23 February 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Zynyz (retifanlimab)
Treatment of Merkel cell carcinoma
EU/3/22/2743

Sponsor: Incyte Biosciences Distribution B.V.

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	Retifanlimab
Other name	--
International Non-Proprietary Name	Retifanlimab
Tradename	Zynyz
Orphan condition	Treatment of Merkel cell carcinoma
Sponsor's details:	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Incyte Biosciences Distribution B.V.
COMP opinion	8 December 2022
EC decision	13 January 2023
EC registration number	EU/3/22/2743
Marketing authorisation	
Rapporteur / Co-rapporteur	Peter Mol / Selma Arapovic Dzakula
Applicant	Incyte Biosciences Distribution B.V.
Application submission	27 February 2023
Procedure start	23 March 2023
Procedure number	EMA/H/C/006194
Invented name	Zynyz
Therapeutic indication	Zynyz is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy. Further information on Zynyz can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/zynyz
CHMP opinion	22 February 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Dinko Vitezic
Sponsor's report submission	10 October 2023
COMP discussion	13-15 February 2024
COMP opinion (adoption via written procedure)	23 February 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in designation in 2022 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing retifanlimab was considered justified based on preliminary clinical data showing responses in patients with Merkel cell carcinoma;
- the condition is chronically debilitating due to aggressive skin lesions and neuroendocrine features and life-threatening with limited life expectancy in patients with advanced disease;
- the condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 retifanlimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary data indicating that the proposed product has higher responses compared with the authorised treatment based on indirect comparisons. 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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing retifanlimab as an orphan medicinal product for the orphan condition: treatment of Merkel cell carcinoma.

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

Merkel cell carcinoma (MCC) refers to primary neuroendocrine malignant tumours of the skin (Pulintzer 2017, Surgical Pathology Clinics 10:2 399-408). MCC was originally thought to arise from the Merkel cells of the epidermis, but nowadays it is proposed that pluripotent dermal stem cells are the origin of MCC. A causal link between the Merkel cell gamma polyomavirus (MCPyV) and the pathogenesis of MCC has been established (Hughes et al, Curr Derm Rep (2014) 3:46–53). Associated risk factors include immune suppression (e.g. due to other malignancies, HIV infection, post-transplantation), high age, male gender, fair skin and exposure to ultraviolet radiation.

Initial presentation of MCC is usually painless nonspecific, erythematous lesion(s) in sun-exposed areas. Lesions may grow and metastasize quickly; At the time of diagnosis, about 26% to 36% of patients present MCC with lymph node involvement, and 6% to 16% of the patients present with distant metastatic disease (Agelli and Clegg 2003, Albores-Saavedra et al 2010, Harms et al 2016, Hodgson 2005, Lemos et al 2010, Sridharan et al 2016). MCC metastasizes first to lymph nodes and spread is typically to lung, adrenal glands, pancreas, liver, brain, and bones (Dellambra et al 2021).

Merkel cell carcinoma is a distinct medical entity, and there have not been changes in the classification since the orphan designation date.

The approved therapeutic indication "Zynyz is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma not amenable to curative surgery or radiation therapy" falls within the scope of the designated orphan condition "Treatment of Merkel cell carcinoma".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

Survival largely depends on the disease stage at the time of the diagnosis. Although surgery and/or radiation therapy are potentially curative for local-regional disease, recurrence is common and difficult to treat. The prognosis of metastatic or recurrent locally advanced MCC is very poor with 5-year overall survival rate of 35% for nodal involvement and 14% for metastatic disease (Harms et al 2016, Trinidad et al 2019).

The sponsor has not identified any changes on the chronically debilitating or life-threatening nature of MCC since the orphan designation was granted in December 2022.

The COMP has previously acknowledged that the condition is chronically debilitating due to aggressive skin lesions and neuroendocrine features and life-threatening with limited life expectancy in patients with advanced disease. This view is maintained by the COMP.

Number of people affected or at risk

The sponsor proposed a prevalence estimate for the condition of less than 0.39 per 10,000 people in the EU.

The sponsor derived the prevalence estimate indirectly from data on disease incidence and duration (i.e., overall survival) using the standard formula P (point prevalence) = I (incidence) x D (mean duration) under the assumptions of stable incidence and duration of the condition.

Estimates derived from the GLOBOCAN 2020 database were used for the calculation of the estimated prevalence of MCC in the EU.

According to GLOBOCAN, about 3500 new cases of MCC are diagnosed annually in Europe with 5-year overall survival rate ranges from 48% to 64% for MCC (Gauci et al 2022, Paulson et al 2018) and a population of 448.6 million for the EU-27 reported by Eurostat.

The prevalence calculation is presented in the table below (Table 1).

Table 1. Estimated prevalence of MCC in the EU-27

Estimated annual incident cases in Europe	**Disease mean duration**	**Total population in the EU-27**	**Estimated prevalence per 10,000 persons in the EU-27**
3500	5 years	448,600,000	0.39

The COMP considered that the above proposed estimation is acceptable and line with figures recently accepted however the figure was rounded to approximately 0.4 in 10,000 persons.

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

Avelumab (Bavencio) is indicated as monotherapy for the treatment of adult patients with metastatic MCC.

Recommended treatment depends on the stage of the disease, the location of the tumour, and patient comorbidities. While surgery and radiation therapy can be curative for local and nodal MCC, systemic therapy is usually required for extensive, metastatic, and recurrent disease.

There is a European consensus treatment guideline "Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline-Update 2022" developed by the European dermatology forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) (published by Gauci et al., Eur J Cancer. 2022 Aug:171:203-231.).

The approved indication for retifanlimab (Zynyz) is as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy. This is in line with the inclusion criteria for the main study (POD1UM-201) of retifanlimab which included both patients with metastatic MCC as well as patients with recurrent locally advanced disease not amenable to curative surgery or radiation therapy. Subgroup analyses showed a clinically relevant response in both patient groups.

The COMP considered that avelumab (Bavencio), which is indicated as monotherapy for the treatment of adult patients with metastatic MCC, is not considered as satisfactory method since it cannot be used to treat patients who are non-metastatic. Patients with recurrent locally advanced disease not amenable to curative surgery or radiation therapy have a very poor prognosis and are formally not eligible for treatment with avelumab.

Significant benefit

Significant benefit is not applicable as discussed above.

4. COMP position adopted on 23 February 2024

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 Merkel cell carcinoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to aggressive skin lesions and neuroendocrine features and life-threatening with limited life expectancy in patients with advanced disease;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Zynyz.

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 Zynyz, retifanlimab for treatment of Merkel cell carcinoma (EU/3/22/2743) is not removed from the Community Register of Orphan Medicinal Products.