15 September 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Tevimbra (Tislelizumab)
Treatment of oesophageal cancer
EU/3/20/2357

Sponsor: Novartis Europharm 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(s)	Tislelizumab
Other name(s)	Tevimbra, Tislelizumab
International Non-Proprietary Name	Tislelizumab
Tradename	Tevimbra
orphan condition	Treatment of oesophageal cancer
Sponsor's details:	Novartis Europharm Limited Vista Building Merrion Road Elm Park Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BeiGene Ireland Limited
COMP opinion	08 October 2020
EC decision	13 November 2020
EC registration number	EU/3/20/2357
Post-designation procedural history	
Transfer of sponsorship	Transfer from BeiGene Ireland Limited to Novartis Europharm Limited – EC decision of 13 December 2021
Marketing authorisation	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Aaron Sosa Mejia
Applicant	Novartis Europharm Limited
Application submission	03 March 2023
Procedure start	24 March 2023
Procedure number	EMA/H/C/005919/0000
Invented name	Tevimbra
Proposed therapeutic indication	Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy. Further information on Tevimbra can be found in the European public assessment report (EPAR) on the Agency's website www.ema.europa.eu/en/human/EPAR/Tevimbra
CHMP opinion	20 July 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Bozenna Dembowska-Baginska
Sponsor's report submission	01 February 2023

COMP discussion	13-15 June 2023 11-13 July 2023
Oral explanation	N/A
COMP opinion (adoption via written procedure)	21 July 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing tislelizumab was considered justified based on preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product;
- the condition is chronically debilitating due to dysphagia, regurgitation, odynophagia, upper gastrointestinal bleeding, acid indigestion and life-threatening with 5-year survival reported in the range of 15%-25%;
- the condition was estimated to be affecting less than 1 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 tislelizumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product as a monotherapy. The Committee considered that this constitutes a clinically relevant advantage.

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

Oesophageal cancer cases have most commonly a histology of squamous cell carcinoma (OSCC, 90% of cases worldwide) or adenocarcinoma (EAC). Although OSCC accounts for ~90% of cases of oesophageal cancer worldwide, mortality rates associated with AC are rising and have surpassed those of SCC in several regions in the EU (Lordick et al, Annals of Oncology 27 (Supplement 5): v50–v57, 2016.)

The main risk factors for SCC in Western countries are smoking and alcohol consumption, whereas AC predominantly occurs in patients with chronic gastro-oesophageal reflux disease and their risk is correlated with the patient's body mass index with a higher risk for obese persons (Lordick et al,

Annals of Oncology 27 S5: v50–v57, 2016.). The target population for this product (Tislelizumab) are patients with oesophageal squamous cell carcinoma (OSCC).

Clinically patients usually present with progressive dysphagia and weight loss. Chronic gastrointestinal bleeding is common and may result in iron deficiency anaemia. Early intramucosal adenocarcinomas of the distal oesophagus that are recognized at endoscopy in an area of Barrett's oesophagus are not specifically symptomatic (UpToDate, Saltzmann 2020).

The approved therapeutic indication "*Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy"* falls within the scope of the designated orphan condition "Treatment of Oesophageal cancer".

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

The COMP considers the condition as chronically debilitating due to dysphagia, regurgitation, odynophagia, upper gastrointestinal bleeding, acid indigestion and life-threatening. The 5-year survival for localized disease is 46% but drops to 26% for regional disease and 5% for subjects with distant metastases. Patients diagnosed or treated once oesophageal squamous cell carcinoma (OSCC) has progressed, face a very poor prognosis (SEER 2021).

Number of people affected or at risk

During the initial orphan designation in 2020 the COMP accepted a prevalence estimate of less than 1 per 10,000. The sponsor did not propose a new prevalence estimate in their orphan maintenance report but summarised the updated prevalence information according to the 5-year partial prevalence data from GLOBOCAN 2020 and concluded that the prevalence of the proposed condition remains below 5 per 10,000 persons.

The EU dataset of GLOBOCAN 2020 is summarized below in Table 1 and indicates a 5-year partial prevalence of 0.84 per 10,000 persons for the EU-27.

