National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma ID1441

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Immunocore	While we agree that it's appropriate to refer tebentafusp to NICE for appraisal we believe tebentafusp fulfils **all** the entry criteria for consideration via the Highly Specialised technology programme. In summary: • Metastatic uveal melanoma is biologically distinct and ultra-rare ocular cancer, as recognised by the orphan designation of tebentafusp by multiple regulators (FDA and EMA). • The total UK patient population for uveal melanoma is estimated to be 540 patients[1], of whom about 40-50% develop metastatic disease.[2] • Tebentafusp is a highly indication-specific targeted therapy for metastatic uveal melanoma. The anticipated indication is for the treatment of adult patients with HLA-A*02:01-positive unresectable or metastatic uveal melanoma. Tebentafusp is an HLA allele-specific targeted treatment for HLA-A*02:01. The T cell receptor domain of tebentafusp targets cells presenting HLA-A*02:01 complexed with a peptide derived from the melanoma-associated antigen gp100.[3] Uveal melanoma cells are unique in their homogenous high	Thank you for your comment. The feedback from the scoping workshop indicates that tebentafusp is not suitable to be reviewed under the HST pathway. No change to scope.

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		expression of gp100 which enables tebentafusp's uniquely high specificity.[4] • Of those developing metastatic disease, around 47%[5] will be HLA-A*02:01-positive, giving a total eligible population size of approximately 154 across the UK. • Uveal melanoma is a rare condition requiring referral to the ocular oncology service, which is an NHSE/I designated Highly Specialised Service.[6] Specialist centres should be involved in treatment decisions for metastatic disease and review.[7] • The need for national commissioning is significant as there are no proven effective or licensed treatments specifically for metastatic uveal melanoma. Tebentafusp will be the first proven effective treatment for metastatic uveal carcinoma and the first-in class of a new type of biologic for the treatment of cancer. Further information for all of the HST criteria is provided in the Section 'Questions for consultation'.	
Wording	Immunocore	In order to accurately reflect the anticipated licensed indication for tebentafusp the remit should be re-worded as follows: 'To appraise the clinical and cost effectiveness of tebentafusp within its marketing authorisation for treating HLA-A*02:01 positive adults with metastatic or unresectable uveal melanoma'.	Thank you for your comment. The remit has been updated to reflect the HLA-A*02:01 status and the use of 'metastatic or unresectable' as a definition of 'advanced' disease.

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Timing Issues	Immunocore	An appraisal of tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma is urgent. There are no systemic treatments currently available which are specifically licensed for the treatment of uveal melanoma. Current treatment guidelines recommend patients be recruited to clinical trials where possible as the standard of care.[7]	Thank you for your comment. No action needed.

Comment 2: the draft scope

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The technology/ intervention	Immunocore	The description of the technology should be amended as per the following underlined text to include information on the anticipated indication: 'Tebentafusp does not currently have a marketing authorisation in the UK for treating uveal melanoma. <u>The anticipated licensed indication for tebentafusp is for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma</u>. It has been studied….'	Thank you for your comment. Details of the anticipated marketing authorisation wording are not included in scopes. No action needed.

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Population	Immunocore	The population should be amended as follows to include the anticipated indication: 'HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma' **Subgroups** For this rare cancer there are no subgroups that need to be considered in the context of a NICE submission. Immunocore have conducted subgroup analyses according to the study protocol that show benefit across all groups.	Thank you for your comment. The population section has been updated as suggested.. The 'Other considerations' section of the scope now states that, if the evidence allows, consideration will be given to the clinical and cost effectiveness of tebentafusp at different lines of therapy.
Comparators	Immunocore	There are no licensed therapies specifically targeting metastatic uveal melanoma and there is no proven standard of care for this patient population. Current clinical guidelines recommend consideration of patients for inclusion within a clinical trial as the standard of care.[7] Best supportive care is not a relevant comparator as it is generally provided later in the treatment process and in the case of tebentafusp would be used after tebentafusp. Systemic treatments used in clinical practice vary and in the absence of other options include those which have a broad licence for melanoma: pembrolizumab, ipilimumab, nivolumab in combination with ipilimumab, systemic chemotherapy (dacarbazine). None have shown any survival benefit in randomised trials in patients with metastatic uveal melanoma.[8] As described above there is no 'best alternative'. The tebentafusp phase 3 clinical trial was designed to reflect the range of treatments currently used,	Thank you for your comment. Following feedback at the scoping workshop, the following treatments have been added to the scope as comparators due to their current use in NHS practice: - Pembrolizumab - Ipilimumab - Nivolumab (alone or in combination with ipilimumab)

