1.9, 3.7). The PFS rate at 6 months was 25.8% (95% CI: 18.5%, 33.7%) and at 12 months was 12.8% (95% CI: 7.6%, 19.4%).

ORR of partial response was observed in 9 (7.1%) patients per investigator assessment. No patient had a complete response.

The median DOR per investigator assessment was not estimable. The landmark analysis of duration of response was 75.0% (95% CI: 31.5%, 93.1%) at 6 months and 56.3% (95% CI: 14.7%, 84.2%) at 12 months.

- 6.24 Overall, the results from the IMCgp100-102 study were consistent with the results for tebentafusp arm in the IMCgp100-202 trial. The submission could have performed a comparison of survival data from IMCgp100-202 and IMCgp100-102 trial to inform the efficacy of tebentafusp among patients who have received prior systemic therapy and those patients who have not. The comparison would have been informative given the wording of the proposed restriction does not restrict the use of tebentafusp in patients who have received prior systemic treatments for metastatic UM.

### ***Comparative harms***

- 6.25 The submission presented safety data for safety analysis set (SAS) (data cut-off: October 2020) as well as for subgroup population (tebentafusp PCP and pembrolizumab; data sweep: April 2022) from the IMCgp100-202 trial. A summary of key adverse events in SAS and subgroup populations is summarised in Table 7.

**Table 7: Summary of key adverse events in the trials in SAS population (data cut-off: October 2020) and the subgroup population (data sweep: April 2022)**

SAS Population	Tebentafusp n/N (%)	Investigator choice n/N (%)	RD (95% CI)	RR (95% CI)
Any TEAE	245/245 (100%)	105/111 (94.6%)	0.05 (0.01, 0.10)	1.06 (1.01, 1.11)
Any related TEAE a	243/245 (99.2)	91/111 (82.0%)	0.17 (0.10, 0.24)	1.21 (1.11, 1.32)
Any TEAE with CTCAE Grade ≥ 3	133/245 (54.3%)	40/111 (36.0%)	0.18 (0.07, 0.29)	1.51 (1.15, 1.98)
Any related TEAE with CTCAE Grade ≥ 3	109/245 (44.5%)	19/111 (17.1%)	0.27 (0.18, 0.37)	2.60 (1.69, 4.01)
• Rash	9.4%	0.0%	NR	NR
• Maculo-papular rash	8.6%	0.0%	NR	NR
• Hypertension	8.6%	2.7%	NR	NR
• Increased AST	5.3%	0.9%	NR	NR
• Fatigue	5.3%	0.9%	NR	NR
Any TESAE	69/245 (28.2%)	26/111 (23.4%)	0.05 (-0.05, 0.14)	NR (0.81, 1.78)
Any related TESAE	54/245 (22.0%)	8/111 (7.2%)	0.15 (0.08, 0.22)	3.06 (1.51, 6.21)
Any TEAE leading to death	1/245 (0.4%)	2/111 (1.8%)	-0.01 (-0.04, 0.01)	0.23 (0.02, 2.47)
Any related TEAE leading to death	0	0	NA	NA
Any TEAE leading to study drug discontinuation	8/245 (3.3%)	7/111 (6.3%)	-0.03 (-0.08, -0.02)	0.52 (0.19, 1.339)
Any related TEAE leading to study drug discontinuation	5/245 (2.0%)	5/111 (4.5%)	-0.02 (-0.07, -0.02)	0.45 (0.13, 1.53)
Subgroup Population	Tebentafusp PCP n/N (%)	Pembrolizumab n/N (%)	RD (95% CI)	RR (95% CI)
Any TEAE	193/193 (100%)	87/91 (95.6%)	4.4 (0.2, 8.6)	1.05 (1.00, 1.09)
Any related TEAE	191/193 (99.0%)	73/91 (80.2%)	18.7 (10.4, 27.1)	1.23 (1.11, 1.37)
Any TEAE with CTCAE Grade ≥ 3	115/193 (59.6%)	32/91 (35.2%)	24.4 (12.4, 36.4)	1.69 (1.25, 2.29)
Any related TEAE with CTCAE Grade ≥ 3	88/193 (45.6%)	15/91 (16.5%)	29.1 (18.7, 39.5)	2.77 (1.70, 4.50)
Any TESAE	57/193 (29.5%)	16/91 (17.6%)	12.0 (1.8, 22.1)	1.68 (1.02, 2.76)
Any related TESAE	35/193 (18.1%)	5/91 (5.5%)	12.6 (5.5, 19.8)	3.30 (1.34, 8.14)
Any TEAE leading to study drug discontinuation	7/193 (3.6%)	6/91 (6.6%)	-3.0 (-8.7, 2.8)	0.55 (0.19, 1.59)
Any related TEAE leading to study drug discontinuation	4/193 (2.1%)	4/91 (4.4%)	-2.3 (-7.0, 2.3)	0.47 (0.12, 1.84)

Source: Table 2.5.8, p81 and Table 2.5.9, pp81-82 of the submission.

CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, n = number of participants reporting data, N = total participants in group, NR = not reported, PCP = pre-choice pembrolizumab, RD = risk difference, RR = relative risk, SAS = safety analysis set, TEAE = treatment-emergent adverse event, TESAE = treatment emergent serious adverse event.

6.26 For the SAS population, all patients in the tebentafusp arm experienced a treatment-emergent adverse event (TEAE), compared to 94.6% patients in the investigator's choice arm. Tebentafusp was associated with more Grade ≥ 3 treatment-related TEAEs when compared with investigator's choice arm (44.5% compared with 17.1%) and more treatment-related serious TEAE (22.0% compared with 7.2%). The PSCR noted that 3.3% of patients in the tebentafusp arm and 6.6% in the pembrolizumab discontinued treatment due to TEAE.

- 6.27 A total of 84 (34.3%) patients in the tebentafusp arm and 57 (51.4%) patients in the investigator's choice arm died. The majority of patients in both treatment arms died due to disease progression and none of the deaths in either arm was considered to be treatment related.
- 6.28 Similar to the SAS population, all patients in the tebentafusp PCP arm experienced a TEAE compared to 95.6% patients in the pembrolizumab arm. Tebentafusp PCP was associated with more Grade  $\geq 3$  treatment-related TEAEs when compared with pembrolizumab (45.6% compared with 16.5%) and more treatment-related serious TEAE (18.1% compared with 5.5%). The submission did not report death-related data for the subgroup population.
- 6.29 According to the TGA Product Information (PI) for tebentafusp, a boxed warning is included for CRS as it has the potential to become serious or life-threatening if not managed appropriately. Special warning for skin reactions and elevated hepatic enzymes are also included in the TGA PI.
- 6.30 In the IMCgp100-202 trial (SAS population), 89% of patients in the tebentafusp arm experienced any grade CRS (Grade 1: 12%; Grade 2: 76%; Grade 3: 0.8%); however, no patients experienced CRS of Grade 4 or died due to CRS. The most common CRS associated AEs were pyrexia (76%), hypotension (38%), chills (47%), nausea (43%), vomiting (26%), fatigue (41%) and headache (22%). The ESC noted that Australian prescribing clinicians would have little experience managing CRS. The ESC therefore considered that it was possible that the incidence of adverse events associated with CRS in IMCgp100-202 underestimated the real-world potential harms of tebentafusp, particularly with regard to the risk of death from CRS.
- 6.31 Additionally, acute skin reactions occurred in 91% of patients treated with tebentafusp, including any grade rash (83.0%), pruritus (69.0%), erythema (25.0%) and cutaneous oedema (grouped term, 27.0%). Most skin reactions observed in the tebentafusp were of were Grade 1 (27.0%), Grade 2 (38.0%) and Grade 3 (18.4%). No patient experienced skin reactions of Grade 4 or died due to skin reactions.
- 6.32 In IMCgp100-102 trial, the most common Grade  $\geq 3$  treatment-related TEAEs were maculopapular rash (13%), hypotension (8%), increased aspartate aminotransferase (AST; 5%), and hypophosphatemia (5%).

### ***Benefits/harms***

- 6.33 A summary of the comparative benefits and harms for tebentafusp versus investigator's choice is presented in Table 8.

