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 second resubmission assessed under the end of life and orphan medicine process

tebentafusp (Kimmtrak®) is accepted 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.

Evidence from an open-label, phase III study demonstrated that tebentafusp improved overall survival (OS) compared with investigator's choice of treatment (which included pembrolizumab monotherapy), in HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma. Indirect comparisons suggest improved OS and progression-free survival (PFS) compared with nivolumab plus ipilimumab.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

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 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]

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. Approximately 45% of patients with metastatic uveal melanoma are HLA A*02:01 positive. 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]

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 for unresectable or metastatic uveal melanoma. 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] Some experts consulted by SMC highlighted that the combination nivolumab-relatlimab may be an alternative treatment option for selected patients, although the evidence base is limited.

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 and an exploratory 3-year follow-up analysis (July 2023 data cut) are presented in Table 2.2.

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

Data cut 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 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)
CR, n	1	0	1	0
PR, n	22	6	27	6
PD, n	131	78	132	82

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 1.1.

As part of the second resubmission, additional overall survival data from a post-hoc 5-year analysis was presented (July 2025 data cut). The results were consistent with the June 2023 data cut with a median overall survival (OS) of 21.6 months in the tebentafusp group and 16.9 months in the investigator's choice groups (hazard ratio [HR] 0.67, 95% confidence interval [CI]: 0.53 to 0.85). The estimated OS rate at 60 months was 15% and 8%, respectively. PFS data were not collected following the July 2023 data cut as most events had occurred and data from earlier data cuts were considered sufficiently mature. A subgroup of 199 patients from the tebentafusp group, who were designated to receive pembrolizumab if they had been randomised to the investigator's choice group, was used in the economic analysis (referred to as 'tebentafusp pre-choice pembrolizumab'). At the July 2025 data cut, the median OS for this subgroup (21.7 months) was similar to the tebentafusp group (21.6 months).[19]

Based on the survival benefit observed at the first interim analysis (data cut October 2020), patients in the investigator's choice group were subsequently permitted to cross over to receive tebentafusp. Between the data cut of October 2020 and July 2023, 16/126 (13%) patients (including 14/103 (14%) who were receiving pembrolizumab) had crossed over to the tebentafusp group; by the 2025 data cut 25/103 (24%) patients who received pembrolizumab in the investigator's choice group had received tebentafusp as a subsequent treatment. A survival analysis was conducted with data (July 2023 data cut) from patients who crossed over to the tebentafusp group censored at the start of treatment with tebentafusp, the effect on the hazard

ratio for OS was minimal (0.70; 95% CI: 0.54 to 0.90). All patients had progressed and discontinued their original treatment at the time point of cross over.[3, 19]

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). At the October 2020 data cut, 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 study. During phase II, HLA-A*02:01-positive patients (n=127) with metastatic uveal melanoma and disease progression after at least one previous treatment (majority with immunotherapy) 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 base case in the economic analysis. 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, 19] for tebentafusp (data cuts: OS: July 2025, PFS: April 2022) and GEM-1402 (data cuts: OS: August 2023, PFS: July 2019)[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 was superior compared with nivolumab plus ipilimumab for OS and PFS. In the propensity score analysis, the hazard ratio (HR) for OS was 0.53 (95% confidence interval [CI]: 0.36 to 0.78). In the unanchored MAIC, the HR for PFS was 0.70 (95% CI: 0.50 to 0.99).

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] Safety results from the July 2023 data cut-off were broadly consistent.[3]

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

- 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]
- IMCgp100-202 was a randomised phase III study that provides direct evidence versus investigators choice of treatment. This included 82% of patients that received pembrolizumab monotherapy which was identified as a relevant comparator by SMC clinical experts.
- At the October 2020 data cut-off, tebentafusp was associated with a significant improvement in median OS of 5.7 months compared with investigator's choice of treatment as a first-line treatment of HLA-A*02:01-positive patients with metastatic uveal melanoma.[6] This was considered clinically relevant by the regulator in a population which has a median overall survival of approximately 12 months.[2, 8] Updated OS data from an exploratory 3-year and 5-

year follow-up analysis (July 2023 and July 2025 data cut-offs) were also consistent with the earlier data cut-off.[3, 19]

- Uncontrolled results from the phase II study (IMCgp100-102) provided evidence in previously treated patients as second or subsequent therapy for metastatic disease which was considered clinically meaningful and supportive in the second line and beyond setting.[2, 9, 10]

