tebentafusp concentrate for solution for infusion (Kimmtrak®)

Immunocore Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life and orphan medicine process

tebentafusp (Kimmtrak®) is not recommended for use within NHSScotland.

Indication under review: as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Tebentafusp improved overall survival compared with investigator's choice of treatment, in (HLA)-A*02:01-positive adults with unresectable or metastatic uveal melanoma.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tebentafusp is a bispecific fusion protein that consists of a T-cell receptor (TCR) domain fused to an anti-CD3 antibody fragment (effector domain). The TCR domain binds with high affinity to a gp100 peptide that is presented by human leukocyte antigen-A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumour cells, whilst the effector domain binds to the CD3 receptor present on polyclonal T cells. These bindings result in the formation of an immune synapse, which causes the redirection and activation of polyclonal T cells. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of uveal melanoma tumour cells.[1, 2]

Tebentafusp is administered by intravenous (IV) infusion over 15 to 20 minutes at a dose of 20 micrograms on day 1, 30 micrograms on day 8, 68 micrograms on day 15, and then 68 micrograms weekly thereafter. Treatment is continued until disease progression or unacceptable toxicity.[1] See Summary of Product Characteristics (SPC) for more details.

1.2. Disease background

Uveal melanoma is a rare and life-threatening disease that arises from the melanocytes in the middle layer (the uvea) of the eye; it is biologically and clinically distinct from cutaneous melanoma and as such is managed differently.[2] Up to 50% of all patients diagnosed with primary and localised uveal melanoma go on to develop metastatic disease; in 90% of these cases, the first metastatic site is the liver. With eventual liver failure being the predominant cause of death from the condition, metastatic uveal melanoma has a median survival of approximately 12 months.[2-5] Tebentafusp is the first medicine to be licensed for HLA-A*02:01-positive patients, this marker is present on T cells in approximately 45% of patients with metastatic uveal melanoma.[6]

1.3. Treatment pathway and relevant comparators

In the absence of any recommended standard of care, treatments approved for advanced non-uveal cutaneous melanoma have been used. Clinical experts consulted by SMC indicated that pembrolizumab monotherapy or nivolumab in combination with ipilimumab may be used in patients unsuitable for radiofrequency ablation. It has been estimated that less than 10% of patients achieve an overall response to these treatments.[7]

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Tebentafusp received an Innovation Passport allowing entry into the Medicines and Healthcare products Regulatory Agency Innovative Licensing and Access Pathway (ILAP).

Eligibility for a PACE meeting

Tebentafusp meets SMC end of life and orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of tebentafusp comes from IMCgp100-202. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	IMCgp100-202 study.[3, 6]
Study design	A phase III, multicentre, randomised, open-label study.
Eligible patients	• ≥ 18 years old with metastatic uveal melanoma. • Human Leukocyte Antigen (HLA)-A*02:01 positive. • ECOG PS score of 0 or 1. • Had ≥1 measurable lesion (as per RECIST v1.1). • No prior systemic or localised (liver-directed) therapy for advanced or metastatic uveal melanoma (except for a prior surgical resection of oligometastatic disease). • No symptomatic or untreated central nervous system metastases.
Treatments	**Tebentafusp IV (n=252)** 20 micrograms (day 1), 30 micrograms (day 8), 68 micrograms (day 15), then 68 micrograms weekly; **OR,** **Investigator's choice of treatment (n=126):** • Pembrolizumab IV (n=103) 2 mg/kg up to a maximum of 200 mg per dose or (where approved locally) a fixed dose of 200 mg on day 1 of each 21-day cycle. • Ipilimumab IV (n=16) 3 mg/kg on day 1 of each 21-day cycle (maximum of four doses). • Dacarbazine (n=7) 1,000 mg/m^2 on day 1 of each 21-day cycle. All treatments (except ipilimumab) continued until disease progression or unacceptable toxicity. Patients receiving tebentafusp, pembrolizumab, or ipilimumab could continue treatment beyond disease progression if the investigator considered they were clinically stable, deriving clinical benefit and showed no signs of unacceptable toxicity.
Randomisation	Patients were randomised in a 2:1 ratio to receive tebentafusp or investigator's choice of treatment (selected prior to randomisation). It was stratified by centrally assessed LDH status (> ULN or ≤ ULN).
Primary outcome	Overall survival, defined as time from randomisation to death from any cause, was assessed in the ITT population. The ITT population included all randomised patients regardless of whether they received treatment.
Secondary outcomes	• PFS - defined as the time from randomisation to the date of progression (according to RECIST v1.1) or death. • ORR – defined as the number of randomised patients with at least one visit response of the best overall response [BOR] divided by the number of randomised patients as a percentage for each treatment arm in the ITT set. • BOR - defined as the best overall response designation (according to RECIST v1.1) up until progression or last evaluable assessment in the absence of progression.
Statistical analysis	Analysis was performed on the ITT population using hierarchal ranking of primary and secondary outcomes in the following order: OS, PFS, ORR.