**Table 8: Summary of comparative benefits and harms for tebentafusp and investigators choice (data cut-off: October 2020; median duration of follow up = 14.1 months)**

<b>Benefits</b>						
	<b>Tebentafusp</b>	<b>Investigator choice</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>		
<b>Progression free survival</b>						
Progressed, n (%)	198/252 (78.6%)	97/126 (77.0%)	-	<b>0.73 (0.58, 0.94)</b>		
Median PFS, months (95% CI)	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)	0.4 months			
% not progressed at 12 months	14.1 (9.5, 19.5)	6.2 (2.3, 13.0)	7.9			
% not progressed at 24 months	9.2 (5.1, 14.8)	0.0	9.2			
<b>Overall survival</b>						
Deaths, n/N (%)	87/252 (34.5%)	63/126 (50.0%)	-	<b>0.51 (0.37, 0.71)</b>		
Median OS, months (95% CI)	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)	5.7 months			
% alive at 12 months (95% CI)	73.2 (66.4, 78.8)	58.5 (48.3, 67.3)	14.7			
% alive at 24 months (95% CI)	44.8 (34.9, 54.2)	20.3 (9.1, 34.7)	24.5			
<b>Harms</b>						
	<b>Tebentafusp</b>	<b>Investigator choice</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients</b>		<b>RD (95% CI)</b>
				<b>Tebentafusp</b>	<b>Investigator choice</b>	
Any TEAE	245/245 (100%)	105/111 (94.6%)	1.06 (1.01, 1.11)	100	95	0.05 (0.01, 0.10)
Any related TEAE	243/245 (99.2)	91/111 (82.0%)	1.21 (1.11, 1.32)	99	82	0.17 (0.10, 0.24)
Any TEAE with CTCAE Grade ≥ 3	133/245 (54.3%)	40/111 (36.0%)	1.51 (1.15, 1.98)	54	36	0.18 (0.07, 0.29)
Any related TEAE with CTCAE Grade ≥ 3	109/245 (44.5%)	19/111 (17.1%)	2.60 (1.69, 4.01)	45	17	0.27 (0.18, 0.37)
Any TESAE	69/245 (28.2%)	26/111 (23.4%)	NR (0.81, 1.78)	28	23	0.05 (-0.05, 0.14)
Any related TESAE	54/245 (22.0%)	8/111 (7.2%)	3.06 (1.51, 6.21)	22	7	0.15 (0.08, 0.22)
Any TEAE leading to death	1/245 (0.4%)	2/111 (1.8%)	0.23 (0.02, 2.47)	1	2	-0.01 (-0.04, 0.01)
Any TEAE leading to study drug discontinuation	69/245 (28.2%)	26/111 (23.4%)	0.52 (0.19, 1.39)	28	23	-0.03 (-0.08, -0.02)
Any related TEAE leading to study drug discontinuation	54/245 (22.0%)	8/111 (7.2%)	0.45 (0.13, 1.53)	22	7	-0.02 (-0.07, -0.02)

Source: Table 5, p8 of the Executive Summary; Table 2.5.8, p81 of the submission; Table 16, p67 and Table 18, pp69-70 of Clinical Study Report.

AE = adverse event, CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, n = number of participants reporting data, N = total participants in group, OS = overall survival, HR = hazard ratio, Pembro = pembrolizumab, PFS = progression-free survival, RD = risk difference, RR = risk ratio, TEAE = treatment emergent adverse event, TESAE = treatment emergent serious adverse event.

**Bold** indicates statistically significant results.

6.34 On the basis of direct evidence presented by the submission, for every 100 patients treated with tebentafusp in comparison with investigators choice:

Approximately 8 additional patients will remain progression free after 12 months and 9 additional patients will remain progression free after 24 months.

Approximately 15 additional patients will be alive after 12 months and 25 additional patients will be alive after 24 months.

- 6.35 On the basis of direct evidence presented by the submission, for every 100 patients treated with tebentafusp in comparison with investigator's choice, over a median duration of follow-up of 14.1 months:
- Approximately 27 additional patients would experience treatment related adverse events ( $\geq$  Grade 3).
  - Approximately 15 additional patients would experience treatment related serious adverse events.
- 6.36 As noted above, the ESC considered that Australian prescribing clinicians would have little experience managing CRS. The ESC therefore considered that it was possible that the harms associated with tebentafusp in IMCgp100-102 underestimated the real-world potential for adverse events, particularly the risk of death associated with CRS.

### ***Clinical claim***

- 6.37 The submission described tebentafusp as superior in terms of effectiveness compared to pembrolizumab. The PBAC agreed with ESC and considered that this claim was adequately supported.
- 6.38 The submission described tebentafusp as non-inferior in terms of safety compared to pembrolizumab. The PBAC agreed with ESC and considered that this claim was not supported as tebentafusp was associated with:
- CRS, which may be serious or life-threatening;
- more treatment-related TEAEs ( $\geq$  Grade 3) compared to investigator's choice (44% compared to 17%); and
- more Grade  $\geq$  3 treatment-related TEAEs when compared with pembrolizumab (45.6% compared to 16.5%) and more treatment-related serious TEAEs (18.1% compared with 5.5%).

### ***Economic analysis***

- 6.39 The submission presented a cost-utility analysis (CUA) comparing tebentafusp versus pembrolizumab. A summary of the model structure is presented in Table 9.

**Table 9: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Tebentafusp versus pembrolizumab
Time horizon	20 years in the model base case versus a maximum duration of follow-up of 50 months in the trial. Reduced to 15 years in the pre-PBAC response.
Outcomes	LYs gained; QALYs gained
Methods used to generate results	Partitioned survival model
Health states	3 mutually exclusive health states: pre-progression; post-progression; and death
Cycle length	One-week cycle
Transition probabilities or Allocation to health states (if partitioned survival model)	The proportions of patients in each health state at each cycle are based on the OS and PFS curves.
Extrapolation method	<p>For tebentafusp, OS was modelled using a piecewise approach whereby OS KM estimates from the IMCgp100-202 trial were used up to 28 months, after which extrapolation was applied using log-normal distribution.</p> <p>For pembrolizumab, a standard parametric model, using Weibull distribution, was fitted to observed OS KM estimates from IMCgp100-202 trial.</p> <p>For both treatment arms, PFS was modelled using a piecewise approach whereby PFS KM estimates from the IMCgp100-202 trial were used up to the time point when 10% of the patients remain at risk, after which extrapolation was applied using generalised gamma distribution.</p> <p>For both treatment arms, TTD was modelled using a piecewise approach whereby TTD KM estimates from the IMCgp100-202 trial were used up to the time point when 10% of the patients remain at risk, after which extrapolation was applied using exponential distribution.</p> <p>83% of the incremental LYGs (discounted) occurred in the extrapolated period.</p>
Health-related quality of life	Utility values were based on a time-to-death approach.

Source: Table 3.1.1, p120 and Section 3.2, pp120-130 of the submission.

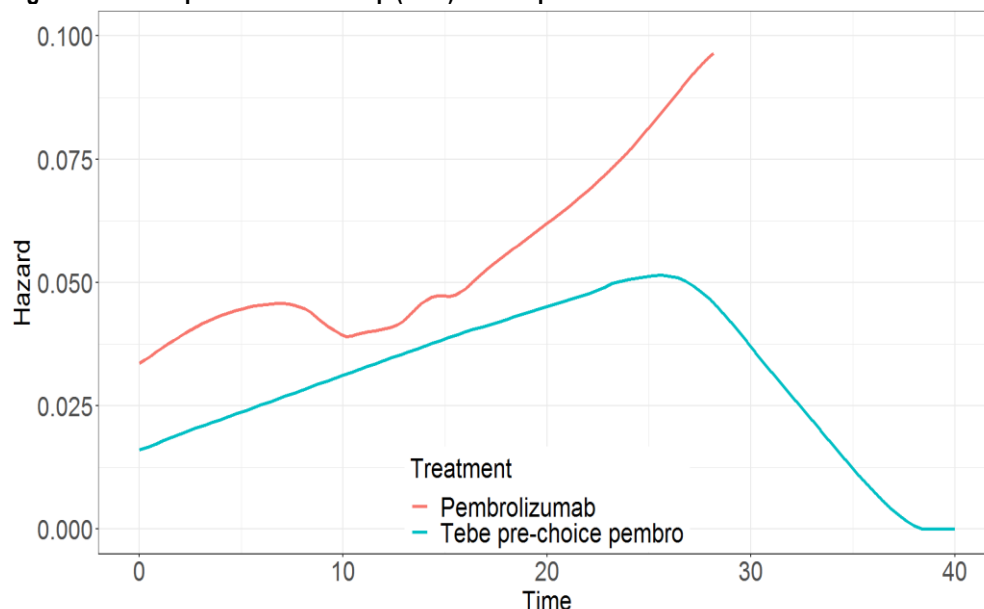
EQ-5D = European Quality of Life Five Dimension, LY = life-years, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life years, TA = technology appraisal, TTD = time-to-treatment discontinuation.

- 6.40 The submission presented a partitioned survival model with three mutually exclusive health states: pre-progression, post-progression, and death, to model the costs and health outcomes for tebentafusp versus pembrolizumab for the treatment of advanced UM. In the partitioned model, extrapolation of the hazard was based only on the time trend in the hazard observed for the within-trial period (up until 28 months in this model) which was unrealistically generalised throughout the extrapolation period (up to 20 years).
- 6.41 In the base case, the intervention arm of the economic model was informed by the subgroup of patients in the tebentafusp arm pre-selected to receive pembrolizumab prior to randomisation (tebentafusp PCP) and the control arm was informed by the subgroup of the investigator's choice arm who received pembrolizumab in the IMCgp100-202 trial.
- 6.42 The trial-based economic evaluation was based on observed KM estimates from the IMCgp100-202 trial, using the latest data cut-off (April 2022), at which point the

maximum duration of follow-up was approximately 50 months. Parametric distributions with best relative fit according to Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC), visual inspection and clinical plausibility were used to extrapolate the KM function curves (OS, PFS, time-to-treatment discontinuation (TTD)) over a time horizon of 20 years.

