18 July 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Lonafarnib EigerBio Europe Limited (lonafarnib)
Treatment of Hutchinson-Gilford progeria syndrome
EU/3/18/2118
Sponsor: Eigerbio Europe 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)	Lonafarnib
Other name(s)	--
International Non-Proprietary Name	Lonafarnib
Tradename	Zokinvy
Orphan condition	Treatment of Hutchinson-Gilford progeria syndrome
Sponsor's details:	Eigerbio Europe Limited 1 Castlewood Avenue Rathmines Dublin 6 D06 H685 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Eiger Biopharmaceuticals Europe Limited
COMP opinion	8 November 2018
EC decision	14 December 2018
EC registration number	EU/3/18/2118
Post-designation procedural history	
Transfer of sponsorship	Transfer from Eiger Biopharmaceuticals Europe Limited to Eigerbio Europe Limited – EC decision of 8 August 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Kirstine Moll Harboe
Applicant	Eigerbio Europe Limited
Application submission	9 March 2020
Procedure start	23 April 2020
Procedure number	EMA/H/C/005271
Invented name	Zokinvy
Therapeutic indication	Treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation. Further information on Zokinvy can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/zokinvy
CHMP opinion	19 May 2022

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Johanne Rook
Sponsor's report submission	23 July 2021
COMP discussion	10-12 May 2022
COMP opinion (adoption via written procedure)	20 May 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing lonafarnib was considered justified based on clinical observations supporting a lower mortality rate after treatment with the product compared to no treatment;
- the condition is life-threatening and chronically debilitating in particular due to atherosclerotic cardiovascular disease and strokes, with death occurring at an average age of 14.6 years;
- the condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made;
- the sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

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

For the purpose of orphan designation, it was originally considered by the COMP that the condition named as Hutchinson-Gilford progeria syndrome would cover both classic and atypical syndromes, including progeroid laminopathies.

Hutchinson-Guildford progeria is a rare and uniformly fatal, segmental "premature aging" disease. Initial presentation in early childhood is primarily based on growth and dermatologic findings. Primary morbidity and mortality for children with HGPS is from atherosclerotic cardiovascular disease and strokes with death occurring at an average age of 14.6 years. (Ulrich et al, 2015).

With regards to the aetiology of the condition, Hutchinson-Gilford Progeria Syndrome is caused by aberrant splicing of the LMNA gene which results in a farnesylated truncated mutant lamin A protein called progerin (Eriksson et al, 2003). By way of background, ground, the products of LMNA gene, primarily lamin A and C, are key components of the nuclear lamina, and mutations of laminins has been associated with neuropathies, muscular dystrophies, lipodystrophies, and premature aging diseases (Gonzalo et al, 2017).

Most "classic" HGFS harbour a single-base substitution G608G(GGC > GGT), within exon 11(Eriksson et al, 2003, De Sandre-Giovannoli et al, 2003). "Atypical" progeria syndromes have also been reported in the literature and variants for atypical progeria have also been attributed to LMNA. While there is considerable overlap in the phenotype, variability remains in the severity, onset, and lifespan as compared with HGPS. Progeroid laminopathies, which are even rarer than HGPS, have clinical features that overlap HGPS, but are caused by mutations in the LMNA gene or in proteins affecting the post-translational pathway of LMNA such as Zmpste24 that result in farnesylated progerin-like proteins.

The approved therapeutic indication "Zokinvy is indicated for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation." falls within the scope of the designated orphan condition "Treatment of Hutchinson-Gilford Progeria Syndrome".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

There have been no changes in the chronically debilitating or life-threatening nature of the condition since the orphan designation. Neither have there been any approved therapies which have improved the morbidity or mortality of the condition since the original designation.

Primary morbidity and mortality for children with HGPS (including atypical progeria syndrome like progeroid laminopathies) is from atherosclerotic cardiovascular disease and strokes with death occurring at an average age of 14.6 years. (Ulrich et al, Handb Clin Neurol. 2015;132:249-64).

Children have a severe failure to thrive, with typical lipoatrophy, mandibular and cranial malformations, short stature, delayed dentition, thin skin with sclerodermatous areas, and baldness . Bone resorption is also common. Usually, these individuals do not become sexually mature. Intellectual development is not affected. Death is almost exclusively due to myocardial infarction, heart failure or stroke, due to widespread atherosclerosis.

Number of people affected or at risk

The sponsor bases the prevalence estimate on the Progeria Research Foundation (PRF) International Registry database and identified the number of patients living with the diagnosis in EU member states. Table 1 below recapitulates the numbers identified at the time of submission which has slightly increased since the orphan designation.

Table 1. Summary of Estimates of Prevalence of HGPS (including atypical syndrome PL): EU Countries with Identified Living Individuals with Condition (as of June 2021)

Country	**Country Population***	**Reported Patient Number**	**Calculated Prevalence****
Belgium	11,566,041	HGPS: 3 PL: 0	1 per 4 million
Denmark	5,840,045	HGPS: 1 PL: 0	1 per 6 million
France	67,439,599	HGPS: 5 PL: 0	1 per 13 million
Germany	83,155,031	HGPS: 1 PL: 0	1 per 83 million
Ireland	5,006,907	HGPS: 1 PL: 0	1 per 5 million
Italy	59,257,566	HGPS: 3 PL: 1	1 per 15 million
Poland	37,840,001	HGPS: 1 PL: 0	1 per 37 million
Portugal	10,298,252	HGPS: 1 PL: 0	1 per 10 million
Spain	47,394,223	HGPS: 1 PL: 0	1 per 47 million
Sweden	10,379,295	HGPS: 1 PL: 0	1 per 10 million
United Kingdom***	67,081,000	HGPS: 2 PL: 1	1 per 22 million

*Each of the country (except United Kingdom) population as of January 1, 2021 was sourced from website: http://ec.europa.eu/eurostat. For United Kingdom, it is the data released on 25 June 2021 from UK office of national statistics: https://www.ons.gov.uk/ .
** Calculated Prevalence = combined patient number (HGPS and atypical syndrome: PL)/Country population
*** As of 1 January 2021, EU pharmaceutical law applies to and in the UK in respect of Northern Ireland only.

Using the highest prevalence noted as the most conservative number (i.e., 1 case per 4 million), it is estimated that the prevalence of the disease is 0.0025 per 10,000 persons in EU. At the time of designation, the number was rounded up to less than 0.01 but as the data provided by the sponsor seems to be quite reliable, and assuming that indeed most patients are captured in the registry, a figure of 0.003 could be used instead.

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

No authorised products have been identified in the EU. Treatment of HGPS is directed toward the specific symptoms that are apparent in each individual. Medications used to treat HGPS include low-

dose aspirin, statins, antihypertensives, anticoagulants, but these do not prevent early death to a satisfactorily extent. Management may require the coordinated efforts of a team of specialists who may need to systematically and comprehensively plan an affected child's treatment (NORD).

Significant benefit

Not applicable.

4. COMP position adopted on 20 May 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 Hutchinson-Gilford progeria syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.003 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 atherosclerotic cardiovascular disease and strokes, with death generally occurring in early teenage years, and chronically debilitating with typical lipoatrophy, facial dysmorphia, premature aging, short stature, delayed dentition, and thin skin with sclerodermatous areas.
- there is, at present, no satisfactory method for the 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 Lonafarnib EigerBio Europe Limited, lonafarnib for treatment of Hutchinson-Gilford progeria syndrome (EU/3/18/2118) is not removed from the Community Register of Orphan Medicinal Products.