Abbreviations: BOR = best overall response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous; ITT = intention-to-treat; LDH = lactate dehydrogenase; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; ULN = upper limit of normal.

Detailed results from the first interim analysis (October 2020 data cut-off) and an exploratory 3-year follow-up analysis (July 2023 data cut-off) are presented in Table 2.2.

Table 2.2. Primary and selected secondary outcomes from the IMCgp100-202 study.[2, 3, 6]

Data cut-off date	**October 2020**		**July 2023**	
Median follow-up	14.1 months		43.3 months	
	Tebentafusp (n=252)	**Investigator's choice (n=126)**	**Tebentafusp (n=252)**	**Investigator's choice (n=126)**
Primary outcome: Overall survival				
Deaths, n	87	63	189	103
Median OS (months)	21.7	16.0	21.6	16.9
HR (95% CI), p-value	0.51 (0.37 to 0.71), p<0.001		0.68 (0.54 to 0.87)	
KM estimated OS at 12 months	73%	58%	72%	60%
KM estimated OS at 24 months	45%	20%	45%	30%
KM estimated OS at 36 months	NA	NA	27%	18%
Secondary outcome: Progression-free survival assessed by investigator using RECIST v1.1				
PFS events, n	198	97	NA	NA
Median PFS (months)	3.3	2.9	3.4	2.9
HR (95% CI), p-value	0.73 (0.58 to 0.94), p=0.014		0.76 (0.60 to 0.97)	
KM estimated PFS at 12 months	14%	6.2%	17%	9%
KM estimated PFS at 24 months	NA	NA	8%	3%
Secondary outcome: Best Overall Response assessed by investigator using RECIST v1.1				
ORR, n (%)	23 (9.1)	6 (4.8)	28 (11)	6 (4.8)
Odds ratio (95% CI)	1.98 (0.79 to 4.97)		2.46 (1.00 to 6.06)	
CR, n	1	0	1	0
PR, n	22	6	27	6
PD, n	131	78	132	82
SD ≥ 12 weeks, n	92	28	87	28
NE, n	6	14	5	10

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; KM = Kaplan-Meier; NA = not available; NE = not evaluable; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1SD = stable disease.

Based on the survival benefit observed at the first interim analysis (data cut-off October 2020), patients in the investigator's choice group were subsequently permitted to cross over to receive tebentafusp. Between the data cut-off of October 2020 and July 2023, 16 patients (of whom 14 were receiving pembrolizumab) had crossed over to the tebentafusp group; 24 patients in the investigator's choice group had received tebentafusp as a subsequent treatment. Results presented in the subsequent analyses (that is for data cut-offs April 2022 and July 2023) included this subset of patients. When this analysis was repeated (July 2023 data cut-off) with data from patients who crossed over to the tebentafusp group censored at the start of treatment with tebentafusp, the effect on the hazard ratio for overall survival (OS) was minimal (0.70; 95% confidence interval [CI]: 0.54 to 0.90). All patients had progressed and discontinued their original treatment at the time point of cross over.[3]

However, the submitting company considered that the July 2023 dataset was biased and confounded by high censoring in the tebentafusp group as a result of study closure, and the inclusion of patients who received tebentafusp (21%) and immunotherapy (48%) after

discontinuing pembrolizumab.[3] Therefore, the submitting company used an April 2022 data cut-off for their cost-effectiveness analyses. Results from the April 2022 data cut remain confidential.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed as secondary outcomes using the EuroQoL-5 Dimension-5 Level (EQ-5D-5L) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). No differences in baseline HRQoL scores were observed between the tebentafusp and investigator's choice groups for any of the domains. During the study, the EQ-5D-5L and EORTC QLQ-C30 overall scores were similar between the treatment groups and remained stable for most domains.[2]