- 6.43 The time horizon of 20 years was long for this population, given patients with metastatic disease have poor prognosis, with a median overall survival of 10-12 months. The PSCR stated that although the survival of patients treated with the current standard of care is short, a proportion of patients in the IMCgp100-202 trial experienced long-term survival as demonstrated by the sustained plateau effect beyond Year 3 in the tebentafusp arm. The ESC noted that the number of patients remaining at risk beyond 3 and 4 years was small (i.e. < 10% and < 2% respectively, see Figure 2), meaning the Kaplan Meier estimates were unreliable and the assumption of a plateau effect was not supported by the available data. The pre-PBAC response presented a revised base case in which the time horizon was reduced to 15 years.
- 6.44 The submission used different modelling approaches for the extrapolation of OS in the tebentafusp and pembrolizumab arms as the assumption of proportional hazards was not met. The submission stated that the hazard plots for OS, presented in Figure 4, were distinct between the tebentafusp arm and the pembrolizumab arm. This was reasonable for the trial period.
- 6.45 The submission used the trial data to create the hazard plot (Figure 4); however, it did not provide information as to how the hazard would look beyond the duration of the trial to validate the modelling approach used. According to the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 21, to accurately capture OS functions, there is a need to consider the hazards both within the trial period and beyond the duration of the trial. Registry data or data from the single-arm study of tebentafusp (IMCgp100-102) could have been used to provide external validation of the model. The ESC considered that the submission should follow the advice of NICE TDS 21 (page 88) and:
- Present the fitted and extrapolated hazard and survival functions;
  - Plot the expected general population survival and hazard functions (to test plausibility);
  - Incorporate background mortality into the model (to avoid highly implausible assumptions);
  - Incorporate other external information, such as registry data if available, being careful to account for any differences in the external population; and
  - Apply these principles to both arms of the trial.

Figure 4: Hazard plot for tebentafusp (PCP) versus pembrolizumab



Source: Figure 3.4-4, p137 of the submission.  
PCP = pre-choice pembrolizumab.

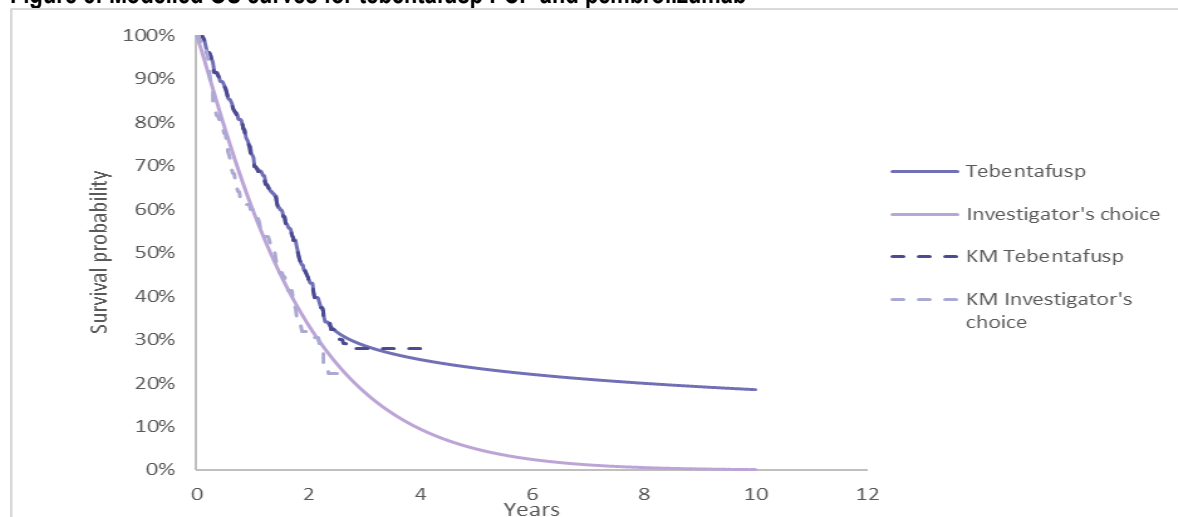
6.46 For tebentafusp, the submission used piecewise modelling given the biphasic hazard plot (increasing then decreasing hazard) observed in the tebentafusp PCP arm. The OS KM data from the IMCgp100-202 trial were used up to 28 months (where the change in hazard was observed; piece 1). For the plateau period beyond 28 months, a log-normal distribution was applied to the remaining Kaplan Meier data (piece 2). The modelling was piecewise as the Kaplan Meier data prior to the cut-point (i.e. 28 months) were not used to inform the extrapolation after the cut-point. The use of the piecewise approach and the appropriateness of the chosen cut-point was not clinically justified by the submission given the assumed sudden change in hazard at 28 months. Additionally, the splitting of the dataset at the chosen cut-point results in a reduced sample size in the later segment of the curve. This results in increased uncertainty in the extrapolated component over the remaining time horizon. Standard parametric models such as log-log, log-normal or generalised gamma can represent hazard that initially increases and then decreases (one turning point). It may have been more appropriate to use a standard survival modelling approach to estimate the economic impact of tebentafusp. The PSCR acknowledged that standard parametric models, such as log-logistic, log-normal, and generalized gamma can comprise a time-dependent mix of increasing hazard followed by decreasing hazard. However, the PSCR stated that the shape of the hazard plot of tebentafusp was distinct to that of these models which were unable to fit the plateau and capture the long-term survivors. Therefore, the PSCR stated that standard parametric models are not appropriate to model OS for tebentafusp and that the piece wise approach was

reasonable. The ESC reiterated that the low number of patients remaining at risk after approximately 36 months meant that the assumption of a plateau effect for OS in the tebentafusp arm was unreliable. Additionally, the ESC noted that the hazard plots also become unstable when there a small number of patients remaining at risk. Thus, the ESC considered that the piecewise model applied to the tebentafusp arm was highly optimistic.

6.47 The submission used a standard parametric approach to extrapolate OS for the pembrolizumab arm. Although the log-normal function had the lowest AIC/BIC values, the submission stated that the Weibull distribution was applied to the pembrolizumab OS curve based on clinical plausibility and a comparison with published historical pooled data from Rantala et al. (2019)<sup>8</sup>. As the pooled data did not include treatment modalities such as protein kinase inhibitors or checkpoint inhibitors, including anti-CTLA4 or anti-PD-L1 antibodies, the comparison of the modelled curves was not appropriate. The PSCR stated that choice of a model is informed by the goodness of fit, visual inspection and clinical plausibility of the predictions in the long-term. The PSCR noted that the log-normal extrapolation predicted that 11.5% of patients would be alive at 5 years which did not align with the historical data that indicated a 0 to 5% survival probability at 5 years (Ranata, 2019).

6.48 Modelled OS curves for tebentafusp PCP and pembrolizumab are presented in Figure 5.

Figure 5: Modelled OS curves for tebentafusp PCP and pembrolizumab



Source: 'Model setting' worksheet in 'Immunocore\_tebentafusp UM\_CEM v1' workbook  
KM = Kaplan-Meier, OS = overall survival, PCP = pre-choice pembrolizumab.

<sup>8</sup> Rantala E, Hernberg M, and Kivela T, (2019), 'Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis', *Melanoma Research*, 29(60):561-568.

- 6.49 The submission's selected extrapolation method for tebentafusp resulted in overestimation of survival over the remaining time horizon, with approximately 20% of tebentafusp patients surviving beyond 10 years. The relative treatment effect of tebentafusp over pembrolizumab was maintained over the time horizon (i.e. the curves did not converge) and the majority of the OS gained occurred in the extrapolated period (83%). The ESC considered that this was not reflective of the trial evidence, given that the median OS benefit observed with tebentafusp over pembrolizumab in IMCgp100-202 was 4.8 months. Furthermore, in Attachment 19 of the submission, the clinical experts<sup>9</sup> stated that a long-term survival benefit beyond five years was optimistic. The ESC considered that the non-convergence of the survival curves beyond 5 years was not supported by the currently available data.
- 6.50 Overall, the ESC considered that the use of a piecewise model for OS in the tebentafusp arm may be justified if best practice recommendations, such as in the NICE TDS 21 (p88), are followed. Additionally, the ESC advised that the choice of extrapolation function should be better justified given the sensitivity of the model to the time horizon and the assumption that the survival curves do not converge. As noted above, the ESC considered that it would be appropriate for the curves to converge over the longer term.
- 6.51 The PFS and TTD data from the trial were mature, with a high proportion of events observed (88% of PFS events, and 90% of TTD events) across both arms at the latest data sweep (April 2022) and extrapolation was applied from when 10% of patients remained at risk. Considering the maturity of the data, the application of the extrapolations from when 10% of patients remained at risk was likely reasonable.
- 6.52 The submission applied utility values based on a time-to-death approach, adopting a multiplicative approach to derive the utility values for the different time-to-death categories. Baseline utility value ( $\geq 360$  days) was derived from the IMCgp100-202 trial, with the utility values for the different time-to-death categories derived by multiplying the baseline utility with an adjustment factor (which was derived as the ratio of utility at  $\geq 360$  days from death and the utility at subsequent time-to-death categories from the NICE TA 366).
- 6.53 Table 10 summarises the utilities used in the economic evaluation.

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<sup>9</sup> Immunocore Australia advisory board: tebentafusp for the treatment of metastatic uveal melanoma – report.

**Table 10: Utility values used in the economic evaluation**

Health state	Utility	Nature of estimate/translations	Source of estimate
Base Case (Time to Death approach)			
≥ 360 days	0.84	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202
270-360 days	0.73	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202 adjusted based on EQ-5D data of NICE TA366 of pembrolizumab
180-270 days	0.68	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202 adjusted based on EQ-5D data of NICE TA366 of pembrolizumab
90-180 days	0.68	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202 adjusted based on EQ-5D data of NICE TA366 of pembrolizumab
30-90 days	0.59	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202 adjusted based on EQ-5D data of NICE TA366 of pembrolizumab
< 30 days	0.34	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202 adjusted based on EQ-5D data of NICE TA366 of pembrolizumab
Scenario Analyses			
On-treatment	0.845	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202
Off-treatment	0.761	EQ-5D data, UK value set	EQ-5D data of study IMCgp100-202

Source: Table 3.5.7, p173 of the submission.