Table 1. Oesophageal cancer 5-year prevalence count and prevalence proportion per 10,000 persons by European Country, and EU-27

European Country	GLOBOCAN Database Prevalence count (5-year duration)	GLOBOCAN Database Prevalence proportion (5-year duration per 10 000 persons)
Austria	580	0.64
Belgium	1 418	1.22
Bulgaria	255	0.37
Croatia	243	0.59
Republic of Cyprus	25	0.21
Czech Republic	870	0.81
Denmark	669	1.16
Estonia	101	0.76
Finland	438	0.79
France	6315	0.97
Germany	10113	1.21
Greece	276	0.26
Hungary	745	0.77
Ireland	663	1.34
Italy	2543	0.42
Latvia	171	0.91
Lithuania	279	1.02
Luxembourg	51	0.81
Malta	24	0.54
Netherlands	3512	2.05
Poland	2246	0.59
Portugal	783	0.77
Romania	957	0.50
Slovakia	468	0.86
Slovenia	128	0.62
Spain	2766	0.59
Sweden	721	0.71
UK	12141	1.79
EU-27	37 360	**0.84**

The sponsor points out that compared to the 2018 GLOBOCAN prevalence values (used as one of the main data sources during the initial OD), all European countries had a slight increase in oesophageal cancer prevalence proportion rates per 10 000 persons except Denmark (from 1.32 to 1.16 per 10 000) and Hungary (from 0.82 to 0.77 per 10 000). Nevertheless, the 5-year prevalence proportion estimates by European country, EU-27 and 4 European regions remain below 5 per 10 000 prevalence rate required for orphan designation.

During the initial orphan designation for this product in 2020 the COMP considered that given the chronicity of the condition, a complete prevalence for the proposed condition should also be supplemented (incidence multiplied with the duration/survival of the condition). Considering that the population-based datasets examined by the sponsor previously showed that less than 50% of people diagnosed in the previous year were alive after one year, a median survival of less than a year was assumed. Combining this median survival with the then crude incidence figure in ECIS of 0.79 per 10,000 led to a complete prevalence estimate of 0.68 per 10,000. The sponsor has not presented an updated complete prevalence estimate. However, considering that the crude incidence from ECIS is 6.8/100,000, and the prognosis is poor (5-year survival of approximately 20%), the COMP agreed on a prevalence estimate of less than 1 per 10,000, in line with the initial designation.

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

Several medicinal products are authorized in the EU for the treatment of oesophageal cancer. The choice of treatment mostly depends on the location, tumour stage, histological type, biomarker expression (e.g. PD-L1 and HER2 status), patient's performance status and comorbidities. The treatment of oesophageal cancer in Europe is informed by the recommendations for OSCC and EAC in the ESMO Clinical Practice Guidelines (Lordick et al 2022, Obermannová et al 2022). The main treatments are surgery, radiotherapy, chemotherapy, chemoradiotherapy and immune(chemo)therapy. The sponsor lists several recommended agents used off-label to treat oesophageal cancer (taxanes, fluoropyrimidines, platinums, oxaliplatin/fluoropyrimidine and cisplatin-based combinations) and identified two centrally authorised products for the treatment of OSCC: pembrolizumab and nivolumab, two other checkpoint inhibitors.

Pembrolizumab is authorised for first-line treatment only and is therefore not considered a satisfactory method for the purpose of this procedure. Nivolumab is authorised in several settings (line of treatment, stage, biomarker expression, combination treatment), one of which overlaps with the proposed product Tevimbra. The therapeutic indication of nivolumab is as follows:

- *Opdivo (nivolumab) as monotherapy is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy*

In comparison, the therapeutic indication for Tevimbra is less restrictive and only refers to prior platinum-based chemotherapy:

- *Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy*

Importantly, the latest ESMO treatment guideline points out that platinum-based chemotherapy regimens can be combined either with a fluoropyrimidine or a taxane, in the first line setting of locally advanced OC. The COMP further noted that more than 50% of patients included in the pivotal study for Tevimbra received prior taxane-based chemotherapy.

The COMP therefore considers the target patient population of Tevimbra broader than the one for nivolumab (in second and subsequent lines of treatment for advanced oesophageal SCC), as it also covers patients that received prior platinum-based chemotherapy. Nivolumab was therefore not considered to be a satisfactory method, for the purpose of this procedure.

Significant benefit

As discussed above and based on the therapeutic indication of Tevimbra vis a vis the one of other authorized medicinal products in the treatment of OSCC (including nivolumab), no satisfactory methods exist for the entirety of the target patient population covered by Tevimbra. Therefore, the significant benefit is not considered applicable, for the purpose of this procedure.

4. COMP position adopted on 21 July 2023

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 oesophageal cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 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 dysphagia, regurgitation, odynophagia, upper gastrointestinal bleeding, acid indigestion and life-threatening with 5-year survival reported in the range of 15%-25%;
- 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 Tevimbra.

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 Tevimbra, tislelizumab, for treatment of oesophageal cancer (EU/3/20/2357) is not removed from the Community Register of Orphan Medicinal Products.