7 January 2021
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EMA/OD/0000004627
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Elzonris
Recombinant human interleukin-3 truncated diphtheria toxin fusion protein
Treatment of blastic plasmacytoid dendritic cell neoplasm
EU/3/15/1567

Sponsor: Stemline Therapeutics B.V.

Note

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

Table of contents

1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Recombinant human interleukin-3 truncated diphtheria toxin fusion protein
Other name(s)	-
International Non-Proprietary Name	Tagraxofusp
Tradename	Elzonris
Orphan condition	Treatment of blastic plasmacytoid dendritic cell neoplasm
Sponsor's details:	Stemline Therapeutics B.V. Prins Bernhardplein 200 1097 JB Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Spector Consulting SAS
COMP opinion date	8 October 2015
EC decision date	11 November 2015
EC registration number	EU/3/15/1567
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Spector Consulting SAS to TMC Pharma Services Ltd - EC decision of 23 August 2017 - 2nd transfer from TMC Pharma Services Ltd to TMC Pharma (EU) Limited - EC decision of 19 November 2018 - 3rd transfer from TMC Pharma (EU) Limited to Stemline Therapeutics B.V. – EC decision of 28 November 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	A. Moreau / B. Bolstad
Applicant	Stemline Therapeutics B.V.
Application submission date	7 January 2019
Procedure start date	25 January 2019
Procedure number	EMA/H/C/005031/0000
Invented name	Elzonris
Proposed therapeutic indication	Treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). Further information on Elzonris can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/elzonris
CHMP opinion date	12 November 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	B. Dembowska-Baginska / B. Schwarzer-Daum
EMA scientific officer	M. Sheean
Sponsor's report submission date	13 February 2019
COMP opinion date	16 November 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2015 designation was based on the following grounds:

The sponsor Spector Consulting SAS submitted on 16 July 2015 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing recombinant human interleukin-3 truncated diphtheria toxin fusion protein for the treatment of blastic plasmacytoid dendritic cell neoplasm (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing recombinant human interleukin-3 truncated diphtheria toxin fusion protein was considered justified based on preliminary clinical data demonstrating patient responses to treatment;
- the condition is life-threatening due to the aggressive progression leading to a mean survival of 12-14 months and overall survival rates of 75-52% after one year;
- the condition was estimated to be affecting approximately 1.2 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.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

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 recombinant human interleukin-3 truncated diphtheria toxin fusion protein as an orphan medicinal product for the orphan indication: treatment of blastic plasmacytoid dendritic cell neoplasm.

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

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a haematological neoplasm derived from the precursor of plasmacytoid dendritic cells. The aetiology of BPDCN is unknown.

The nomenclature of BPDCN has evolved over the last 20 years and it was also previously named "agranular CD4+/CD56+ hematodermic neoplasm" and "blastic NK-cell lymphoma". Since the World Health Organization classification of tumours of hematopoietic and lymphoid tissues in 2008, the condition is classified as a distinct entity under acute myeloid leukaemia (AML) and related precursor neoplasms (Facchetti et al., 2008). The status as distinct entity remains under the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia (Arber et al, 2016).

The approved therapeutic indication "ELZONRIS is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)" falls within the scope of the designated orphan condition "blastic plasmacytoid dendritic cell neoplasm".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP (please refer to the EPAR).

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was life-threatening. At the time of this review, BPDCN is presented to the COMP to have the same prognosis without any new treatments available. The COMP concluded that the condition remains life-threatening due to the aggressive progression leading to a mean survival of 12-14 months and overall survival rates of 52-75% after one year.

Number of people affected or at risk

At the time of designation, the prevalence was agreed to be approximately 1.2 per 10,000. At the time limited epidemiological data on the condition were available and the figure was considered to be a conservative (under) estimate based on epidemiological data from NHL/AML.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 0.1 per 10,000.

First it is clarified that annual incidence figures can be used to estimate prevalence for this condition when taking into consideration published literature that describe disease duration and survival to be around 1 year.

A systematic literature search has been conducted to identify epidemiological literature. One recent report from the SEER database in the USA has been identified. The primary epidemiological database reports a consistent annual incidence rate at 0.03 or 0.04 per 100,000 for each of the 7 years assessed (2008-2014). This would give a prevalence value of 0.004 per 10,000.

Since this is US data, an attempt to estimate prevalence for the EU has been presented by using incidence data of all haematological malignancies and taking into consideration a proportion of BPDCN of 0.44%. This proportion is also reported in the scientific literature. When using this proportion in combination with HAEMACARE data (Sant et al, 2010) on all haematological malignancies a prevalence of 0.014 per 10,000 across the EU has been calculated (0.44% of 3.21 per 10,000).

Both attempts, the US data and the EU estimation, have certain limitations to establish prevalence in the EU at the time of this review. It can be acknowledged that there are limited epidemiological sources at this point in time. Taking into consideration all data that has been presented, the COMP could accept the estimate of less than 0.1 per 10,000.

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

At the time of this review, there are no products authorised products in the EU to treat the condition.

There are no ESMO or other consensus treatment guidelines for treating the condition.

The current standard of care include radiotherapy and off label use of chemotherapy treatments authorised for lymphoma (e.g. cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or CHOP-like), AML (e.g. cytarabine plus an anthracycline), or acute lymphoblastic leukaemia (ALL) (e.g. cyclophosphamide, vincristine, doxorubicin, dexamethasone, [hyper-CVAD] alternating with methotrexate, and cytarabine).

Furthermore, it is reported that stem cell transplantation can be a successful treatment. BPDCN patients should be referred for an allo-HCT evaluation as soon as possible to determine their candidacy for the procedure and to initiate donor identification in eligible cases.

Significant benefit

No authorised medicines or satisfactory methods have been identified for the treatment of the condition. Significant benefit is not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 16 November 2020

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 blastic plasmacytoid dendritic cell neoplasm (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to the aggressive progression leading to a mean survival of 12-14 months and overall survival rates of 52-75% after one year;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

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 Elzonris, recombinant human interleukin-3 truncated diphtheria toxin fusion protein, tagraxofusp, EU/3/15/1567 for treatment of blastic plasmacytoid dendritic cell neoplasm is not removed from the Community Register of Orphan Medicinal Products.