16 July 2021
EMADOC-1700519818-687119
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

IMCIVREE (Setmelanotide)
Sponsor: Rhythm Pharmaceuticals Limited

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introductory comment

The approved therapeutic indication "IMCIVREE is indicated in the treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above" falls within the scope of the two designated orphan conditions "treatment of leptin receptor deficiency" and 'treatment of pro-opiomelanocortin deficiency', and are covered in this one document.

2. Setmelanotide for the treatment of leptin receptor deficiency - EU/3/18/2101 (EMA/OD/0000040440)

2.1. Product and administrative information

Product	
Designated active substance(s)	Setmelanotide
Other name(s)	-
International Non-Proprietary Name	Setmelanotide
Tradename	Imcivree
Orphan condition	Treatment of leptin receptor deficiency
Sponsor's details:	Rhythm Pharmaceuticals Limited 10 Earlsfort Terrace Dublin 2 D02 T380 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	TMC Pharma Services Ltd
COMP opinion	18 October 2018
EC decision	19 November 2018
EC registration number	EU/3/18/2101
Post-designation procedural history	
Transfer of sponsorship	Transfer from TMC Pharma Services Ltd to TMC Pharma (EU) Limited – EC decision of 14 March 2019 Transfer from TMC Pharma (EU) Limited to Rhythm Pharmaceuticals Limited – EC decision of 5 November 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Karin Janssen van Doorn / Kirstine Moll Harboe
Applicant	Rhythm Pharmaceuticals Limited
Application submission	26 June 2020
Procedure start	16 July 2020
Procedure number	EMA/H/C/005089/0000
Invented name	Imcivree

Proposed therapeutic indication	Treatment of obesity and the control of hunger associated with deficiencies in the leptin-melanocortin pathway Further information on Imcivree can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree
CHMP opinion	20 May 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Dinah Duarte / Vallo Tillmann
Sponsor's report submission	3 August 2020
COMP discussion	10-12 May 2021
COMP opinion (adoption via written procedure)	21 May 2021

2.2. 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 grounds for the COMP Opinion at the designation stage were as follows:

"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 early clinical data showing significant reductions in hunger score and body weight in patients.
- The condition is life-threatening and chronically debilitating due to unrelenting hunger leading to morbid obesity and related comorbidities such as cardiovascular, metabolic, respiratory and orthopaedic impairments.
- The condition was estimated to be affecting approximately 0.1 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.

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 indication: treatment of leptin receptor deficiency."

2.3. 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

Congenital leptin receptor (LEPR) deficiency is caused by bi-allelic mutations (either homozygous or compound heterozygous) in the LEPR gene that result in loss of function in the leptin receptor. The LEPR gene is located on chromosome 1p31.1 and encodes the leptin receptor, which is expressed on hypothalamic pro-opiomelanocortin (POMC) neurons responsible for producing mature melanocyte-stimulating hormone (MSH) peptides from the POMC precursor peptide in the MC4 pathway (Lee 2009, Balthasar 2004). The LEPR is also expressed on other tissues and responds to leptin in reproductive and immune function regulation in addition to its central role in body weight regulation (Dalamaga 2013, Myers 2009).

The LEPR deficiency phenotype develops because POMC neurons are not activated based on the missing leptin signal mediated by the LEPR. The disease manifests itself by extreme early onset obesity and hyperphagia.

The approved therapeutic indication "IMCIVREE is indicated in the treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above" falls within the scope of the two designated orphan conditions "Treatment of leptin receptor deficiency" in this designation and EU/3/16/1703 covering setmelanotide in the 'treatment of pro-opiomelanocortin deficiency'.

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

Monogenic obesity disorders are characterised by onset in infancy and early childhood, marked hyperphagia apparent to parents and caregivers early in childhood development, and with continued excess hunger coupled with progressive and unrelenting body weight gain thereafter. Given the strong genetic underpinnings in these forms of extreme obesity, it is not surprising that refractoriness to diet, exercise and existing medical / surgical therapeutic interventions is the norm.

Beyond the hyperphagia, somatic conditions frequently associated with severe obesity include premature death, heart disease, obstructive sleep apnoea, hypertension, dyslipidaemia, and type 2 diabetes mellitus, which have significant and well-documented cardiac, renal, and ophthalmic complications for children and young adults.

Children and especially adolescents with extreme obesity experience increased mortality and morbidity, including cardiovascular, metabolic, respiratory and orthopaedic complications (Norris 2011, Schwimmer 2003, Amin 2002, Karlson 2003) and global impairments in daily functioning (Zeller 2006).

In fact, several cases (at least 5 among the reported cases) of early mortality – most often as a consequence of respiratory and cardiovascular complications – have been reported among congenital LEPR-deficient patients.