2.3. Supportive studies

The submitting company provided supportive data for pre-treated patients from the IMCgp100-102 study, a phase I/II, single-arm, open-label, uncontrolled, multicentre trial. It consisted of a dose-finding (phase I) and escalation (phase II) phase. During phase II, HLA-A*02:01-positive patients (n=127) with metastatic uveal melanoma and disease progression after at least one previous treatment received the licensed dose of tebentafusp. When assessed by independent central review, the primary outcome of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) was 4.7% (6/127). Additionally, after a median follow-up of 19.6 months, the median OS (secondary outcome) was 16.8 months whilst median progression-free survival (PFS) (secondary outcome) was 2.8 months.[2, 9] At the final analysis (median follow-up of 48.5 months), the median OS was 17.4 months with OS rates of 62% (12 months), 40% (24 months), 23% (36 months) and 14% (48 months).[10]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence against nivolumab plus ipilimumab combination therapy, the submitting company performed an indirect treatment comparison. This was used to inform a scenario analysis in the economic case. See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Propensity score weighting analysis (for overall survival [OS]) and unanchored matching adjusted indirect comparison (MAIC) (for progression-free survival [PFS]).
Population	Adults with previously untreated metastatic uveal melanoma.
Comparators	Nivolumab plus ipilimumab combination therapy.
Studies included	IMCgp100-202[6] (for tebentafusp) and GEM-1402[11, 12] (for nivolumab plus ipilimumab). The propensity score analysis (for OS) was based on individual patient data (IPD) from both studies.
Outcomes	OS and PFS.
Results	Tebentafusp had superior efficacy compared to nivolumab plus ipilimumab combination therapy. In the primary propensity score analysis, the hazard ratio (HR) for OS was 0.50 (95% confidence interval [CI]: 0.34 to 0.75). In the unanchored MAIC, the HR for PFS was 0.70 (95% CI: 0.50 to 0.99). The results of two propensity score analyses have been published, using data from two different data cuts (October 2020 and July 2023 for IMCgp100-202 and July 2019 and August 2023 for GEM-1402 respectively). A MAIC based on the 2020 and 2019 data cuts has also been published.[13, 14] The results

	used in the economic scenario analysis were based on data from April 2022 for IMCgp100-202 and July 2019 for GEM-1402.

3. Summary of Safety Evidence

Safety analyses were performed in the safety analysis set which included all patients who had received at least one dose of study medicine. At the October 2020 data cut-off, treatment-emergent adverse events (AEs) were reported by 100% (245/245) of patients in the tebentafusp group and 95% (105/111) in the investigator's choice group, and these were treatment-related in 99% and 82% of patients, respectively. For 57% of patients in the tebentafusp group, treatment-related AEs occurred during the first 4 weeks of treatment and the incidence and severity of these events reduced with repeated dosing.[2, 6]

More patients in the tebentafusp versus the investigator's choice group had grade ≥3 treatment-related AEs: 45% versus 17%; the most common (occurring in >2% of patients in either group), in the tebentafusp and the investigator's choice groups respectively, were: rash (18% versus 0%), pruritis (4.5% versus 0%), aspartate aminotransferase increased (4.5% versus 0%), lipase increased (3.7% versus 5.4%), pyrexia (3.7% versus 0%), hypertension (3.7% versus 0.9%), hypotension (3.3% versus 0%), alanine aminotransferase increased (2.9% versus 1.8%), fatigue (2.9% versus 0.9%), hypophosphataemia (2.9% versus 0%), lymphopenia (2.4% versus 0%), hyperbilirubinaemia (2.0% versus 0%), cytokine release syndrome (CRS) (0.8% versus 0%) and diarrhoea (0.8% versus 2.7%).[2, 6]