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		with patients randomised to receive tebentafusp or investigator's choice of treatment. Due to the rarity of the condition, patient numbers for individual comparative treatments are very limited so within our submission comparative analysis will be performed comparing tebentafusp versus a basket of the treatments used within the clinical trial.	- Dacarbazine chemotherapy - Best supportive care
Outcomes	Immunocore	The outcomes are appropriate. The primary outcome in the tebentafusp pivotal phase 3 trial is overall survival. Within the tebentafusp phase 3 trial progression free survival and the RECIST response rate were both low in comparison with the magnitude of overall survival benefit. Tumour shrinkage of any magnitude was seen at a higher frequency in tebentafusp-treated patients. Tebentafusp-treated patients with disease progression as best response had improved survival compared to the control arm implying a clinically meaningful impact on outcomes for patients even if tumour size did not decrease radiographically. Disease progression by RECIST was not associated with clinically meaningful survival.[9]	Thank you for your comment. No action needed.
Economic analysis	Immunocore	The costs for the diagnostic testing for HLA-A*0201 will be included in the model. The required CE-IVD assay system is commonly used in the clinical setting for transplantation patient selection therefore costs associated with the testing infrastructure will not be included as this is already in place within NHS clinical immunology laboratories consequently no infrastructure change will be required. Cost effectiveness analysis considering the benefit in the best and worst seeing eye is not relevant to tebentafusp, which will be indicated for the treatment of unresectable or metastatic disease.	Thank you for your comment. The 'economic analysis' section has been updated in line with the comment.

Innovation	Immunocore	An application for Tebentafusp has been submitted to the MHRA for the Innovative Licensing and Access Pathway (application number ILAP/IP/21/36781/01). Tebentafusp is a highly targeted immunotherapy which acts in a completely new way. It is from a new class of treatment – bispecific soluble T-cell receptor therapeutics, termed ImmTACs (Immune mobilising monoclonal T-cell receptors Against Cancer), that are designed to activate a patient's own T-cells against specific cancer cells. Tebentafusp is the first ImmTAC based therapy to show survival benefit in a randomised trial, the first bispecific drug to show a survival benefit in a solid tumour and the first therapy to show a significant survival benefit in metastatic uveal melanoma.[10] Tebentafusp has been developed specifically for the treatment of the metastatic form of this ultra-rare cancer, which affects around 540 patients in the UK. Tebentafusp will set a new standard of care offering the first effective treatment option for HLA-A*02:01-positive patients with unresectable or metastatic disease. Tebentafusp is designed to recognise and direct the body's immune system to destroy uveal melanoma cells that express a gp100 peptide presented by HLA-A*02:01. Hence, immune activation by tebentafusp is specific to uveal melanoma cells. **Benefits outside of the QALY** By providing patients and clinicians with the first treatment specifically licensed for metastatic uveal melanoma, tebentafusp has the potential to catalyse improvement in the treatment pathway, by providing an effective treatment following early detection of metastatic disease.	Thank you for your comment. No action needed.

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Questions for consultation	Immunocore	<u>Appraisal via the HST programme</u> It would be inappropriate to appraise tebentafusp via an STA, given the ultra-rare nature of the condition. Whilst recognising treatments for oncology have not previously been reviewed through HST, we welcome the confirmation from NICE in March 2021 on the question of cancer medicines being eligible for HST that ''if a topic meets the meets all of the Highly Specialised Technologies criteria then it can be routed to Highly Specialised Technologies''[11]. Tebentafusp fulfils all the entry criteria for consideration via the Highly Specialised Technology programme (see below) and should be appraised via this route and not via the STA programme. Details for each criterion are as follows: *Criterion 1: The target patient group for the technology and its licensed indication is so small that treatment will usually be concentrated in very few centres in the UK* • Tebentafusp is a targeted immunotherapy for the treatment of unresectable or metastatic uveal melanoma for HLA-A*02:01-positive adult patients. • Uveal melanoma is an ultra-rare condition with a total patient population in the UK of approximately 540 patients. • Uveal melanoma is a specific condition which is biologically distinct from cutaneous melanoma. The small target patient group is discrete and readily identified. • Treatment of ocular oncology (including uveal melanoma) is undertaken via an NHSE/I designated highly specialised service (included in the 2019 manual).[6]	Thank you for your comment. The feedback from the scoping workshop indicates that tebentafusp is not suitable to be reviewed under the HST pathway. No change to scope.