The condition remains chronically debilitating and life threatening.

Number of people affected or at risk

At the time of designation, the sponsor's formal estimate of the prevalence of LEPR deficiency was approximately 0.1 per 10,000. This was based on two separate approaches to prevalence estimation:

- Literature searching which revealed that fewer than 50 biallelic LEPR deficiency patients had been identified worldwide and estimated that there were 3,540 to 4,130 patients with some form of LEPR deficiency in the EU, equivalent to an overall prevalence of 0.07 to 0.08 per 10,000 people (Andiran 2011, Clement 1998, Chung 1997, Farooqi 2007, Gill 2014, Hannema 2016, Heo 2001, Huvenne 2015, Kimber 2008, LeBeyec 2013, Mammès 2001, Matsuoka 1997, Mazen 2011, Montague 1997, Saeed 2014, Saeed, 2015, Thompson 1997; Nordang, 2017; NCD Risk Factor Collaboration 2016; Ogden, 2016).
- The prevalence of LEPR gene LOF alleles (Ayers, 2018), which led to an estimate of 0.12 per 10,000.

In addition to the literature and reports presented at the time of initial designation, the sponsor presented also a systematic review of LEPR deficiency including a prevalence estimate that has very recently been published (Kleinendorst et al, 2020). The authors noted that 88 patients with LEPR deficiency are reported in the worldwide literature (including 2 reported for the first time in this publication), of which 21 are European. Based on assumptions in conjunction with these data, a predicted European prevalence of 998 cases is derived. This corresponds to a prevalence of 1.34 per million (95% CI=0.95, 1.72) which can be expressed as 0.0134 per 10,000 (95% CI=0.0095, 0.0172). This prevalence estimate is somewhat lower than that presented at the time of designation and due to uncertainties around the point prevalence of LEPR deficiency, the value of 0.1 in 10,000 was adopted.

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 designation, no drugs were approved in the EU for the treatment of obesity due to LEPR deficiency and no medicines have been authorised since then.

Potential surgical approaches, such as gastric or intestinal bypass operations, were considered contraindicated because LEPR deficiency patients continue to experience extreme appetite and therefore overeat, even after surgery, often leading to anatomical complications. Medicines used in treatment of obesity do not address the issue of hyperphagia in these patients.

There has been no change regarding the available therapeutic options since the designation date. The situation described above therefore remains current.

Significant benefit

Not applicable.

2.4. COMP position adopted on 21 May 2021

The COMP concluded that:

- the proposed therapeutic indication includes the orphan condition of the designated Orphan Medicinal Product. The therapeutic indication is covered entirely by this and an additional orphan designation (EU/3/16/1703), which is covered by a separate opinion document.
- the prevalence of leptin receptor deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 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 and chronically debilitating due to unrelenting hunger leading to morbid obesity and related comorbidities such as cardiovascular, metabolic, respiratory and orthopaedic impairments;
- there is, at present, no satisfactory method for the treatment of the condition 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 leptin receptor deficiency (EU/3/18/2101) is not removed from the Community Register of Orphan Medicinal Products.

3. Setmelanotide for the treatment of pro-opiomelanocortin deficiency - EU/3/16/1703 (EMA/OD/0000040443)

3.1. Product and administrative information

Product	
Designated active substance(s)	Setmelanotide
Other name(s)	-
International Non-Proprietary Name	Setmelanotide
Tradename	Imcivree
Orphan condition	Treatment of pro-opiomelanocortin deficiency
Sponsor's details:	Rhythm Pharmaceuticals Limited 10 Earlsfort Terrace Dublin 2 D02 T380 Co. Dublin Ireland

Orphan medicinal product designation procedural history	
Sponsor/applicant	TMC Pharma Services Ltd
COMP opinion	16 June 2016
EC decision	14 July 2016
EC registration number	EU/3/16/1703
Post-designation procedural history	
Transfer of sponsorship	Transfer from TMC Pharma Services Ltd to TMC Pharma (EU) Limited – EC decision of 14 March 2019 Transfer from TMC Pharma (EU) Limited to Rhythm Pharmaceuticals Limited – EC decision of 5 November 2020
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Rapporteur / Co-rapporteur	Karin Janssen van Doorn / Kirstine Moll Harboe
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Invented name	Imcivree
Proposed therapeutic indication	Treatment of obesity and the control of hunger associated with deficiencies in the leptin-melanocortin pathway Further information on Imcivree can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree
CHMP opinion	20 May 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Dinah Duarte / Vallo Tillmann
Sponsor's report submission	3 August 2020
COMP discussion	10-12 May 2020
COMP opinion (adoption via written procedure)	21 May 2021

3.2. Orphan medicinal product designation

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

The grounds for the COMP Opinion at the designation stage were as follows:

> "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 clinical data demonstrating reduction of hunger score and significant weight loss in patients.
- The condition is life-threatening due to failure to thrive in infancy and secondary adrenal insufficiency and chronically debilitating due to morbid obesity and endocrinopathies.
- The condition was estimated to be affecting less than 0.1 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.