EQ-5D = European Quality of Life Five Dimension

**6.54** The ESC considered that the application of the utility values was uncertain as:

The use of the time-to-death approach was not appropriate. The PSCR stated that as patients receiving tebentafusp experienced survival gains beyond progression and discontinuation of therapy, it was reasonable to expect that their quality of life would be maintained over this period. Hence, an approach based on treatment status would underestimate the QALY benefit in the tebentafusp arm. The ESC disagreed, stating that different utility values should have been assigned to progression free and progressed health states based on whether patients were receiving or not receiving treatment.

The time-to-death adjustment factor was derived from the NICE TA 366 which focused on pembrolizumab for treating advanced melanoma in adults who had not received ipilimumab and may not accurately reflect utility values for patients with metastatic UM.

**6.55** The economic model included costs associated with the drug acquisition and administration, subsequent therapies, health-states, end-of-life care, and management of adverse events.

**6.56** The submission included immunotherapies (pembrolizumab, nivolumab and ipilimumab) in the calculations of subsequent therapy costs. The proportion of patients receiving subsequent treatment in the pembrolizumab arm may not be reflective of actual practice in Australia as the current PBS listings for nivolumab and pembrolizumab for unresectable Stage III or Stage IV malignant melanoma state that “patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or

Stage IV malignant melanoma” (Schedule of Pharmaceutical Benefits – Efficient Funding of Chemotherapy), thus preventing subsequent PD-1 inhibitor treatment.

6.57 The economic model incorporated the costs of managing Grade  $\geq 3$  AEs which occurred in  $> 3\%$  of patients in the IMCgp100-202 trial. The submission also incorporated the costs for managing endocrine disorder and colitis of any grade. A high proportion of patients in the pembrolizumab arm experienced endocrine disorder (11.7% vs 0.4%) and colitis (2.7% vs 0.0%) compared to the tebentafusp arm, favouring tebentafusp. Of note, the submission did not incorporate the cost of managing CRS into the model. In IMCgp100-202, CRS occurred in 217 of 245 (89%) tebentafusp-treated patients. Although the majority of CRS cases were Grade 1 or 2 (99.6%), some patients required escalation of care (e.g., tocilizumab, vasopressor).

6.58 A summary of the key drivers of the model are presented in Table 11.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ [redacted] <sup>1</sup> per QALY gained
Extrapolation	The economic model was driven by large OS gains for tebentafusp patients (resulting in 1.69 QALYs gained) that were not well-supported by the clinical data. OS for the tebentafusp arm was modelled using a piecewise approach, whereby OS KM data from the IMCgp100-202 trial were used up to 28 months, after which extrapolation was applied using log-normal distribution. The use of the piecewise model was not clinically justified by the submission. A standard parametric approach to extrapolate OS for the pembrolizumab arm was used applying the Weibull model. The log-normal model was the best fit based on AIC and BIC values.	High, favours tebentafusp. A standard survival modelling approach applying the log-normal function to both arms increased the ICER to \$ [redacted] <sup>2</sup> per QALY gained.
Population	Subgroup population (tebentafusp PCP) data was used.	High, favours tebentafusp. Use of the ITT population data increased the ICER to \$ [redacted] <sup>3</sup> per QALY gained.
Time Horizon	The 20 year modelled time horizon was long given that the median OS survival for patients with metastatic UM is 10 to 12 months.	High, favours tebentafusp. Reducing the time horizon of 10 years increased the ICER to \$ [redacted] <sup>3</sup> per QALY gained.
Utilities	Utility values were based on time-to-death approach	Low, favours tebentafusp. Application of utilities based on health states (i.e., progression free and progressed) and including an age adjustment increased the ICER to \$ [redacted] <sup>1</sup> per QALY gained.

Source: Table 3.9.1, p203-206 of the submission and 'Immunocore\_tebentafusp UM\_CEMv1' workbook.

AIC = Akaike's information criterion, BIC = Bayesian information criterion, ITT = intention-to-treat, ICER = incremental cost-effectiveness ratio, KM = Kaplan-Meier, OS = overall survival, PCP = pre-choice pembrolizumab, QALY = quality-adjusted life years; UM = uveal melanoma.

*Italics corrected during evaluation using the correct MBS fee of \$114.20 by changing cell D95 in the 'Cost data' worksheet in the 'Immunocore\_tebentafusp UM\_CEM v1' workbook.*

*The redacted values correspond to the following ranges:*

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$455,000 to < \$555,000

<sup>3</sup> \$155,000 to < \$255,000

6.59 The results of the modelled economic evaluation are summarised in Table 12. The pre-PBAC response provided a revised base case in which the time horizon was reduced 15 year (from 20 years) and the ex-manufacturer price per 100 mcg vial was reduced to \$█ (from \$█).

**Table 12: Results of the stepped economic evaluation**

Step and component	Tebentafusp	Pembrolizumab	Increment
<b>Step 1: trial-based costs and outcomes</b>			
Costs (\$)	█	\$63,121	█
LYG	2.11	1.73	0.38
Incremental cost/extra LYG gained			█ <sup>1</sup>
<b>Step 2: time horizon extended to 20 years</b>			
Costs (\$)	█	\$62,118	█
LYG	4.94	1.77	3.16
Incremental cost/extra LYG gained			█ <sup>2</sup>
<b>Step 3: discounting (5%) included</b>			
Costs (\$)	█	\$60,634	█
LYG	3.63	1.64	1.98
Incremental cost/extra LYG gained			█ <sup>3</sup>
<b>Step 4: incorporation of medical resource costs</b>			
Costs (\$)	█	\$140,503	█
LYG	3.63	1.64	1.98
Incremental cost/extra LYG gained			█ <sup>3</sup>
<b>Step 5: utility weights applied</b>			
Costs (\$)	█	\$140,503	█
QALYs	2.93	1.24	1.69
Incremental cost/extra QALY gained (base case)			█ <sup>4</sup>
<b>Pre-PBAC revised base case</b>			
Costs (\$)	█	\$140,502	█
QALYs	2.66	1.24	1.43
Incremental cost/extra QALY gained (base case)			█ <sup>5</sup>

Source: Table 3.8.3, p198 of the submission and 'Immunocore\_tebentafusp UM\_CEMv1' workbook.

ICER = incremental cost-effectiveness ratio, LYG = life-year gains, QALY = quality-adjusted life-years

Italics corrected during evaluation using the correct MBS fee of \$114.20 by changing cell D95 in the 'Cost data' worksheet in the 'Immunocore\_tebentafusp UM\_CEM v1' workbook.

The redacted values correspond to the following ranges:

<sup>1</sup> \$555,000 to < \$655,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$75,000 to < \$95,000

6.60 The resultant base case ICER presented in the submission was \$ 115,000 to < \$ 135,000 per QALY gained. The ICER was considered to be underestimated, particularly when the OS gain demonstrated in the trial (4.8 months, 0.38 life years gained) was compared to the large quality of life gains produced by the model (1.98 discounted life-years gained and 1.69 discounted quality-adjusted life-years gained). The revised base case ICER presented in the pre-PBAC was \$ 75,000 to < \$ 95,000 per QALY.

6.61 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
<b>Base case</b>		1.69		0.00%
<b>Discount rate (base case = 5% for costs and outcomes)</b>				
0% costs and outcomes		2.69		-33%
3.5% costs and outcomes		1.93		-10%
<b>Time horizon (base case = 20 years)</b>				
5 years		0.47		253%
7.5 years		0.77		116%
10 years		1.03		63%
15 years		1.43		18%
<b>Utility (base case = time-to-death approach (no age adjustment))</b>				
On/Off treatment utilities including age-adjustment		1.50		13%
Time to death approach including age-adjustment		1.63		4%
<b>Extrapolation of OS for tebentafusp (base case = piecewise-28; log-normal (Tebentafusp PCP))</b>				
Standard Parametric; Log-normal		0.76		129%
Standard Parametric; Log-logistic		0.76		130%
<b>Extrapolation of OS for pembrolizumab (base case = standard parametric Weibull)</b>				
Standard Parametric; Log-normal		1.38		23%
Standard Parametric; Log-logistic		1.33		28%
<b>Population (base case = Tebentafusp PCP and Pembrolizumab)</b>				
Tebentafusp (ITT) and Investigator's choice (ITT)		1.23		39%
<b>Multivariate sensitivity analyses</b>				
Standard parametric model of OS for both arms using log-normal distribution		0.45		289%
Standard parametric model of OS for both arms using log-normal distribution + Time horizon of 10 years		0.42		315%
Standard parametric model of OS for both arms using log-normal distribution + Time horizon of 10 years + On/off treatment utilities		0.43		307%

Source: Table 3.9.4, p207; Table 3.9.55, p209; Table 3.9.6, p210; Table 3.9.7, p211; Table 3.9.8, p211; Table 3.9.9, p212; Table 3.9.10, p214 of the submission and 'Immunocore\_tebentafusp UM\_CEMv1' workbook.

AIC = Akaike's information criterion, BIC = Bayesian information criterion, AE = adverse event, ICER = incremental cost-effectiveness ratio, ITT = intention-to-treat, KM = Kaplan-Meier, OS = overall survival, PCP = pre-choice pembrolizumab, PFS = progression-free survival, QALY = quality-adjusted life-years, TTD = time to treatment discontinuation.