4.2. Key uncertainties

- 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%). The precise magnitude of survival benefit for treatment with tebentafusp beyond disease progression is uncertain .[2, 6]
- After the first interim analysis (October 2020 data cut-off), patients in the investigator's choice group were permitted to crossover to receive tebentafusp, and by the July 2025 data cut-off 24% who received pembrolizumab in the investigator's choice group had either crossed over or received tebentafusp as a subsequent treatment. Fifteen patients enrolled in Germany (12 in the tebentafusp arm; 3 in the investigator's choice arm) were alive but lost to follow-up and were censored at study closure due to local regulations. Therefore, OS data presented in the subsequent analyses are likely to be confounded; no statistical adjustment was planned for crossover. The submitting company subsequently provided a post hoc OS analysis adjusting for subsequent treatments using inverse probability of censoring weighting and other censoring methods which indicated a maintained survival benefit. This analysis was not included in the cost-effectiveness analysis. As the hazard ratios are more favourable to tebentafusp it is likely that the cost-effectiveness results would improve, but this cannot be confirmed.[2]
- Tebentafusp treatment resulted in a statistically significant improvement in the secondary endpoint of PFS, but this was a modest improvement of 0.4 months despite the data being mature (approximately 80% of PFS events had occurred at the first interim analysis) and was not considered clinically meaningful. However, the OS benefits may provide assurance.[2]
- In the absence of direct evidence compared with nivolumab plus ipilimumab, the submitting company presented an indirect comparison which they concluded demonstrated a clear OS benefit for tebentafusp. 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.
- Some experts consulted by SMC highlighted that nivolumab-relatlimab may be an additional comparator in this setting for selected patients. However there appears to be variation in use across Scottish clinical practice and some experts noted there is limited evidence in the population under review. This combination is licensed as a first-line treatment for advanced (unresectable or metastatic) melanoma and was accepted by SMC in June 2024 (SMC2645).[18] No clinical or cost-effectiveness comparisons with this treatment combination have been provided in this submission.

- There is no direct or indirect comparative evidence of tebentafusp as a second or subsequent treatment in the metastatic setting. IMCgp100-102 provides supportive evidence in this setting but was a phase II single arm uncontrolled study.
- The IMCgp100-202 study was not designed to compare tebentafusp with the individual treatments included within the investigator's choice group and there may be some differences in efficacy between these treatments based on the study data (specifically the subgroup analyses for these three treatments).[2]

4.3. 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.

4.4. 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 summary of product characteristics (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] 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, 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. Loss of vision or monovision can particularly impact daily functioning and independence.
- 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 24% 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 in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime (38 years) based on starting model age of 62 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	Two comparators were included, pembrolizumab and nivolumab plus ipilimumab.
Model description	The model was a partitioned survival model with states for pre-progression, progressed disease and death.
Clinical data	In the pembrolizumab comparison, clinical data were taken from the IMCgp100-202 study using the July 2025 cut for OS and July 2023 cut for PFS and time to treatment discontinuation (TTD). Tebentafusp data in this comparison were from patients in the 'tebentafusp pre-choice pembrolizumab' subgroup, with pembrolizumab data from patients that received pembrolizumab in the investigator's choice arm. In the nivolumab plus ipilimumab comparison, clinical data were sourced from indirect treatment comparisons. For overall survival, a propensity score analysis (specifically an inverse probability of treatment weighting (IPTW) weighting using the average treatment of the treated (ATT) approach) was used. This used the July 2025 IMCgp100-202 and the August 2023 GEM-1402 data cuts. For PFS, an unanchored MAIC was used as IPD were not available. This used the April 2022 IMCgp100-202 and the July 2019 GEM-1402 data cuts.
Extrapolation	In the pembrolizumab comparison, parametric curves were fitted to OS, PFS and TTD data. For tebentafusp OS a log-logistic curve was used, for PFS a generalised gamma curve was used, and for TTD an exponential curve was used. For pembrolizumab an exponential curve was used for OS, PFS and TTD. In the nivolumab plus ipilimumab comparison, parametric curves were fitted to OS and PFS data. For tebentafusp OS a log-logistic curve was used, and for PFS a generalised gamma curve was used. For nivolumab plus ipilimumab a generalised gamma curve was used for OS and PFS. TTD in this comparison was modelled using PFS plus a further treatment duration due to a lack of TTD data for nivolumab plus ipilimumab.
Quality of life	Time to death utility values were used in the base case. The utility value for patients with 360 days or more before time to death was derived from the EQ-5D-5L data from IMCgp100-202. This was then adjusted using multipliers based on the time to death utility values from NICE TA366 (Pembrolizumab for advanced melanoma not previously treated with ipilimumab). Utility decrements were also applied for age and to account for adverse event disutilities.
Costs and resource use	Medicines costs included drug acquisition costs, administration costs and subsequent treatment costs, health state costs, and the cost of adverse events. Adverse events included the cost of dealing with specific cytokine-related events requiring monitoring in early dose escalations of tebentafusp. Subsequent treatment costs included the cost of tebentafusp in the pembrolizumab arm.
PAS/contract price	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. Across the base case and scenario analyses, results in the pembrolizumab comparison showed a less favourable economic case.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of key scenarios are provided in Table 6.2 and Table 6.3 below.