Serious adverse events (SAEs) that were considered treatment-related were substantially higher in the tebentafusp arm compared to the investigator's choice group (22% versus 7.0%) in IMCgp100-202, with the most common being CRS and acute skin reactions.[2] The proportion of treatment-related AEs that led to dose or infusion interruptions were 18% versus 21% and patients discontinuing therapy due to a treatment-related AE was 2.0% versus 4.5%, respectively.[2, 6]

Overall, regulators considered that although tebentafusp had a higher degree of toxicity than the investigator's choice group, the risks were considered manageable in the context of the disease condition.[2, 8]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the IMCgp100-202 study, tebentafusp resulted in a significant improvement in median OS of 5.7 months at the October 2020 data cut-off when compared with investigator's choice of treatment (which included comparators used in current practice) as a first-line treatment of HLA-A*02:01-positive patients with metastatic uveal melanoma.[6] This was considered clinically relevant in a population who only has a median overall survival of approximately 12 months.[2, 8] Updated OS data from an exploratory 3-year follow-up analysis (July 2023 data cut-off) were also consistent with the earlier data cut-off.[3]
- Uncontrolled results from the phase II study (IMCgp100-102) provided supporting evidence in previously treated patients as second or subsequent therapy for metastatic disease.[9, 10] Whilst

the study methodology had limitations (for example single-arm, open-label, uncontrolled), the results from the final OS analysis (approximately 4 years of follow-up) are consistent with those in the IMCgp100-202 study with untreated patients.[10]

- Despite tebentafusp having more treatment-related AEs and SAEs compared with the investigator's choice of treatment, it was noted that these adverse drug reactions usually diminished over time with continued treatment beyond the first three treatment cycles. Additionally, the discontinuation and dose reduction rates for tebentafusp were low, and no treatment-related deaths were reported in the IMCgp100-202 study.[2, 6] The regulators concluded that despite the higher number and variety of AEs associated with tebentafusp, these were manageable and tolerable after the first month.[2, 8]
- Tebentafusp is the first medicine to be licensed for HLA*02:01-positive adults with metastatic or unresectable uveal melanoma.[1]

4.2. Key uncertainties

- After the first interim analysis, patients in the investigator's choice group were permitted to crossover to receive tebentafusp; therefore, data presented in the subsequent analyses included some patients who had switched which may have confounded OS. No adjustment was made for crossover.[2] However, the proportion of patients who crossed over from pembrolizumab to tebentafusp treatment was small, and censoring at the time of crossover was shown to be unlikely to have an impact on analysis of OS compared to not including adjustment for crossover from pembrolizumab to tebentafusp post-progression following the first interim analysis.[3]
- The IMCgp100-202 study had an open-label design which could have introduced potential bias on the decision to continue treatment beyond progression, which was notably larger in the tebentafusp group (43%) compared with the investigator's choice group (14%). This difference may have confounded subsequent OS data.[2, 6]
- It should be noted that the IMCgp100-202 study was not designed to compare tebentafusp with the individual treatments included within the investigator's choice group; there may be some differences in efficacy between these treatments based on the study data (specifically the subgroup analyses for these three treatments). The proportion of patients that received each of the different investigator's choice of treatment (n=126) were: 103 (82%) for pembrolizumab, 16 (13%) for ipilimumab, and 7 (6%) for dacarbazine[2]; the study therefore provides a comparison of tebentafusp with pembrolizumab monotherapy but is probably too small to provide direct comparisons with the other two treatments (which are not relevant comparators, as monotherapies).
- Tebentafusp treatment resulted in a statistically significant improvement in the secondary endpoint of PFS, but this was a modest improvement of 0.4 months and was not considered clinically meaningful. However, the PFS data were mature (approximately 80% of PFS events had occurred) at the first interim analysis and the OS benefits provide assurance; additionally, there may be some benefit on OS after disease progression but the reasons for this are unclear.[2]

- With no standard of care for patients with metastatic uveal melanoma, the use of investigator's choice of treatment as a comparator was considered acceptable.[2] Clinical experts consulted by SMC considered pembrolizumab a relevant comparator and also noted that ipilimumab is used in combination with nivolumab in practice. The submitting company provided indirect evidence which they claimed demonstrated a clear OS benefit for tebentafusp compared with nivolumab plus ipilimumab combination therapy. This had some limitations including differences in the population, the definition of OS, that the analysis was unanchored and choice of data cut. However, despite these limitations the company's conclusion seems reasonable.

