27 March 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Imcivree (setmelanotide)
Treatment of acquired hypothalamic obesity
EU/3/23/2833

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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Table of contents

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 acquired hypothalamic obesity
Sponsor's details:	Rhythm Pharmaceuticals Netherlands B.V. Radarweg 29 1043 NX Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Rhythm Pharmaceuticals Netherlands B.V.
COMP opinion	7 September 2023
EC decision	13 October 2023
EC registration number	EU/3/23/2833
Type II variation procedural history	
Rapporteur	Karin Janssen van Doorn
Applicant	Rhythm Pharmaceuticals Netherlands B.V.
Application submission	24 July 2025
Procedure start	16 August 2025
Procedure number	EMA/VR/0000288021
Invented name	Imcivree
Proposed therapeutic indication	Treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment. Further information can be found in the European public assessment report (EPAR) on the Agency's website Imcivree | European Medicines Agency (EMA)
CHMP opinion	26 March 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann / Joao Rocha
Sponsor's report submission	17 September 2025
COMP discussion and adoption of list of questions	17-19 February 2026
COMP opinion (adoption via written procedure)	27 March 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2023 was based on the following grounds:

The sponsor Rhythm Pharmaceuticals Netherlands B.V. submitted on 20 May 2023 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing setmelanotide for treatment of hypothalamic obesity. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the condition originally proposed by the sponsor should be renamed as "treatment of acquired hypothalamic obesity" (hereinafter referred to as "the condition") to clearly differentiate it from the genetic forms of obesity which can also originate from defects in the hypothalamus.

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 in patients with the condition who showed reductions in body weight, BMI and hunger scores;
- the condition is chronically debilitating due to severe obesity, hyperphagia, an increased risk to develop severe atherosclerotic disease and type 2 diabetes mellitus, and life-threatening due to an increased risk of fatal cardiovascular events;
- the condition was estimated to be affecting approximately 0.4 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 setmelanotide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in two patients with the proposed condition who have been previously treated with currently authorized weight loss drugs and who showed reductions in body weight, BMI and hunger scores while treated with setmelanotide. The Committee considered that this constitutes a clinically relevant advantage.

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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing setmelanotide as an orphan medicinal product for the orphan condition: treatment of acquired hypothalamic obesity.

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 orphan condition is "Treatment of acquired hypothalamic obesity (aHO)".

The condition is most often caused by tumours (e.g., craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumour (Hochberg 2010). Much rarer causes of injury include inflammatory conditions involving the hypothalamus or trauma. Craniopharyngiomas represent the most common tumour associated with the development of aHO and account for 5% to 15% of paediatric intracranial tumours (Muller 2022). Imaging studies show that lesions of the ventromedial nucleus of the hypothalamus and the region of the arcuate nucleus are more often associated with hyperphagia and excessive weight gain (Ahmet 2006; DeVile 1996; Roth 2011; Holmer 2010; Elfers 2011).

The clinical presentation differs quite distinctly from both general obesity and genetic causes of an impaired MC4 pathway since the change in body weight dates from the onset of the injury, due to either the tumour itself growing into the hypothalamus or the surgery/radiation deployed to treat the tumour.

The approved therapeutic indication ""*IMCIVREE is indicated for the treatment of obesity and control of hunger in adults and children aged 4 years of age and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment" (tbc according to final SmPC)* falls within the scope of the designated orphan condition "Treatment of acquired hypothalamic obesity".

Intention to diagnose, prevent or treat

The medical plausibility is expected to be confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Hypothalamic obesity is a severe, devastating disease characterized by rapid and sustained weight gain and other metabolic disturbances (e.g., hyperphagia, hyperleptinemia and hyperinsulinemia) that are triggered by hypothalamic injury.

Regardless of the specific underlying cause, patients with aHO develop a highly aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain (Roth & McCormack 2024) which is most dramatic in the first 6 to 12 months after injury/impairment (Sterkenburg et al 2015, Rydin et al 2022, Shoemaker & Tamaroff 2023, Roth & McCormack 2024).