*Italics* corrected during evaluation using the correct MBS fee of \$114.20 by changing cell D95 in the 'Cost data' worksheet in the 'Immunocore\_tebentafusp UM\_CEM v1' workbook. Multivariate sensitivity analyses were conducted during evaluation.

Data sweep: April 2022

a Refer to Attachment 3.9 for an explanation how these sensitivity analyses were conducted.

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$355,000 to < \$455,000

<sup>5</sup> \$255,000 to < \$355,000

<sup>6</sup> \$155,000 to < \$255,000

<sup>7</sup> \$135,000 to < \$155,000

<sup>8</sup> \$455,000 to < \$555,000

### Drug cost/patient/course

Table 14: Drug cost per patient for proposed and comparator drugs

	Tebentafusp			Pembrolizumab <sup>a</sup>		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean duration	10.3 months or 44.6 cycles	11.06 months <sup>b</sup> or 48.0 cycles	10.3 months or 44.6 cycles	4.5 months or 6.5 cycles	5.4 months <sup>b</sup> or 7.8 cycles	Unclear
Cost/patient/cycle <sup>c</sup> (\$)				\$7,847.00	\$7,847.00	Unclear
Cost/patient/course <sup>d</sup> (\$)				\$51,006	\$61,227	Unclear

Source: Section 2.4, p43 of the submission; Table 3.8.1, p196 and Table 3.8.2, p196 of the submission

<sup>a</sup> Based on published price for pembrolizumab

<sup>b</sup> Back-calculated in the model by dividing undiscounted total cost per patient per course by cost per patient per cycle.

<sup>c</sup> Cost/patient/cycle is based on weighted DPMA.

<sup>d</sup> Cost/patient/course = cost/patient/month × mean duration

6.62 The cost per patient per course for tebentafusp included the first three doses, which are administered in the inpatient setting. These doses would not be funded through the PBS for public patients. The approach used by the submission to calculate financial estimates for pembrolizumab was uncertain.

### Estimated PBS usage & financial implications

6.63 This submission was considered by DUSC.

6.64 The submission applied an epidemiological approach to estimate the utilisation and financial impact of listing tebentafusp on the PBS. A summary of key inputs and their data sources are presented in Table 15.

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Table 15: Key inputs for financial estimates

Data	Value	Source	Comments
<b>Eligible population</b>			
Prevalent population	-	-	DUSC considered that the lack of a prevalent population in the submission was reasonable, noting that the cost of tebentafusp was equivalent to a treatment course of 11 months which aligned with the mean time on treatment (10.3 months) in the trial and a mean survival of 10-12 months.
Incidence of primary uveal melanoma	205	7.6 per million based on Beasley et al, 2019 and ABS population	The incidence rate was based on Australian data from 1982-2014. DUSC noted that International Classification of Diseases (ICD) coding reported to Department of Health and linked with Australian Institute of Health and Welfare (AIHW) was used.
Incidence of metastatic uveal melanoma	102	50% patients with UM will have metastatic disease (Kolandjian et al, 2013)	-
HLA-A*02:01-positive patients	50	47% of patients will be HLA-A*02:01-positive (Allele Frequencies database, 2021)	-
Total eligible incident patients	40	80% (Clinical Advisory Board)	DUSC considered that the willingness to use tebentafusp would be high given lack of treatment options.
<b>Treatment utilisation</b>			
Uptake - Initiating	90%	Clinical Advisory Board	DUSC considered that uptake would be high given lack of additional treatment options.
Uptake - Continuing	100%	Clinical Advisory Board	DUSC considered that this was likely overestimated – although treatment discontinuation rate was low in trial (3.3%), managing toxicities in the frailer real-world population would result in a higher discontinuation rate.
Duration of treatment	10.3 months	Mean duration of treatment with tebentafusp in the IMCgp100-20 trial	The PBAC noted that the submission incorrectly included the first 3 doses of tebentafusp for public patients, which are given in the hospital inpatient setting, in the duration of treatment. The submission did not adjust for time on treatment with pembrolizumab. The duration of treatment with pembrolizumab was reduced to 4.5 months in the PSCR. Pembrolizumab cost offsets were removed from the model in the pre-PBAC response as it was assumed that treatment would be displaced, rather than replaced.
Growth rate	Yr 1: - Yr 2: 1.02% Yr 3: 1.01% Yr 3: 1.01% Yr 4: 1.01% Yr 5: 1.01% Yr 6: 1.01%	ABS data	-
<b>Costs</b>			
Wastage			DUSC agreed with the commentary (5.02.COM.5) that there was likely to be significant wastage due to a lower maximum dosage than the dose per single vial use.

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Data	Value	Source	Comments
<b>Eligible population</b>			
			DUSC noted, but disagreed with the Pre-Sub-Committee Response (PSCR), that the extra volume in the vial is needed to account for 'dead-volume'.
Tebentafusp	Published: \$19,624.36 (public) <sup>1</sup> ; \$19,939.51 (private) Effective: \$ [REDACTED] (public) <sup>1</sup> ; \$ [REDACTED] (private)	Requested DPMA	Inappropriate dispensing fees were applied to the AEMP.
Pembrolizumab	\$7,742.39 (public), \$7,883.27 (private), \$7,848.91 (weighted)	PBS items 10493G, 10436G, 10475H and 10424P. Effective prices for pembrolizumab are not available in the public domain.	Inappropriate dispensing fees were applied to the AEMP.
MBS costs	\$114.20	MBS item 13950	DUSC commented that MBS costs may be considerably underestimated if patients are needing to be admitted to a hospital.
Patient co-payment	PBS: \$18.10 RPBS: \$6.32	Average co-payment was estimated using PBS statistics items for pembrolizumab (10424P, 10436G, 10475H, 10439G)	-
Public/Private weighting	24.39% public and 75.61% private	PBS statistics for calendar year 2021 for pembrolizumab	-

Source: Table 4.1.1 5.01.COM.102 pp219-220 and Table 4.1.2, p222 of the submission.

ABS = Australian bureau of statistics, AEMP = approved ex-manufacturer price, HLA = human leukocyte antigen, MBS = Medicare Benefits Scheme, PBS = Pharmaceutical Benefit Scheme, UM = uveal melanoma.

<sup>1</sup> Corrected during evaluation by changing E306 cell to \$0 in '3c.Impact – affected (eff)' Worksheet in 'Immunocore\_UCM\_v02\_uploaded into HPP' Workbook and changing E307 cell to \$0 in '3c.Impact – proposed (eff)' Worksheet in 'Immunocore\_UCM\_v02\_uploaded into HPP' Workbook to adjust for incorrect dispensing fee in public DPMA.

6.65 The main sources of uncertainty relating to the estimated use of tebentafusp were:

The estimated incident population with primary UM (7.6 per million) was based on average age-standardised incidence rate data from 1982 to 2014. In 2022, Australian Institute of Health and Welfare (AIHW) estimated that there will be 428 cases of eye cancer, with an age-standardised incidence rate of 1.4 per 100,000.

The eligibility and treatment uptake rates were based on expert opinion which consisted of three clinicians experienced in the treatment of metastatic UM.

6.66 In addition, there were some uncertainties associated with the approach used by the submission to calculate cost-offsets, including that the:

mean duration of treatment with pembrolizumab was assumed to be the same as that in the tebentafusp arm (10.3 months). This was not appropriate given the mean duration of treatment with pembrolizumab in the IMCgp100-202 trial was 4.5 months. The PSCR provided updated financials in which the duration of

pembrolizumab was reduced to 4.5 months (and corrected for an error in the calculations of the continuing patient years of treatment).

submission did not account for the decreased number of IV administrations associated with pembrolizumab as compared to tebentafusp.

submission did not consider the increase in the utilisation of medicines to manage AEs associated with tebentafusp (e.g., CRS and acute skin reactions).

- 6.67 Estimated use and financial implications are presented in Table 16. Estimates from the PSCR, corrected for the error, are also presented.
- 6.68 The pre-PBAC response provided further revised estimates which included the reduced ex-manufacturer price and removed cost off-sets associated with pembrolizumab (see paragraph 6.70). Further, the PBAC noted that the submission incorrectly included the first 3 doses of tebentafusp, which are given in the hospital inpatient setting, in the calculations. These would not be funded by the PBS/RPBS for public patients. This is corrected in the pre-PBAC calculations below.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of tebentafusp</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated financial implications for pembrolizumab</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Increased cost to MBS <sup>b</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Net cost to PBS/RPBS/MBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Corrected estimates provided in the PSCR (duration of pembrolizumab reduced from 10.3 months to 4.5 months)</b>						
<b>Estimated financial implications of tebentafusp</b>						
Cost to PBS/RPBS less co-payments <sup>c</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated financial implications for pembrolizumab</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Increased cost to MBS <sup>b</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Net cost to PBS/RPBS/MBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Corrected estimates provided in the pre-PBAC response (pembrolizumab cost offsets removed)</b>						
<b>Estimated financial implications of tebentafusp</b>						
Number of patients treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>d</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Cost to PBS/RPBS less co-payments <sup>c</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated financial implications for pembrolizumab</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Increased cost to MBS <sup>b</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Net cost to PBS/RPBS/MBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>

Source: 'Immunocore\_UCM\_v02\_uplaoded into HPP' Workbook.

MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> Assuming 44.63 scripts per year (adjusted for duration of treatment with tebentafusp (10.3 months)).