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		In 2022 there are anticipated to be approximately 540 patients in England with uveal melanoma. As this number is drawn from ONS data there is robustness in the patient number.[1] Tebentafusp will be indicated for patients with metastatic disease and is pharmacologically appropriate only for those who are HLA-A*02:01-positive. Based on its mode of action tebentafusp will not work in patients who are HLA-A*02:01 negative.[3] Around 40-50% patients develop metastatic disease[2] and of these 47% will be HLA-A*02:01-positive[5] which means the treatment population is around 154 patients. The HLA status can be confirmed by a simple, reliable blood test that is already routinely undertaken by immunology departments. *Criterion 2: The target patient group is distinct for clinical reasons* • Uveal melanoma is a clinically and biologically distinct condition. • The target population must fulfil specific clinical criteria: metastatic or unresectable disease and HLA-A*02:01-positive. Uveal melanoma is biologically distinct from skin (cutaneous) melanoma with different physiological, genetic, and epidemiologic characteristics.[12] Although cutaneous and uveal melanomas derive from melanocytes that share the same embryonic origin, they display extreme differences in their genetic alterations and biological behaviour.[12] Tebentafusp is pharmacologically restricted to those adults who are HLA-A*02:01-positive. The drug target for tebentafusp is the gp100 peptide	

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		complexed with HLA-A*02:01 at the cell surface and expressed uniquely at a homogenously high level by uveal melanoma cells.[4] The distinct nature has been formally recognised with orphan designation granted for tebentafusp by both the EMA (EMA/OD/0000047566) and the FDA (#15-5036). Criterion 3: The condition is chronic and severely disabling • Median survival from development of metastatic disease is 2 - 12 months, and 1-year survival is 10 - 15%.[7] The liver is the most common site for metastases. 50% of patients have liver-only disease, and 90% of those with metastases elsewhere (bowel, bone, lung and lymph nodes) also have liver metastases. Liver involvement is the cause of death in the majority of patients.[13,14] Criterion 4: The technology is expected to be used exclusively in the context of a highly specialised service Ocular oncology is an NHSE/I designated highly specialised service.[6] Criterion 5: The technology is likely to have a very high acquisition cost While a price has yet to be agreed given this is a treatment for an ultra-rare condition the final price will likely be high by comparison to treatments for more commonly occurring conditions. Criterion 6: The technology has the potential for lifelong use Tebentafusp does not have the potential for lifelong use. Treatment with tebentafusp will be continued until disease progression, at which point there are no further treatment options and patients will receive supportive care. Criterion 7: The need for national commissioning of the technology is significant	

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		• Tebentafusp will be the first approved treatment for metastatic uveal melanoma • There are no licensed therapies specifically targeting metastatic uveal melanoma and there is no standard of care for patients with metastatic uveal melanoma.[7] • There is considerable variation in treatments offered to metastatic uveal melanoma patients in England.[15] • Because of the lack of treatment options current clinical guidance recommends patients are considered for inclusion in clinical trials where possible.[7] • There is an urgent need for treatment which has demonstrated efficacy in advanced uveal melanoma to be nationally commissioned to offer a new standard of care. <u>NICE Pathway – Managing melanoma</u> The current NICE melanoma pathway refers to NICE guidelines NG14 and CSG8 which refer specifically to skin cancer (cutaneous melanoma). The pathway does not include unresectable or metastatic uveal melanoma which is a distinct condition requiring specialist treatment via ocular oncology services. As a consequence, tebentafusp, the first licensed treatment for this rare disease, does not fit within the NICE melanoma pathway.	