2 September 2022
EMA/OD/0000074865
EMADOC-1700519818-890574
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Imcivree (setmelanotide)
Treatment of Bardet-Biedl syndrome
EU/3/19/2192
Sponsor: Rhythm Pharmaceuticals Netherlands 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(s)	Setmelanotide
Other name(s)	-
International Non-Proprietary Name	Setmelanotide
Tradename	Imcivree
Orphan condition	Treatment of Bardet-Biedl syndrome
Sponsor's details:	Rhythm Pharmaceuticals Netherlands B.V. Herengracht 280 1016 BX Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	TMC Pharma (EU)
COMP opinion	18 July 2019
EC decision	21 August 2019
EC registration number	EU/3/19/2192
Post-designation procedural history	
Transfer of sponsorship	Transfer from TMC Pharma (EU) Limited to Rhythm Pharmaceuticals Limited – EC decision 5 November 2020
Transfer of sponsorship	Transfer from Rhythm Pharmaceuticals Limited to Rhythm Pharmaceuticals Netherlands B.V.. – EC decision 11 October 2021
COMP opinion on review of orphan designation at the time of marketing authorisation	26 April 2022
Marketing authorisation type II variation procedural history	
Rapporteur	Karin Janssen van Doorn
PRAC Rapporteur	Anna Mareková
Applicant	Rhythm Pharmaceuticals Netherlands B.V.
Application submission	13 October 2021
Procedure start	30 October 2021
Procedure number	EMA/H/C/005089/II/002/G
Invented name	Imcivree
Proposed therapeutic indication	Treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above. Further information on Imcivree can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/imcivree

CHMP opinion	21 July 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Dinah Duarte / Vallo Tillmann
Sponsor's report submission	5 November 2021
COMP discussion	11-13 April 2022
COMP opinion (adopted via written procedure)	25 July 2022

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The Committee for Orphan Medicinal Product (COMP) opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

"The sponsor TMC Pharma (EU) Limited submitted on 20 May 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing setmelanotide for treatment of Bardet-Biedl syndrome (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 setmelanotide was considered justified based on preliminary clinical data showing significant decrease in hyperphagia and weight in patient's with the condition;
- the condition is chronically debilitating due to rod-cone dystrophy which leads to visual impairment and blindness. This can be associated with speech and learning difficulties as well as ataxia, renal disease and obesity. Less common are diabetes mellitus, congenital heart disease and anosmia;
- the condition was estimated to be affecting 0.2 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 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 setmelanotide as an orphan medicinal product for the orphan condition: treatment of Bardet-Biedl syndrome".

3. Review of criteria for orphan designation at the time of type II variation

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

The approved therapeutic indication "treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above" falls within the scope of the designated orphan condition "Treatment of Bardet Biedl syndrome (BBS)".

Bardet-Biedl syndrome (BBS) is a rare pleiotropic autosomal recessive disorder caused by mutations in as many as 24 different genes, all of which participate in cilia functioning and is therefore considered a primary ciliopathy. Extensive research suggests the obesity phenotype in BBS is caused by impaired transport of the leptin receptor (LEPR) to the ciliary membrane of pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. Pro-opiomelanocortin (POMC) neurons are activated by energy surfeits and inhibited by energy deficits. When activated, these cells inhibit food intake and facilitate weight loss. Conversely, decreased activity in POMC cells is associated with increased food intake and obesity. Under normal conditions, leptin, a hormone predominantly made by adipose cells, stimulates firing and gene expression in POMC neurons, promoting the secretion of alpha-melanocyte stimulating hormone (α-MSH). Alpha-MSH stimulates the melanocortin-4 receptor (MC4R) located in the second order neurons in the paraventricular nucleus (PVN) of the hypothalamus and results in decreased hunger and weight and increased energy expenditure. Impaired or absent LEPR signalling in POMC neurons would be expected to reduce MC4R stimulation in second order neurons, resulting in an increase in appetite, reduced metabolic rate, and increased weight.

Genotype–phenotype correlations are poor which leads to considerable variability in the phenotypic expression. The BBS phenotype evolves slowly throughout the first decade of life with the result that most patients are diagnosed in late childhood or early adulthood. Features associated with BBS include retinopathy (rod-cone dystrophy), obesity, polydactyly, genital abnormalities, renal defects, neurocognitive and behavioral impairments, speech deficits, ataxia, and developmental delay.

