



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMADOC-360526170-973727
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Kimmtrak (tebentafusp)
Treatment of uveal melanoma
EU/3/21/2397

Sponsor: Immunocore Ireland Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.



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1. Product and administrative information

Product	
Designated active substance	Tebentafusp
Other names	IMCgp100, <i>E. coli</i> expressed soluble gp100 T cell receptor CD3 single chain variable fragment (scFv) fusion bispecific biologic therapeutic Antineoplastics; Recombinant fusion proteins
International Non-Proprietary Name	Tebentafusp
Tradename	Kimmtrak
Orphan condition	Treatment of uveal melanoma
Sponsor's details:	Immunocore Ireland Limited Unit 1 Sky Business Centres Unit 21 Block Port Tunnel Business Park Clonsaugh Dublin D17 FY82 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharma Gateway AB
COMP opinion	21 January 2021
EC decision	16 February 2021
EC registration number	EU/3/21/2397
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pharma Gateway AB to Immunocore Ireland Limited – EC decision of 28 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	S. B. Sarac / A. Moreau
Applicant	Immunocore Ireland Limited
Application submission	23 July 2021
Procedure start	12 August 2021
Procedure number	EMA/H/C/004929
Invented name	Kimmtrak
Proposed therapeutic indication	KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA-A)*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Further information on Kimmtrak can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Kimmtrak
CHMP opinion	24 February 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	A. Magrelli / P. Evers
Sponsor's report submission	20 August 2021
COMP opinion (adoption via written procedure)	25 February 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 designation was based on the following grounds:

"The sponsor Pharma Gateway AB submitted on 19 May 2020 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing tebentafusp for treatment of uveal melanoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a), first subparagraph, of Regulation (EC) No 141/2000 on orphan medicinal products.

- the condition is a distinct medical entity that would be acceptable for the purpose of orphan designation on the basis of distinct aetiology, histopathological, pathophysiological, genetic and clinical characteristics;
- the intention to treat the condition with the medicinal product containing tebentafusp was considered justified based on objective responses in patients with relapsed/refractory uveal melanoma;
- the condition is life-threatening with a reduced survival in relapsed/refractory metastatic disease and chronically debilitating due to vision impairment (enucleation of the affected eye) and pain;
- the condition was estimated to be affecting approximately 0.88 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tebentafusp will be of significant benefit to those affected by the condition. The sponsor has provided data that show objective responses in patients with relapsed/refractory disease. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1)(a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing tebentafusp, as an orphan medicinal product for the orphan condition: "treatment of uveal melanoma".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Uveal melanoma (UM) is a cancer that develops exclusively from melanocytes of the uvea (reviewed by Jager et al., 2020). The uveal tract is the middle layer of the eye and consists of the choroid, ciliary body and iris (Milam and Daniels, 2018; Shain et al., 2019). UM accounts for 85% of all primary intraocular neoplasms (Patel et al., 2011; Maio et al., 2013). Primary UM arise predominantly in the choroid (85–90% of cases), the layer that lies between the retina and the white sclera, and, rarely in the ciliary body (5–8% of cases) and iris (3–5% of cases) (Nathan et al., 2015; Krantz et al., 2017).

The aetiology of UM is unclear. Unlike cutaneous melanomas (CMs), exposure to ultraviolet radiation (UVR), specifically UV-B (Ferguson et al., 2015), is not a risk factor in UM. Most primary UM arise *de novo* but a small proportion can develop from a naevus or mole. The clinical signs and symptoms of UM vary considerably between UM patients and are dependent on the site of the tumour within the uvea; however, most patients present with a mixture of symptoms including 'flashing lights', an increasing 'blind spot' within their visual field, blurred visual acuity, 'floaters', pain, and/or a visible tumour mass (if anteriorly located, e.g., in the iris) (Damato, 2012). Many patients actually have no symptoms, and a 'black lump' is seen at the back of the eye on vision testing, as an incidental finding.

Examination of the eye (fundoscopy) typically reveals a mass, which can be pigmented or non-pigmented, and an associated retinal detachment. Fluorescein angiography, which highlights the blood vessels, shows a double circulation within choroidal melanomas. Angiogenesis is a prominent feature in choroidal melanomas and is likely to be associated with the relationship described between the melanocytes and the vasculature. It is also likely to explain the dissemination route of UM, with this process occurring even quite early in tumour growth. Finally, ultrasound echography demonstrates a mottled appearance with low to medium attenuation and vascular pulsations can also be seen when using A-scan ultrasound (Singh et al., 2019).

Up to 50% of UM patients will develop metastatic disease usually between 2–10 years after diagnosis (Jager et al., 2020). UM spreads exclusively via the blood from the eye to the liver and then spreads systemically to other organs, principally the lung and bones (Lorigan et al., 1991). UM exceptionally rarely spreads to lymph nodes or to the brain (Lorigan et al., 1991), unlike other melanomas (Keung and Gershenwald, 2018).