<sup>b</sup> The submission did not calculate the cost-offset to MBS due to decreased number of IV administration for pembrolizumab

<sup>c</sup> Total continuing patient years of treatment corrected by changing N54 cell to 0.00 in '2d.Patients – DTG' Worksheet

<sup>d</sup> Assuming 41.63 scripts per year ( 9.6 months of treatment) for public patients (24.39% of patients) and 44.63 scripts per year (10.3 months of treatment for private patients (75.61% of patients)

Italics corrected DPMA (public) for tebentafusp during evaluation by changing E307 cell to \$0 in '3c.Impact – proposed (eff)' Worksheet in 'Immunocore\_UCM\_v02\_uplaoded into HPP' Workbook and DPMA (public) for pembrolizumab by changing E306 cell to \$0 in '3c.Impact – affected (eff)' Worksheet in 'Immunocore\_UCM\_v02\_uplaoded into HPP' Workbook to adjust for incorrect dispensing fee in public DPMA.

The redacted values correspond to the following ranges:

<sup>1</sup> <500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

- 6.69 The submission estimated that listing of tebentafusp on the PBS would result in a net cost to government of \$ 0 to < \$ 10 million in Year 1, \$ 0 to < \$ 10 million in Year 6 and total \$ 40 million to < \$ 50 million over the first 6 years of listing. The PSCR revisions resulted in a net cost to government of \$ 0 to < \$ 10million in Year 1, \$ 0 to < \$ 10 million in Year 6 and a total of \$ 50 million to < \$ 60 million over the first 6 years of listing. The corrected revisions in the pre-PBAC response resulted in a cost to government of \$0 to < \$ 10 million in Year 1, \$ 0 to < \$ 10 million in Year 6 and a total of \$30 million to < \$40 million over the first 6 years.
- 6.70 DUSC noted the following uncertainties with the estimates:
- The submission assumed that tebentafusp would replace pembrolizumab use. DUSC noted that as the pembrolizumab PBS listing does not exclude use for ocular or UM, nor does it specify the line of therapy, it could potentially be used after tebentafusp for UM treatment. Cost offsets associated with pembrolizumab were removed in the pre-PBAC response as it was assumed that pembrolizumab use would be displaced, rather than replaced.
  - There were no cost offsets included for associated adverse events.

### **Quality Use of Medicines**

- 6.71 The submission outlined a number of activities intended to promote safe and effective use of tebentafusp in clinical practice. These include providing medical training to clinicians, increasing awareness in the community, and collecting post-marketing surveillance safety data.
- 6.72 The ESC suggested that prescribers of tebentafusp would require education on how to manage CRS, given the paucity of experience in Australia managing this potentially fatal adverse event.

*For more detail in PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend tebentafusp for the treatment of HLA-A\*02:01-positive adult patients with advanced (unresectable or metastatic) uveal melanoma (UM). The PBAC noted the unmet clinical need for new treatments in this setting and considered that tebentafusp was superior in terms of efficacy compared to pembrolizumab, but likely inferior in term of safety. The PBAC noted that there were uncertainties associated with the economic model and considered that these could be mitigated by reducing the time horizon applied and adjusting the utility values. The PBAC considered that a price reduction would be required for tebentafusp to be cost effective. The PBAC considered that the utilisation estimates for tebentafusp were reasonable.
- 7.2 The PBAC considered that tebentafusp addressed a high and urgent unmet clinical

need and acknowledged the consumer comments which described the high clinical need for new treatments in the UM setting and the improvements in overall survival (OS) and quality of life that tebentafusp offered.

- 7.3 The PBAC considered that the proposed place in therapy of tebentafusp as a treatment for patients with advanced (unresectable or metastatic) UM was appropriate and noted that it aligned with the key clinical trial, IMCgp100-202.
- 7.4 The PBAC considered that the nomination of pembrolizumab as the comparator was appropriate.
- 7.5 The PBAC noted that the submission was primarily based on one randomised controlled trial, IMCgp100-202, which compared tebentafusp with investigators choice, which consisted of pembrolizumab, dacarbazine or ipilimumab. The PBAC noted that results were presented for the intention-to-treat (ITT) population and for the subgroup of patients who were pre-selected to receive pembrolizumab. The PBAC noted the tebentafusp was associated with a median improvement in OS of 4.8 months, which was statistically significant both populations (ITT HR = 0.63; 95% CI: 0.49, 0.82; pembrolizumab subgroup HR = 0.66; 95% CI: 0.49, 0.89). The PBAC also noted that tebentafusp was associated with improvements in objective response and disease control rates.
- 7.6 Overall, the PBAC considered that the claim that tebentafusp was superior compared to pembrolizumab in terms of efficacy was supported by the data provided in the submission.
- 7.7 The PBAC noted that tebentafusp was associated with more Grade  $\geq 3$  treatment related (45.6% versus 16.5%) and serious (18.1% versus 5.5%) adverse events compared to pembrolizumab. The PBAC also noted that 89% of tebentafusp patients experienced Grade  $\leq 3$  cytokine release syndrome (CRS). Overall, the PBAC considered that tebentafusp was inferior compared to pembrolizumab in terms of safety.
- 7.8 The PBAC noted that the submission presented a cost utility analysis between tebentafusp and pembrolizumab which was informed by the pembrolizumab pre-selected subgroup. The PBAC noted that the revised base case incremental cost effectiveness ratio (ICER) in the pre-PBAC response was \$75,000 to < \$95,000 per quality adjusted life year (QALY). The PBAC considered that the ICER was underestimated as the submission:
- applied a 20-year time horizon to the economic model, which was reduced to 15 years in the pre-PBAC response. The PBAC considered that the application of a 15- or 20-year time horizon was inappropriate as (i) patients with metastatic disease have poor prognosis, and (ii) the maximum duration of follow up in the IMCgp100-202 trial was 50 months. The PBAC considered that a more reasonable time horizon would be 7.5 years.
  - assumed that approximately 20% of patients receiving tebentafusp were alive at

10 years due to OS in the model being sustained beyond Year 3 (see Figure 5). The PBAC, noting that the number of patients remaining at risk beyond Years 3 and 4 was small (< 10% and < 2% respectively) and that the median OS benefit in IMCgp100-202 was 4.8 months, considered that the Kaplan Meier estimates were unreliable beyond Year 3 and that the assumption of a plateau effect was not supported by the available data. The PBAC further noted that clinical experts<sup>10</sup> stated that a long-term survival benefit with tebentafusp was optimistic. The PBAC considered that the application of a 7.5-year time horizon would reduce the magnitude of the uncertainties associated with the modelling.

- applied utility values based on a time-to-death approach. The PBAC agreed with the ESC in considering that utility values should have been assigned to the progression free and progressed health states, based on whether patients were receiving or not receiving treatment.
- 7.9 The PBAC, noting that UM was a rare disease for which there were limited treatments available, considered that an ICER that was no higher than the revised base case presented in the pre-PBAC response would be reasonable if the time horizon was reduced to 7.5 years and utility weights based on whether patients were or were not receiving treatment were applied. The PBAC noted that a price reduction would be required to attain cost effectiveness.
- 7.10 The PBAC noted that the utilisation and financial impact estimates presented incorrectly included the first 3 doses of tebentafusp, which are given in the hospital inpatient setting and would not be funded by the PBS for public patients. The PBAC considered that revised estimates provided in the pre-PBAC response, in which the cost offsets associated with pembrolizumab were removed, were reasonable as it was likely that treatment with pembrolizumab would be displaced rather than replaced. Overall, the PBAC considered that the utilisation and financial impact estimates presented in the pre-PBAC response, corrected for the inpatient use of tebentafusp in public patients, were reasonable.
- 7.11 The PBAC considered that the proposed restriction, with included edits by the Secretariat, was reasonable. The PBAC noted that the restriction stipulated that the first three doses of tebentafusp were to be given in the inpatient setting due to the risk of CRS and considered that this was appropriate. The PBAC considered that the proposed stopping rule in the continuing restriction which allowed use until it was no longer clinically beneficial to the patient was reasonable and aligned with the IMCgp100-202 trial.
- 7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for tebentafusp. The PBAC also considered that tebentafusp addresses

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<sup>10</sup> Immunocore Australia advisory board: tebentafusp for the treatment of metastatic uveal melanoma – report.

a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- Provide a revised economic analysis as outlined in paragraph 7.9 that results in an ICER that is no higher than that presented in the revised base case in the pre-PBAC response;
- Provide revised financial impact estimates that incorporate the price of tebentafusp as determined by the revised economic analysis; and
- Provide a revised restriction that incorporates the changes proposed by the Secretariat.

7.13 The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.

## **10 Corrigendum**

The following changes were made:

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<b>Change made</b>	<b>Date of revision</b>
Table 16: corrected the pre-PBAC utilisation and financial impact estimates	6/09/2023
Paragraph 6.69: corrected the estimated cost to government.	6/09/2023

**Addendum to the March 2023 PBAC PSD:**

**7.02 TEBENTAFUSP,  
Solution concentrate for I.V. infusion 100 mcg in  
0.5mL vial,  
Kimmtrak<sup>®</sup>,  
Synevi Pty Limited**

**11 Background**

- 11.1 The resubmission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required (telephone/online) listing for tebentafusp for the treatment of HLA-A\*02:01-positive adult patients with advanced (unresectable or metastatic) UM.
- 11.2 The resubmission was made under the early resolution pathway and sought to address the PBAC's concerns from the March 2023 meeting.
- 11.3 In March 2023, the PBAC considered that the outstanding issues could be resolved in a simple resubmission. The PBAC considered that if the following issues were addressed, then the resubmission would not require further re-evaluation:
- A revised economic analysis based on that presented in the pre-PBAC response and which had a reduced time horizon of 7.5 years and utility weights based on whether patients were or were not receiving treatment. The PBAC advised that a price reduction would be required to result in an ICER that was no higher than that presented in the pre-PBAC response;
  - Revised financial estimates that incorporate the revised price of tebentafusp; and
  - A revised restriction that incorporated the changes proposed by the Secretariat.
- 11.4 Table 17 summarises how the resubmission addressed each of these issues.