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

There has been no change to the chronically debilitating and/or life-threatening nature of the condition since the orphan designation in 2019.

The condition is primarily associated with polydactyly and rod-cone dystrophy which leads to visual impairment and blindness. Neurocognitive and behavioral impairments, speech difficulties as well as ataxia, renal disease and obesity are also common. Less common are diabetes mellitus, congenital heart disease and anosmia. It is noted that the condition is not life-threatening.

Number of people affected or at risk

At the time of designation, the sponsor's formal estimate of the prevalence of BBS in the EU was 0.2 per 10,000. This was mainly based on relevant literature searching up to January 2019 which revealed that the most conservative (highest) estimate of BBS prevalence in an EU country (Denmark) was 1:47,000 (Hjortshøj 2007, Eurostat 2019).

To reassess the prevalence, the sponsor conducted a new literature search from January 2019 to August 2021. New prevalence data were available for 3 of the 30 countries in the European Economic Area (EEA), i.e. France [including La Réunion], Italy and Poland, see Table 1.

Table 1. New literature identified from EEA countries with relevant epidemiologic data on Bardet-Biedl Syndrome (January 2019 to August 2021)

Region	**Estimated Prevalence**	**Brief Description**	**Citation**
Countries in the EEA			
France [a]	1:1,100,000	Molecular diagnosis of BBS in 51 foetuses. A total of 11 male patients with BBS were recruited and underwent a complete exploration of the gonadotropic axis. [From Eurostat, the population in France in 2020 was 67,320,216].	Mary 2019 Koscinski 2020 Eurostat 2021
La Réunion	1:45,000	A total of 20 individuals with BBS identified using sequencing.	Gouronc 2020
Italy [a]	1: 810,000	A total of 20 patients diagnosed with BBS in different hospitals across Italy were recruited into the study. Assessment of renal function in 54 patients with BBS. [From Eurostat, the population in Italy in 2020 was 59, 641,488].	Manara 2019 Zacchia 2020 Eurostat 2021
Poland [a]	1:3,800,000	A nationwide genetic study of 575 patients with monogenic diabetes, monogenic obesity and/or syndromic insulin resistance enrolled for genetic testing from February 2017 to July 2019 identified 10 patients with BBS. [Form Eurostat, the population in Poland in 2017 was 37,972,964).	Jeziorny 2020

Prevalence estimates ranged from 1:45,000 (0.2 per 10,000; La Réunion) to 1:3,800,000 (0.002 per 10,000; Poland) for countries in the EEA. As such, the previously agreed prevalence rate of 0.2 per 10,000 persons in the EU for BBS is still considered to be applicable by the COMP and remains well below the 5 in 10,000-patient threshold for orphan 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

There are no approved therapies for treatment of obesity and reduction of hyperphagia in patients with BBS.

The only pharmacologic treatments available are products for general obesity/weight management; however, there is limited experience with these therapies in patients with MCR pathway associated obesity such as BBS. In general, these therapies have not been successful in early-onset extreme genetic obesity as these therapies fail to address the MC4R pathway signalling defect that leads to obesity and hyperphagia in these patients.

The absence of drug therapy and unsuitability of surgical intervention leaves only lifestyle modification (i.e., diet and exercise) as available therapeutic interventions for patients with severe obesity. These, however, are rarely successful over the short-term and almost never effective in the long-term due to the intense drive to eat caused by the absence of satiety signals.

There are no official guidelines in Europe for the treatment or management of BBS.

Significant benefit

Not applicable.

4. COMP position adopted on 25 July 2022

The Committee for Orphan Medicinal Product (COMP) considered that the designated orphan condition is "treatment of Bardet Biedl syndrome."

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 Bardet Biedl syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.2 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 relentless hunger and morbid obesity. The condition can also be associated with rod-cone dystrophy which leads to visual impairment and blindness, speech and learning difficulties as well as ataxia and renal disease. Less common are diabetes mellitus, congenital heart disease and anosmia;
- there is, at present, no satisfactory method for the treatment of 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 Imcivree, setmelanotide for treatment of Bardet Biedl syndrome (EU/3/19/2192) is not removed from the Community Register of Orphan Medicinal Products.