The approved therapeutic indication "KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA-A)*02:01-positive adult patients with unresectable or metastatic uveal melanoma" falls within the scope of the designated orphan condition "treatment of uveal melanoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Metastatic disease develops in approximately 50% of patients after treatment of the primary tumour and 90% of those with metastases elsewhere (bowel, bone, lung and lymph nodes) also having liver metastases. Metastasis is exclusively haematogenous, and the liver is the predominant first site of metastatic disease (Nathan et al., 2015).

The median survival of metastatic uveal melanoma is typically less than 12 months (Rantala et al., 2019). Despite extensive investigation of metastatic UM in the clinic, no systemic treatment has demonstrated improved survival. In Europe, the 5-year relative survival is 68.8% (Virgili et al., 2008;

Mallone et al., 2012). Analysis by Rao and colleagues of outcomes from the Collaborative Ocular Melanoma Study (COMS), which has established modern treatment recommendations for UM, demonstrated an improvement in 5-year survival for eye-preserving treatments versus enucleation (81.4% versus 59.2%, $p < 0.01$) (Rao et al., 2017).

The COMP concluded that the condition is life-threatening with a reduced survival in relapsed/refractory disease and chronically debilitating especially due to enucleation and in metastatic disease due to pain, organ failure, and treatment burden.

Number of people affected or at risk

Based on NORDCAN, IARC and other national databases reporting the ICD-10 code statistics, the sponsor estimated the EU number of malignant neoplasms of the eye and adnexa (ICD-10 C69). This includes both UM and other aetiologies of primary eye cancer. Incidence rates for ICD-10 code C69 was presented per 10,000 inhabitants per year.

Country-specific histological data for UM reported by the International Agency for Research on Cancer (IARC) (IARC XI histology, 2017) were used to determine the proportion of UM patients from the above reported cases for eye cancer. These proportions were applied to country-specific, age- and gender-specific eye cancer incidence data to obtain UM incidence for each country.

Depending on the country, the proportion of UM patients varied from 41.5% to 90%. Extrapolated UM incidence rates based on histological data gave a range from 0.01 per 10,000 (Cyprus) to 0.12 per 10,000 (Netherlands), indicating a geographical variation. On average, UM incidence rate of 0.06 per 10,000 inhabitants is estimated for Europe. The sponsor discussed the variability of patient survival depending on the stage upon diagnosis. In the population-based study based on SEER data (Mahendraraj et al., 2016), a median OS of 14.6 ± 0.2 years was reported, and the sponsor adopted this value to derive prevalence of UM in the EU.

Based on this data, a current point prevalence of 0.88 per 10,000 EEA inhabitants was estimated. This estimate is acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

According to the sponsor, treatment of primary UM is well-established and effective (Afshar and Damato, 2015).

There are no therapies approved specifically for metastatic UM. Treatments introduced for cutaneous melanoma (CM) over the last 10 years have not significantly benefited patients with UM.

Kinase inhibitors approved for BRAF mutation positive CM are ineffective with metastatic UM because of the absence of BRAF mutations in UM. Immunotherapies such as nivolumab and ipilimumab, have not produced significant improvements in overall survival (OS) with metastatic UM and response rates are very low (typically 5%).

Guidelines for the treatment of UM are available from France. Guidelines in Germany are limited to treatment of cutaneous melanoma and state that they are not applicable to UM. The guidance "Prise en

charge des mélanomes oculaires, le minimum pour les oncologues” (Mathis et al., 2018) includes management of primary UM, prognostic factors and monitoring. The guidance states that management of patients with metastatic disease is often complex and that systemic therapies, such as chemotherapy, targeted therapies, and immunotherapy yield limited response rates. No specific drug therapies are recommended.

The sponsor listed all products with a broad label encompassing all melanoma: encorafenib, cobimetinib, dacarbazine, talimogene laherparepvec, interferon alfa-2b, pembrolizumab, trametinib, binimetinib, fotemustine, nivolumab, dabrafenib, ipilimumab and vemurafenib. These products will be discussed as satisfactory methods of treatment of uveal melanoma.

Significant benefit

There are no products authorised for UM. However, all products with a broad label encompassing all melanoma are discussed as satisfactory methods of treatment of uveal melanoma.

The sponsor claimed significant benefit based on improved efficacy. The significant benefit of tebentafusp as compared to investigator's choice was based on results of the pivotal phase 3 study 202, an ongoing phase 3, open-label, multicentre randomised study evaluating the efficacy and safety of tebentafusp versus investigator's choice (dacarbazine, ipilimumab, and pembrolizumab) in adult HLA-A*02:01-positive patients with metastatic UM, who have not received prior systemic therapy in the metastatic setting. In this study, objective response rate (ORR) was 9.1% and a statistically significant improvement in OS was observed, reducing the relative risk of death by 49% compared with investigator's choice of either pembrolizumab, ipilimumab, or dacarbazine. The estimated 1-year OS rate was 73.2% for tebentafusp and 58.5% for investigator's choice.