Table 17: Summary of changes made in the resubmission

Outstanding issues from the March 2023 PBAC PSD	How the issue was addressed in the early resolution resubmission
<b>Restriction</b>	
The restriction should include the changes proposed by the Secretariat and stipulate that the first three doses of tebentafusp were to be given in the inpatient setting due to the risk of CRS (paragraphs 7.11 and 7.12)	The restriction was revised as requested (See Section 9 – Requested listing).
<b>Economic model</b>	
The economic model should: <ul style="list-style-type: none"> <li>- Apply a time horizon of 7.5 years (paragraph 7.9).</li> <li>- Apply utility weights based on whether a patient was or was not receiving treatment (paragraph 7.9).</li> <li>- Reduce the requested price of tebentafusp to result in an ICER that was no higher than that presented in the pre-PBAC response of \$<sup>1</sup> per QALY (paragraph 7.9).</li> </ul>	<ul style="list-style-type: none"> <li>- The resubmission reduced the time horizon from 15 years in the pre-PBAC response to 10 years in the resubmission.</li> <li>- Utility weights remained based on a time-to-death approach, with a sensitivity analysis presented in which the utilities were assigned based on treatment.</li> <li>- The resubmission proposed an AEMP of \$<sup>1</sup> per vial of tebentafusp, which resulted in a revised ICER of \$<sup>1</sup> per QALY.</li> </ul>
<b>Financial estimates</b>	
Revised financial estimates should be presented that incorporate the reduced price of tebentafusp (paragraph 7.12).	The resubmission presented revised financial estimates.

AEMP = approved ex-manufacturer price; CRS = cytokine release syndrome; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

## 12 Requested listing

12.1 The resubmission proposed the following restriction which included the Secretariat proposed changes including the recommendation from the TGA-approved Product Information that the first three doses are to be given in the inpatient setting due to the risk of CRS.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Proprietary Name	Manufacturer
Tebentafusp 100 mcg/0.5 mL injection, 0.5 mL vial	300 mcg	0	KIMMTRAK®	Medison Ltd.

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
<b>Episodicity:</b> [blank]
<b>Severity:</b> Advanced (unresectable or metastatic)

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<b>Condition:</b> Uveal melanoma
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> The patient must have HLA-A*02:01-positive disease <b>AND</b> The patient must have uveal melanoma that has been confirmed either (i) histologically, or (ii) cytologically <b>AND</b> The treatment must be the sole PBS subsidised therapy for this condition <b>AND</b> The patient must not have received prior systemic therapy for metastatic disease
<b>Treatment criteria Prescribing instruction:</b> According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion. <b>AND</b> Tebentafusp is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
<b>Population criteria:</b> Patients must be aged at least 18 years
<b>Prescribing Instructions:</b> Positive HLA-A*02:01- assessment must be documented in the patient's medical records
<b>Caution:</b> Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Proprietary Name	Manufacturer
Tebentafusp 100 mcg/0.5 mL injection, 0.5 mL vial	400 mcg	3	KIMMTRAK®	Medison Ltd.

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised
<b>Episodicity:</b> [blank]
<b>Severity:</b> Advanced disease (unresectable or metastatic)
<b>Condition:</b> Uveal melanoma
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria</b> The treatment must be the sole PBS-subsidised therapy for this condition <b>AND</b> Patient must have previously received PBS-subsidised treatment with this drug for this condition <b>AND</b> Patient must not develop disease progression as determined by the treating clinician while receiving PBS subsidised treatment with this drug for this condition

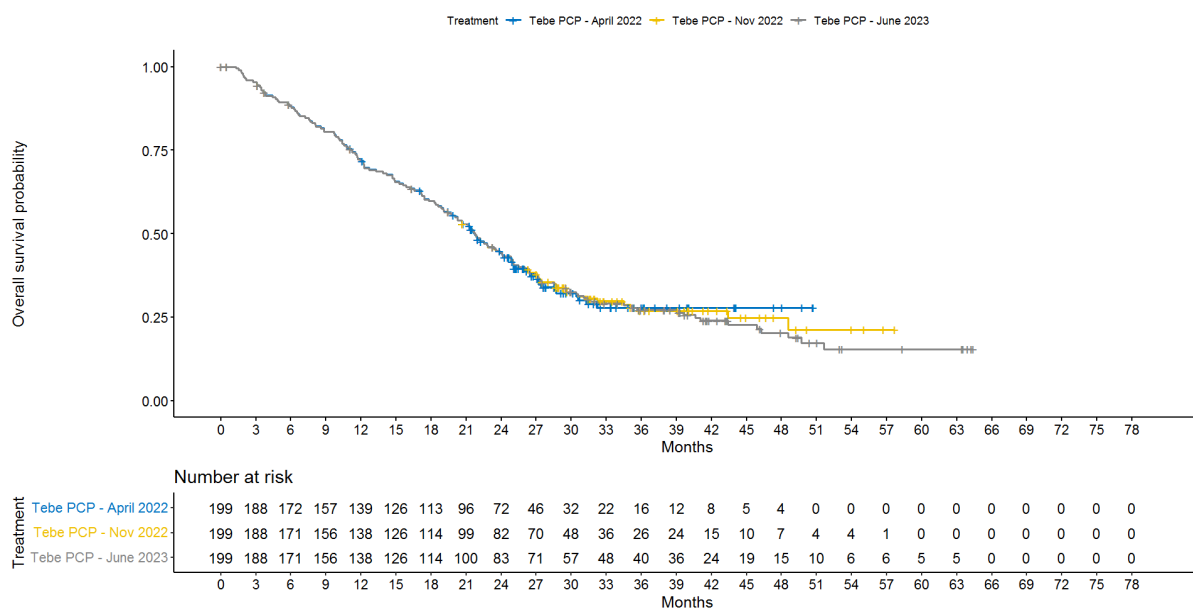
<b>Treatment criteria Prescribing instruction:</b> According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.
<b>Caution:</b> Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).

## 13 Consideration of the evidence

### *Economic analysis*

- 13.1 The resubmission stated that the following inputs were changed in the economic model:
- The time horizon was reduced to 10 years (from 20 years in the original submission and 15 years in the pre-PBAC response).
  - The effective approved ex-manufacturer price (AEMP) of tebentafusp was reduced to \$| per vial (from \$| in the original submission and \$| in the pre-PBAC response).
- 13.2 In March 2023, the PBAC requested that the time horizon be reduced to 7.5 years on the basis that patients with metastatic disease have a poor prognosis and that the maximum duration of follow up in the IMCgp100-202 trial was 50 months. The resubmission acknowledged that the prognosis of patients with metastatic disease was historically poor but considered that a 10-year time horizon better captured the clinical and economic consequences of treatment with tebentafusp. The resubmission presented an updated Kaplan-Meier analysis of overall survival based on the most recent data cut (June 2023, 3-year follow-up) to support the application of a 10-year time horizon (Figure 6).

Figure 6: Updated KM analysis of OS in IMCgp100-202 trial (July 2023 data-cut)



Source: Figure 1, p7 of the resubmission  
 KM = Kaplan-Meier; OS = overall survival

- 13.3 In March 2023, the PBAC also requested that the economic model apply utility values based on whether a patient was or was not receiving treatment, rather than the time-to-death approach that was applied in the base case. The resubmission stated that the time-to-death approach was justified on the basis that both the TTD and PFS measured by the RECIST criteria are not appropriate outcomes for measuring quality of life outcomes for immunotherapies that mediate T-cell antitumour activity. The resubmission stated that instances of tumour ‘growth’ due to tumour inflammation following treatment (pseudo-progression) followed by tumour shrinkage is commonly reported with immunotherapies and was observed in the IMCgp100-202 trial. Hence, it was clinically plausible for patients to show disease progression whilst receiving treatment with tebentafusp yet maintain quality of life and that quality of life is maintained until 3-6 months prior to death. The resubmission presented a sensitivity analysis in which utilities were assigned based on whether patients were receiving or not receiving treatment.
- 13.4 In March 2023, the PBAC requested that the revised base case ICER should be no more than that presented in the pre-PBAC response \$75,000 to < \$95,000 per QALY). The revised base case and the sensitivity analysis are presented in Table 18.

**Table 18: Revised base case and sensitivity analysis**

	Tebentafusp	Pembrolizumab	Increment
<b>March 2023 Pre-PBAC base case</b>			
Costs <sup>a</sup>	\$█	\$140,502	\$█
QALYs	2.66	1.24	1.43
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>1</sup></b>
<b>September 2023 revised base case (using time-to-death utility values)</b>			
Costs <sup>a</sup>	\$█	\$140,440	\$█
QALYs	2.27	1.24	1.03
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>1</sup></b>
<b>September 2023 sensitivity analysis (using on/off treatment utility values)</b>			
Costs <sup>a</sup>	\$█	\$140,440	\$█
QALYs	2.24	1.28	0.96
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>1</sup></b>

Source: 'Immunocore\_tebentafusp UM\_CEMv1' workbook.