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies.

Final results of the ongoing IMCgp100-202 study are unlikely to address the key uncertainties in the clinical evidence presented. There are no additional ongoing studies of tebentafusp in advanced uveal melanoma.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that tebentafusp fills an unmet need and is a therapeutic advancement in this therapeutic area, since it would be the only treatment licensed for, and with OS benefit in, HLA-A*02:01-positive patients with metastatic uveal melanoma. They considered the place in therapy of tebentafusp is for HLA-A*02:01-positive patients with uveal melanoma who have unresectable or metastatic uveal melanoma and considered fit enough for therapy in view of the predicted tebentafusp AEs such as CRS.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may have an impact on the patient and service delivery as the first three treatment doses of tebentafusp require administration in a hospital setting. As per the SPC, there should be provisions for overnight monitoring of the signs and symptoms of CRS for at least 16 hours; however, hospitalisation related to these three doses may be prolonged and require more frequent monitoring than every 4 hours as recommended.[1] In IMCgp100-202, the regulator noted that tebentafusp was associated with a higher degree of hospitalisation compared with the investigator's choice group (41% versus 21%) though these were related to extensions of protocol-mandated hospitalisation and the need for prolonged monitoring of the patient and significant AEs. It was noted that the nature and rate of CRS and acute skin toxicity in the tebentafusp group are quite different from currently available cancer treatments.[2, 6]

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **tebentafusp,** as an **orphan and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic uveal melanoma is a rare form of cancer, and was granted orphan status by the Medicines and Healthcare products Regulatory Agency. It has no licensed treatments, and none of the currently used treatments have shown to be clinically effective. With less than 10% of patients achieving an overall response, patients may only live up to one year following their diagnosis.

- Given the rarity of the condition, the lack of successful treatment options and its life-limiting nature, the diagnosis is devastating for patients and their families. Most people with the condition, and their families, have significant fears about disease recurrence; whether this is not knowing whether it will recur at all or knowing it can be aggressive and terminal if it does recur.

- Tebentafusp is the first licensed treatment for metastatic uveal melanoma in patients who are HLA-A*02:01 positive, a marker which is present in approximately 45% of patients with uveal melanoma and is the only medicine that appears to be clinically effective for this condition.

- In responders, tebentafusp may stabilise or slow the growth of metastatic uveal melanoma, prolong survival, improve or delay the onset of cancer symptoms (if the patient is experiencing any), allow patients to remain active and independent, and preserve their quality of life. Tebentafusp is the first treatment to prolong patients' lives when compared with other treatments that are used in clinical practice.

- After the first month of treatment, tebentafusp has a favourable toxicity profile compared to current treatments. PACE participants described how people in their community forums have experienced few side effects, which is in contrast to the other systemic treatment options, where side effects are usually considerable and prolonged.

- There are also psychological advantages of tebentafusp to patients and their families. The prospect of being offered an effective treatment would not only benefit those with advanced uveal melanoma, but may also allay some of the fear and anxiety patients with non-metastatic uveal melanoma experience.

- Patients who are receiving tebentafusp shared their positive experiences with the medicine with other PACE participants, confirming the positive impact on their condition, mental health, quality of life. Despite the need for weekly travel, and the minimum 16-hour inpatient admission required during the first month, these patients deemed these as ‘minor upsets’ compared to the alternative.

- PACE participants also highlighted that, following discussions during public meetings with clinicians, there was excitement and positivity about this new treatment option.