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 setmelanotide as an orphan medicinal product for the orphan indication: treatment of pro-opiomelanocortin deficiency."

3.3. 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

Pro-opiomelanocortin (POMC) deficiency is a rare genetic disorder in which neuropeptides synthesised and processed from the POMC gene are absent or deficient. The lack of POMC and/or its conversion to melanocyte stimulating hormone (MSH) abolishes signals these satiety and results in an unchecked stimulus to appetite which in turn leads to uncontrolled food intake and obesity. In patients with POMC deficiency neuropeptides synthesised and processed from the POMC gene can be absent or deficient due to defects in two genes: POMC gene itself or proprotein convertase subtilisin/kexin type 1 (PCSK1) gene, which encodes the enzyme processing POMC into derivative MSH neuropeptides.

In patients with PD the lack of POMC and/or its conversion to MSH abolishes these satiety signals and results in an unchecked stimulus to appetite which in turn leads to uncontrolled food intake and subsequent obesity.

The approved therapeutic indication "IMCIVREE is indicated in the treatment of obesity and the control of hunger associated with biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and above" falls within the scope of the two designated orphan conditions "Treatment of pro-opiomelanocortin deficiency" in this designation and EU/3/18/2101 covering setmelanotide in 'treatment of leptin receptor deficiency'.

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

POMC gene defect patients exhibit severe early-onset hyperphagia, obesity, cholestasis and congenital secondary adrenal insufficiency. They also typically have very fair skin in ethnic backgrounds that do not otherwise lead to darker skin pigmentation (Challis & Millington, 2015). If not treated with glucocorticoid therapy soon after birth, children can die due to adrenal insufficiency. Despite glucocorticoid replacement therapy, deficiencies in POMC-derived neuropeptides such as α/β-MSH are not easily remedied, and infants experience exponential feeding and weight gain. If light skinned, they must also remain protected from excessive sun exposure. Additionally, patients may exhibit other endocrine abnormalities, such as central hypothyroidism, growth hormone deficiency, and hypogonadotrophic hypogonadism requiring appropriate hormone supplementation treatment (Challis & Millington, 2015).

No medicines were authorised for the condition since the initial designation. The condition remains life threatening and chronically debilitating.

Number of people affected or at risk

At the time of designation, the sponsor's formal estimate of the prevalence of POMC / PCSK1 deficiency was <0.1 per 10,000. This was based on literature searching which revealed that fewer than 50 POMC gene defect patients and ~25 PCSK1 gene defect patients had been identified worldwide (O'Rahilly et al, 1995; Jackson et al, 1997; Jackson et al, 2003; Farooqui et al, 2007; Martin et al, 2013; Wilschansnski et al, 2014; Challis & Millington, 2015).

The sponsor performed an updated search and added 5 new case reports of POMC deficiency (Anisimova et al, 2017; Ozsu & Bahm, 2017 (2 cases); Cetinkaya et al, 2018; Hilado & Randhawa, 2018) and 2 new case reports of PCSK1 deficiency (Härter et al, 2016; Pépin et al, 2019).

Accordingly, the prevalence description can be updated to say that fewer than 60 POMC gene defect patients and fewer than 30 PCSK1 gene defect patients had been identified worldwide. In line with this, the formal estimate of the prevalence of POMC / PCSK1 deficiency remains at <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 designation, no drugs were approved in the EU for the treatment of obesity due to POMC and/or PCSK1 deficiency.

Two products discussed in the original designation application had approved indications which included the term "obesity". These products are not known to manage the excessive appetite in POMC and/or PCSK1 deficiency.

Potential surgical approaches, such as gastric or intestinal bypass operations, were considered contraindicated because POMC / PCSK1 deficiency patients continue to experience extreme appetite and therefore overeat, even after surgery, often leading to anatomical complications.

Significant benefit

Not applicable.

3.4. COMP position adopted on 21 May 2021

The COMP concluded that:

- the proposed therapeutic indication includes the orphan condition of the designated Orphan Medicinal Product. The therapeutic indication is covered entirely by this and an additional orphan designation (EU/3/18/2101), which is covered by a separate opinion document.
- the prevalence of pro-opiomelanocortin deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 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 failure to thrive in infancy and secondary adrenal insufficiency and chronically debilitating due to morbid obesity and endocrinopathies;
- there is, at present, no satisfactory method for the treatment of the condition 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 pro-opiomelanocortin deficiency (EU/3/16/1703) is not removed from the Community Register of Orphan Medicinal Products.