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-years

<sup>a</sup> Corrected to use the correct MBS fee of \$114.20 by changing cell D95 in the 'Cost data' worksheet in the 'Immunocore\_tebentafusp UM\_CEM v1' workbook.

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

### Estimated PBS usage & financial implications

13.5 The resubmission presented revised financial impact estimates that incorporated the revised AEMP of \$█ per vial for tebentafusp and which removed the costs associated with public hospital patients receiving the first three doses in the inpatient setting. These are presented in Table 19.

**Table 19: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of tebentafusp</b>						
Cost to PBS/RPBS less co-payments (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated financial implications for pembrolizumab</b>						
Cost to PBS/RPBS less co-payments (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net financial implications</b>						
<b>Net cost to PBS/RPBS (\$)</b>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Increased cost to MBS <sup>b</sup> (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net cost to PBS/RPBS/MBS (\$)</b>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>

Source: Table 6, p10 of the resubmission

MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

<sup>1</sup> <500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

13.6 The revised net cost to government of listing tebentafusp on the PBS/RPBS was estimated to be \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6 and totalling \$30 million to < \$40 million over the first 6 years.

- 13.7 The resubmission noted that although there were currently < 500 patients receiving treatment through an early access program, the cost of treatment for these patients would continue to be funded by the sponsor.

## **14 PBAC Outcome**

- 14.1 The PBAC recommended tebentafusp be listed on the PBS as a Section 100 (Efficient Funding of Chemotherapy) item for the treatment of HLA-A\*02:01-positive adult patients with advanced (unresectable or metastatic) uveal melanoma. The PBAC recalled that it had previously noted the high unmet clinical need for new treatments in this setting and had considered that tebentafusp was superior compared to pembrolizumab in terms of efficacy, but likely inferior in terms of safety. The PBAC considered that the resubmission's changes to the proposed restriction, economic model and financial impact estimates adequately addressed its previous concerns and considered that tebentafusp would be acceptably cost-effective at the price proposed in the resubmission.
- 14.2 The PBAC considered that the proposed restriction, which incorporated the Secretariat's suggested changes, including the recommendation from the TGA-approved Product Information that the first three doses are to be given in the inpatient setting due to the risk of CRS, was reasonable. The PBAC noted that, to align with Section 100 (Efficient Funding of Chemotherapy) requirements, the Secretariat proposed that initial treatment supply restriction would be separated into three separate restrictions (for treatment of Days 1, 8 and 15) and that minor changes would be made to the maximum quantity and number of repeats of the continuing supply restriction.
- 14.3 The PBAC noted that in March 2023 it had recommended that the time horizon in the economic model be revised from 15 years in the pre-PBAC response to 7.5 years to better reflect the historical poor prognosis of patients with metastatic disease. The PBAC noted that the resubmission proposed a time horizon of 10 years based on an updated Kaplan-Meier analysis of OS from the most recent data cut in the key clinical trial, IMCgp100-202. The PBAC considered that the updated data indicated that there may be a proportion of patients who would experience improved long-term survival and that the application of a 10-year time horizon was not unreasonable.
- 14.4 The PBAC recalled that in March 2023 it had requested that the utility values in the economic model be based on whether a patient was receiving or not receiving treatment, rather than the time-to-death approach that was applied, for the reasons outlined in paragraph 6.54. The PBAC noted that the resubmission continued to apply the time-to-death approach but presented results using the on/off treatment values as a sensitivity analysis. The PBAC considered that the use of the time-to-death approach was not acceptable and did not provide a more reliable estimate of the ICER and as such considered the sensitivity analysis provided a more reasonable estimate

of the ICER.

- 14.5 The PBAC noted that the resubmission proposed a price reduction for tebentafusp, which, when incorporated into the model in conjunction with a 10-year time horizon and on/off treatment utility values, resulted in an ICER of \$75,000 to < \$95,000 per QALY. The PBAC noted that the ICER was higher than that presented in the March 2023 pre-PBAC response of \$75,000 to < \$95,000 per QALY; however, on balance considered in the context of the high unmet clinical need for new treatments in this setting that tebentafusp that the ICER remained in an acceptable range.
- 14.6 The PBAC noted the revised financial impact estimates which incorporated the reduced proposed price for tebentafusp and removed the costs associated with public hospital patients receiving the first three doses of treatment in the inpatient setting. The PBAC considered that the revised financial impact estimates were reasonable.
- 14.7 The PBAC recommended that the Early Supply Rule should apply.
- 14.8 The PBAC advised that tebentafusp is not suitable for prescribing by nurse practitioners.
- 14.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for tebentafusp:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over pembrolizumab on the basis of the OS gain observed in the IMCgp100-202 trial;
  - b) The treatment is expected to address a high and urgent unmet clinical need in the proposed population;
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 14.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **15 Recommended listing**

- 15.1 Add new item:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts
TEBENTAFUSP	{NEW (Public)} {NEW (Private)}	<del>300</del> 20 mcg	0
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270.			
<b>Episodicity:</b> [blank]			
<b>Severity:</b> Advanced (unresectable or metastatic)			
<b>Condition:</b> Uveal melanoma			
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma			
<b>Treatment Phase:</b> Initial treatment – <i>day 1</i>			
<b>Clinical criteria:</b>			
The patient must have HLA-A*02:01-positive disease			
<b>AND</b>			
<b>Clinical criteria:</b>			
The patient must have uveal melanoma that has been confirmed either (i) histologically, (ii) cytologically			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be the sole PBS-subsidised therapy for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
The patient must not have received prior systemic therapy for metastatic disease			
<b>Population criteria:</b>			
Patients must be at least 18 years of age			
<b>Prescribing instruction:</b>			
According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.			
<b>Prescribing instruction:</b>			
Tebentafusp This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.			

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<b>Prescribing instruction:</b> Positive HLA-A*02:01 assessment must be documented in the patient's medical records
<b>Caution:</b> Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome.

<b>MEDICINAL PRODUCT</b> <i>medicinal product pack</i>	<b>PBS item code</b>	<b>Max. Amount</b>	<b>No. of Rpts</b>
TEBENTAFUSP	{NEW (Public)} {NEW (Private)}	30 mcg	0
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – streamlined (new code)			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270			
<b>Episodicity:</b> [blank]			
<b>Severity:</b> Advanced (unresectable or metastatic)			
<b>Condition:</b> Uveal melanoma			
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma			
<b>Treatment Phase:</b> Initial treatment – day 8			
<b>Clinical criteria:</b>			
The patient must have HLA-A*02:01-positive disease			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have previously received PBS-subsidised initial day 1 treatment with this drug for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be the sole PBS-subsidised therapy for this condition			
<b>Prescribing instruction:</b>			
According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.			
<b>Prescribing instruction:</b>			
This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.			

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<b>Prescribing Instructions:</b> Positive HLA-A*02:01 assessment must be documented in the patient's medical records			
<b>Caution:</b> Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome.			
<b>MEDICINAL PRODUCT</b> <b>medicinal product pack</b>	<b>PBS item code</b>	<b>Max. Amount</b>	<b>No. of Rpts</b>
TEBENTAFUSP	{NEW (Public)} {NEW (Private)}	68 mcg	0
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – streamlined (new code)			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised			
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270.			
<b>Episodicity:</b> [blank]			
<b>Severity:</b> Advanced (unresectable or metastatic)			
<b>Condition:</b> Uveal melanoma			
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma			
<b>Treatment Phase:</b> Initial treatment – day 15			
<b>Clinical criteria:</b> The patient must have HLA-A*02:01-positive disease			
<b>AND</b>			
<b>Clinical criteria:</b> Patient must have previously received PBS-subsidised initial day 8 treatment with this drug for this condition			
<b>AND</b>			
<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised therapy for this condition			
<b>Prescribing instruction:</b> According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.			
<b>Prescribing instruction:</b> This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.			
<b>Prescribing Instructions:</b> Positive HLA-A*02:01 assessment must be documented in the patient's medical records			

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**Caution:**

Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts
TEBENTAFUSP	{NEW (Public)} {NEW (Private)}	400 136 mcg	3 7
<b>Available brands</b>			
Kimmtrak tebentafusp 100 microgram/0.5 mL injection, 0.5 mL vial			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised			
<b>Episodicity:</b> [blank]			
<b>Severity:</b> Advanced disease (unresectable or metastatic)			
<b>Condition:</b> Uveal melanoma			
<b>Indication:</b> Advanced (unresectable or metastatic) uveal melanoma			
<b>Treatment Phase</b> Continuing treatment			
<b>Clinical criteria:</b>			
The treatment must be the sole PBS-subsidised therapy for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have previously received PBS-subsidised treatment with this drug for this condition.			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must not develop disease progression as determined by the treating clinician while receiving PBS subsidised treatment with this drug for this condition.			
<b>Prescribing instruction:</b>			
According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 doses (on Days 1, 8 and 15) and for at least 16 hours after each infusion is completed. If the patient does not experience hypotension that is Grade 2 or worse (requiring medical intervention) with the third dose, subsequent doses can be administered in an appropriate outpatient/ambulatory care setting. Supervision by a health care professional is recommended for a minimum of 30 minutes following each infusion.			
<b>Caution:</b>			
Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).			

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **16 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **17 Sponsor's Comment**

The sponsor had no comment.