Additional Patient and Carer Involvement

We received patient group submissions from Melanoma Focus and Ocular Melanoma UK (previously known as OcuMel UK). Both organisations are registered charities. Melanoma Focus has received 20% pharmaceutical company funding in the past two years, including from the submitting company. Ocular Melanoma UK has received 38% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is described below in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis with partitioned survival.
Time horizon	Lifetime (38 years) based on starting model age of 62 years. Further scenario analyses provided reduced this to 30, 20 and 10 years. Cycle length is 1 week (half-cycle correction applied).
Population	HLA-A*02:01 positive adult patients with metastatic uveal melanoma without prior treatment in the metastatic setting.
Comparators	The main comparator is pembrolizumab. A scenario analysis was conducted comparing tebentafusp with ipilimumab plus nivolumab. This used an indirect treatment comparison since the main clinical study did not have ipilimumab plus nivolumab as a comparator group (though some patients did receive ipilimumab monotherapy). The main comparator in the IMCgp100-202 study was pembrolizumab.
Model description	The model was a partitioned survival model with states for pre-progression, progressed disease and death.
Clinical data	Clinical data were taken from the IMCgp100-202 study using the April 2022 cut-off. This differs from the October 2020 interim analysis cut-off and 3-year exploratory follow up cut-off (June 2023) reported in the clinical case. All patients had been allocated to an investigator's choice of treatment prior to randomisation and those who had been allocated to pembrolizumab but were later randomised to receive tebentafusp were compared to patients who had been allocated to receive the investigators choice of pembrolizumab upon randomisation to the control group. This means that the economic analysis is not the full ITT population but it is consistent across arms.
Extrapolation	Parametric curves were fitted to OS, PFS and TTD data. In some cases, distribution fitting was only applied after a cut point based either at a particular number of weeks or the point when the proportion of patients still at risk of the event (death, progression or discontinuation) reached a certain percentage. Prior to the cut point, the Kaplan-Meier data were used. The submitting company justified the method based on NICE Technical Support Documentation, and the number of weeks and percentages were tested in scenario analysis. In other cases, standard parametric distributions had been fitted to one or both groups. Clarification was provided by the company on what distributions had been tested. This indicated that scenario testing of the OS distributions was incomplete as no standard parametric test had been applied to the tebentafusp arm. The submitting company noted that the choice not to use a standard parametric curve in the base case was due to the bi-phasic hazard for this group.
Quality of life	EQ-5D-5L results were used in sensitivity analysis (cross-walked using the Van Hout method (2012). These values were used to estimate quality of life for patients with 360 days or more before time to death. Time to death utilities were used in the base case rather than state or treatment specific utilities but treatment (on/off treatment) utilities were used in scenario analysis. For time to death utilities, these were adjusted based on the values in NICE TA366 (Pembrolizumab for advanced melanoma not

	previously treated with ipilimumab). Utility decrements were also applied based on population norms as patient ages increase (this is standard) and to account for adverse event disutilities.
Costs and resource use	Medicines costs included drug acquisition costs, administration costs and subsequent treatment costs, as well as the cost of adverse events and dose interruptions/reductions. Adverse events included the cost of dealing with specific cytokine-related events requiring monitoring in early dose escalations of tebentafusp (first three doses), which will require an overnight hospital stay. The base case did not include a 2-year stopping rule, but this was explored in sensitivity analysis. Other tests included scans, hospital visits, consultations, primary care and end of life care.
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for pembrolizumab, nivolumab and ipilimumab and these were included in the results used for decision-making by using estimates of the comparator PAS prices.

Abbreviations: OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; TTD = time to treatment discontinuation

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of some key scenarios are provided in Table 6.3.1 below.

Table 6.3.1 Selected scenario analyses for tebentafusp vs pembrolizumab

Scenario Number	Base case description	Scenario description
1	tebentafusp OS distribution piecewise model 26 months + log-logistic thereafter	tebentafusp OS distribution piecewise model 26 months + Weibull thereafter
2	TTD using KM plus standard parametric model using exponential distribution	TTD using standard parametric model throughout with generalised gamma distribution
3	Two year stopping rule excluded	Two year stopping rule included
4	Utilities based on time to death	Utilities based on treatment status
5	Time horizon 38 years	Time horizon 20 years
6		Time horizon 10 years
7	No exclusion or censoring of crossover patients	Crossover excluded
8		Crossover censored
9	Tebentafusp OS distribution piecewise model 26 months + log-logistic, standard parametric Weibull distribution for pembrolizumab OS data	Log normal standard parametric distribution applied to both tebentafusp OS and pembrolizumab OS data
10		Log logistic standard parametric distribution applied to both tebentafusp OS and pembrolizumab OS data
11		Log logistic standard parametric applied to tebentafusp OS and standard
12	Using October 2022 cut off	Using July 2023 cut off

To further test the comparison with nivolumab plus ipilimumab, a small number of scenario analyses were subsequently provided as summarised in Table 6.3.2.