Table 6.2: Scenario analysis (pembrolizumab)

	Parameter	Base case	Scenario
	Base case		
1a	Time horizon	38 years	20 years
1b			10 years
2	OS curve – tebentafusp	Log-logistic	Log normal
3	OS curve – Pembrolizumab	Exponential	Weibull
4	TTD extrapolation (both arms)	Exponential	Gen. gamma
5	Utility values	Time to death	Treatment status
6	Subsequent tebentafusp treatment duration	9.8 months [IMCgp100-102, 2nd line].	3.9 months [IMCgp100-202 subsequent treatment duration IC arm]
7a	Adjustment for subsequent tebentafusp in pembrolizumab arm	No adjustment	IMCgp100-202 October 2020 data cut – Pembrolizumab OS Weibull
7b			IMCgp100-202 October 2020 data cut – Pembrolizumab OS generalised gamma

Abbreviations: IC = investigators choice: OS = overall survival; TTD = time to treatment discontinuation.

Table 6.3: Scenario analysis (nivolumab plus ipilimumab)

	Parameter	Base case	Scenario
	Base case		
1a	Time horizon	38 years	20 years
1b			10 years
2a	OS curve – tebentafusp	Log-logistic	Log normal
2b			Gen. gamma
3a	OS curve –nivolumab plus ipilimumab	Gen. gamma	Weibull
3b			Log normal
4	PFS curve – nivolumab plus ipilimumab	Gen. gamma	Log logistic
5	TTD extrapolation (both arms)	PFS + further treatment	PFS only
6	Propensity score weights	ATT	ATC
7	Utility values	Time to death	Treatment status

Abbreviations: ATT = average treatment effect of the treated; ATC = Average Treatment Effect on the Control; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation.

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

- There was uncertainty in the extrapolation of OS outcomes in the pembrolizumab comparison. Given a larger proportion of patients continued treatment beyond progression in the tebentafusp arm, and the potential for confounding OS data, a more conservative OS extrapolation for tebentafusp OS was considered (Table 6.2, scenario 2).
- There was uncertainty that subsequent tebentafusp use in the pembrolizumab arm of the pivotal study may have confounded the OS data from the study for use in the economic model. The company provided scenario analyses using a 2020 data cut to explore this (Table 6.2, scenarios 7a and 7b). However, these were potentially limited as they relied on an earlier data cut. The costs attributed to subsequent tebentafusp were also a source of uncertainty as the duration of subsequent tebentafusp treatment was not recorded in IMCgp100-202. Scenario analysis explored an alternative duration, leading to an increased ICER (Table 6.2, scenario 6).
- There was uncertainty around the PFS extrapolations for nivolumab plus ipilimumab. A more conservative, yet plausible, log-logistic PFS extrapolation was considered, which reduced extrapolated PFS and treatment duration for nivolumab plus ipilimumab and resulted in a higher ICER (Table 6.3, scenario 4).
- There was uncertainty in the duration of the lifetime time horizon. This was due to a small proportion of tebentafusp patients remaining alive at extended time horizons, despite this being an end-of-life treatment for metastatic disease. The results were relatively sensitive to reducing the time horizon to 10 years, although this was considered a conservative analysis (Tables 6.2 and 6.3, scenario 1b).
- Some SMC clinical experts highlighted nivolumab-relatlimab as a potential additional comparator. Economic results versus this comparator were not available. The submitting company and clinical experts consulted by SMC highlighted the limited evidence base for nivolumab-relatlimab in the treatment of advanced uveal melanoma.

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

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 in the patient population targeted in the submission 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 accepted 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]

The European Society for Medical Oncology (ESMO) and European Reference Network for Rare Adult Solid Cancers (EURACAN) published the guideline "Uveal melanoma: ESMO—EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up" in April 2026.[20]

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 30March 2026. 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

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*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 15 May 2026.

**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 includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS 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. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees 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.