The rapid and persistent weight gain quickly leads to morbid obesity and related morbidities, including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, disturbances of circadian rhythm, sleep-disordered breathing, metabolic-associated liver disease, reduction in functional capacity and early mortality in some patients (Muller et al 2025, Roth & McCormack 2024, Muller 2011, Olsson et al

2015, Sterkenburg et al 2015). The disease is associated with hyperphagia which is estimated to occur in most patients (50% to 72%), along with lethargy, decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behaviour (Heymsfield et al 2014, Muller 2011, Kayadjanian et al 2023). Acquired HO is one of the most refractory types of obesity and is generally unresponsive to lifestyle or medical interventions (Roth & McCormack 2024).

In summary, the condition is considered potentially life-threatening due to an increased risk of fatal cardiovascular events and chronically debilitating, mainly due to severe obesity, hyperphagia, an increased risk to develop severe atherosclerotic disease and type 2 diabetes mellitus.

Number of people affected or at risk

The sponsor proposes a complete prevalence rate for all-cause aHO of 0.32 in 10,000.

The previously accepted prevalence estimate at time of orphan designation in 2023 was approximately 0.4 in 10,000. The proposed prevalence estimate from the sponsor in this orphan review procedure is based on the combined prevalence values for aHO due to: **1)** tumour and treatment related causes (TTR), **2)** non-tumour related causes including traumatic brain injury (TBI), **3)** unspecified microinjuries (UM) and **4)** structural abnormalities from congenital disorders (Hochberg & Hochberg 2010, Roth & McCormack 2024, Cerbone et al 2020, Nannette et al 2023, Batram et al [draft manuscript]).

1) Tumour-treatment related aHO (TTR-aHO)

Prevalence of TTR-aHO was calculated as a function of estimated incidence and survival rate. Witte et al (2024) conservatively assumed a disease duration of 20 years, following the results of a longitudinal analysis of CP registry data showing a 20-year survival rate of nearly 90% in 280 patients with childhood-onset CP (Sterkenburg et al 2015).

The cumulative incidence of TTR-aHO was 6.8 cases per 1,000,000 persons. Extrapolated to the 2019 total population of Germany of approximately 83 million (Eurostat 2025), this is approximately 80 incident TTR-aHO cases per year. The estimated and extrapolated 2019 prevalence is 1,262 cases in Germany (Witte et al 2024).

Given the limited epidemiology data on TTR-aHO beyond CP in different EU countries, the estimated prevalence rate from the German claims analysis was used for extrapolation purposes. When extrapolated to the EU as a whole using the 2024 total population of 449.31 million (Eurostat 2025), this equates to a prevalence of TTR-aHO in the EU of approximately 6,830 cases, or a prevalence rate of **0.15 in 10,000**.

2) Traumatic brain injury aHO (TBI-aHO)

Prevalence of TBI-aHO was calculated as a function of estimated incidence and survival rate. For TBI patients, a mean survival after a TBI event of 30.6 years (95%-CI: 26.8-34.5) was assumed (Fuller et al 2016). Since patients who died due to the TBI through the two-year follow-up evaluation were excluded, calculations for the long-term survival after TBI can be relied upon (Batram et al [draft manuscript]).

The estimated cumulative TBI-aHO incidence is 1.8 cases per 1,000,000 persons over that period. Extrapolated to the 2022 total population of Germany of approximately 84 million (Eurostat 2025), this is approximately 20 incident TBI-aHO cases per year. The estimated and extrapolated 2022 prevalence is 520 cases in Germany (95%-CI: 460-590) (Batram et al [draft manuscript]).

There are differences in the TBI rates across countries, which could in theory impact the TBI-aHO rates. In the 2016 Global Burden of Disease study, age standardized TBI incidence and prevalence rates of all causes of TBI were reported per country and region (GBD 2016). The study was optimized for comparability across countries by adjusting for different case definitions, enforcing consistency between data for prevalence, incidence, and cause of death estimates, and predicting estimates for locations with sparse data by borrowing information from other locations and covariates. The study did not report the rates by severity of TBI but reported non-fatal burden of TBI accounting for the cause and nature of injury in the underlying regression model. Table 1 shows TBI incidence and prevalence for the EU as a whole and across the most populous European countries.