The sponsor also provided indirect comparison of tebentafusp to available treatment options for UM. Treatment with single agent systemic chemotherapy (e.g., dacarbazine, DHA-paclitaxel, fotemustine) resulted in less than 10% ORR with median progression free survival (PFS) of 1.8 to 3.9 months and median OS of 6.7 to 13.8 months (Bedikian et al., 2003; Honsi et al., 2010; Marshall et al., 2013; Carvajal et al., 2014; Leyvraz et al., 2014; Carvajal et al., 2018). The longest median OS was reported for fotemustine, which provided a 2-year survival of 20.2% (Leyvraz et al., 2014); 1-year survival was not reported.

Safety and efficacy of pembrolizumab was investigated in a Phase 1 study in melanoma patients (KEYNOTE-001). Twenty patients with ocular melanoma treated in this study did not benefit from treatment with pembrolizumab, highlighting the difference in clinical response between UM/ocular melanoma and other melanomas. No patient with ocular melanoma achieved an objective response; stable disease was reported in 6 patients as compared with an ORR of 9.1% with tebentafusp in the randomised controlled study IMCgp100-202.

Nivolumab monotherapy was investigated in a Phase 2 single-arm, open label study in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody (study CA209172). 10% (103) of patients treated had ocular/uveal melanoma. Four of the 61 evaluable patients (6.6%) achieved an objective response as compared to an ORR of 9.1% with tebentafusp.

The efficacy of ipilimumab or PD-1 inhibition tested in UM is limited and similar to the efficacy observed with single agent chemotherapy. Ipilimumab and PD1 inhibition combination therapy demonstrated low response rates of 0–8% with poor durability with metastatic UM (Luke et al., 2013; Maio et al., 2013; Pereira et al., 2013; Nathan et al., 2015; Zimmer et al., 2015). Treatment with PD1 inhibitors have

shown very limited efficacy with metastatic UM (Kottschade et al., 2016; Piperno-Neumann et al., 2016; Tsai et al., 2016).

A systematic review of immune checkpoint inhibitors (Heppt et al., 2017) identified 12 studies published up to 14 August 2017. The highest median OS and 1-year survival were for nivolumab monotherapy at 11 months and 47%, respectively (Schadendorf et al., 2017). The authors concluded that the evidence does not support the use of ipilimumab monotherapy or in combination with PD-1 inhibition for the treatment of metastatic UM. A meta-analysis based on individual patient data from 29 studies published between 1988 and 2015 comprising 965 patients with metastatic UM and most recent study published in 2015 (Zimmer et al., 2015) demonstrated that the median PFS was 3.3 months, median OS was 10.2 months, and 1-year survival was 43% (Khoja et al., 2019). Liver-directed therapy provided longest median OS, 14.6 months, and the highest 1-year survival, 57.2%. Immunotherapy (monotherapy) provided the shortest median OS, 8.9 months. A meta-analysis of survival results from 78 articles across all treatments suggest no clinically significant difference in OS by treatment modality or decade of publication. Most of the difference in reported OS likely is attributable to surveillance, selection, and publication bias rather than treatment-related prolongation (Rantala et al., 2019).

The sponsor also argued that there are no effective treatments for metastatic UM that extend survival, and that no standard of care exists. Available treatments for metastatic UM are mainly adapted from CM protocols, although they are distinct disease entities in terms of biology, genetics, and clinical course. Therapeutic advances that have translated to improved survival in CM have not yielded equal survival benefits in metastatic UM, with 1-year OS rates in metastatic UM of only 43% in the more than 2 lines setting (Khoja et al., 2019) and 52% in the 1st line setting (Rantala et al., 2019).

The COMP agreed on the significant benefit of tebentafusp as compared to investigator's choice based on the results of the pivotal study. In addition, in comparison with pembrolizumab and nivolumab which are authorized for the treatment of melanoma and based on data available for a subset of patients with UM, the ORR observed with tebentafusp is higher. Finally, based on a systematic review of immune checkpoint inhibitors, OS for tebentafusp compares favourably with respect to immunotherapy.

Based on the above, the COMP concluded that the significant benefit of tebentafusp in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma is acceptable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 25 February 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of uveal melanoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a reduced survival in relapsed/refractory disease and chronically debilitating especially due to enucleation and in metastatic disease due to pain, organ failure, and treatment burden;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Kimmtrak may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data from the pivotal clinical trial demonstrating that Kimmtrak improved overall survival in comparison to standard of care treatment in patients with metastatic uveal melanoma, who have not received prior systemic therapy in the metastatic setting.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Kimmtrak, tebentafusp for treatment of uveal melanoma (EU/3/21/2397) is not removed from the Community Register of Orphan Medicinal Products.