Table 6.3.2 Selected scenario analyses for tebentafusp vs nivolumab plus ipilimumab

Scenario Number	Base case description	Scenario description
1	KM data to 24 months followed by log normal distribution for tebentafusp, and the log logistic distribution for ipilimumab plus nivolumab	Standard parametric Gompertz distribution for tebentafusp OS and the log logistic distribution for ipilimumab plus nivolumab OS
2	KM + Generalised gamma for tebentafusp and generalised gamma for nivolumab plus ipilimumab	KM data to 24 months followed by the generalised gamma distribution for PFS for tebentafusp, and a log normal distribution for ipilimumab plus nivolumab
3	October 2022 data cut off	July 2023 data cut off

6.4. Key strengths

- The model structure is appropriate for oncology economic evaluations and is therefore relevant.
- There is a randomised study that directly compares tebentafusp with one of the main comparators of interest.

6.5. Key uncertainties

- Results were sensitive to the modelling approach for OS. The base case analysis used a piecewise approach in the tebentafusp arm only, which can result in over-fitting to the trial data and uncertainty in the extrapolation of the curve from a point where the number of patients at risk is low. The Committee also raised concerns about the use of different extrapolation approaches in each treatment arm with a standard parametric model used in the pembrolizumab arm. Results were sensitive to using the standard parametric approach in both arms of the model.
- The base case analysis did not use the more recent June 2023 data cut-off due to potential bias as a result of high censoring in the tebentafusp group and patients crossing over to receive tebentafusp after discontinuation of pembrolizumab. Sensitivity analysis using the June 2023 data cut was provided which increased the incremental cost-effectiveness ratio (ICER). Additional scenario analyses that excluded or censored crossover patients (using the base case April 2022 data cut-off) had little impact on the ICER. In addition, the submitting company justified their choice of overall survival extrapolation method on the basis of reporting a bi-phasic hazard for the tebentafusp arm, but they did not test this or report whether the bi-phasic hazard was still present at the later June 2023 cut-off when survival data are more mature.
- A scenario analysis comparing tebentafusp with ipilimumab plus nivolumab was provided and this was useful to the Committee as clinical experts consulted by SMC had consistently mentioned this comparator. SMC clinical experts indicated the proportion of patients currently receiving nivolumab plus ipilimumab in clinical practice was between 40% and 50%, confirming this comparator is relevant for decision-making. However, the Committee noted this was presented as a scenario analysis with the full extent of uncertainty around the base case

results not fully explored. This was highlighted as a significant limitation in terms of decision making.

- The submitting company provided further analyses for the time horizon as Committee members felt that shorter timeframes may still be relevant to explore, given that this is an end of life treatment for metastatic disease. The results were relatively sensitive to reducing the time horizon to 10 years, although it was noted this was a conservative analysis.
- The submitting company has provided clarity around the application of costs for treating adverse events in inpatient and outpatient settings, further noting that they do not consider adverse events to have a large effect on the ICER generally. Nevertheless, the inclusion of specific adverse events predominantly affecting only one or the other treatments (cytokine reactions for tebentafusp, endocrine disorders and colitis for pembrolizumab) beyond the typical grade 3 and above adverse events affecting a certain percentage of study participants, may risk certain biases. Although it was noted that this would not have a large impact on the ICER.

7. Conclusion

The Committee considered the benefits of tebentafusp in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as tebentafusp is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept tebentafusp for use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published the guideline "Melanoma: assessment and management" (NG14) in July 2015, which was last updated in July 2022. There are no specific recommendations in the guideline for uveal melanoma.[16]

9. Additional Information

9.1. Product availability date

9 January 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Tebentafusp	**20 micrograms (day 1), 30 micrograms (day 8), 68 micrograms (day 15), then every week by intravenous infusion until disease progression or unacceptable toxicity**	**525,928**

Costs from BNF online on 08 January 2025. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be eight patients eligible for treatment with tebentafusp in each year. The estimated uptake rate was 50% in year 1 and 80% in year 5. This resulted in four patients estimated to receive treatment in year 1 rising to seven patients in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 25 February 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.