Table 1. Traumatic brain injury age-standardised incidence and prevalence

Country/Region	**Age-standardised incidence (per 100,000)**	**Age-standardised prevalence (per 100,000)**
European Union	292 (95%-CI: 244 to 351)	546 (95%-CI: 2519 to 572)
Germany	288 (95%-CI: 2239-346)	535 (95%-CI: 2508-562)
France	307 (95%-CI: 2255 to 372)	564 (95%-CI: 2535 to 593)
Italy	315 (95%-CI: 2263 to 377)	596 (95%-CI: 2566 to 626)
Spain	284 (95%-CI: 2237 to 339)	543 (95%-CI: 2515 to 569)
UK	260 (95%-CI: 2215 to 316)	478 (95%-CI: 2454 to 499)

GBD 2016
Abbreviations: CI=confidence interval

The overall age standardized prevalence of TBI per 100,000 people in Western Europe is 546 cases, (95% CI 519-572), and there is an overlap of age standardized TBI incidence and prevalence amongst individual EU countries suggesting that further adjustment to the epidemiology estimates for countries outside Germany is not warranted. Given this, the estimated TBI-aHO prevalence rate from the German claims analysis (Batram et al [draft manuscript]) was used as the primary estimate for prevalence in other countries. When extrapolated to the EU as a whole using the 2024 total population of 449.31 million (Eurostat 2025), this equates to a prevalence of TBI-aHO in the EU of approximately 2,810 cases, or a prevalence rate of **0.06 in 10,000**.

3) Unspecified microinjuries aHO (UM-aHO)

Prevalence of UM-aHO was calculated as a function of estimated incidence and survival rate. For patients with UM-aHO, no reliable assumptions about life expectancy are available, therefore, the same values as for the TBI cohort were used (30.6 years [95%-CI: 26.8-34.5], Fuller et al 2016).

The estimated cumulative UM-aHO incidence is 2.12 cases per 1,000,000 persons over the study period. Extrapolated to the 2022 total population of Germany of approximately 84 million (Eurostat 2025), this is approximately 28 incident UM-aHO cases per year. The estimated and extrapolated 2022 prevalence is 660 cases in Germany (95%-CI: 585-750) (Batram et al [draft manuscript]).

The rates of UM-aHO in different countries is not known, therefore the prevalence estimate for Germany was used for extrapolation purposes. When extrapolated to the EU as a whole using the 2024 total population of 449.31 million (Eurostat 2025), this equates to a prevalence of UM-aHO in the EU of approximately 3,570 cases, or a prevalence rate of **0.08 in 10,000**.

4) Anatomic defect aHO

The adjusted septo-optic dysplasia (SOD) obesity rate was used as a proxy to estimate a prevalence rate of SOD-aHO of 3.04 cases per 1,000,000 persons. SOD aHO was then used as a proxy for

anatomic defect aHO overall. When extrapolated to the EU as a whole using the 2024 total population of 449.31 million (Eurostat 2025), this equates to a prevalence of anatomic defect aHO in the EU of approximately 1,360 cases, or a prevalence rate of **0.03 in 10,000**.

When summed together, the aHO prevalence estimates for the different aetiologies result in an overall estimate for all-cause aHO in the EU of 14,570 prevalent cases, or a total prevalence rate for all-cause aHO of **0.32 in 10,000**.

The COMP noted that septo-optic dysplasia (SOD) was used by the sponsor as a proxy population for determining epidemiological estimates of hypothalamic obesity (aHO) caused by anatomic defects. The prevalence of SOD was reported to be between 1.9 and 2.5 per 100,000 births. However, two recent review papers (Pasca L. et al, 2025, Cullingford DJ, et al. 2025) have both quoted a prevalence of 1 in 10,000 live births, and a higher obesity rate in SOD of 44% compared to the 30% used in the prevalence calculation of aHO by the sponsor.

The COMP adopted a question on prevalence asking the sponsor to discuss the relevance of these two recent data sources and potentially recalculate the prevalence of aHO accordingly.

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 medicinal products authorized in the EU for the specific treatment of aHO. However, several therapies are approved for general obesity (Table 2).

Table 2. EU-approved therapies for general obesity or overweight

Name	Indication
Wegovy (semaglutide)	Adults Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of • ≥30 kg/m^2 (obesity), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. Adolescents (≥12 years) Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with • obesity* and • body weight above 60 kg.

Name	Indication
	Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose. * Obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov)
Saxenda (liraglutide)	Adults Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of: • ≥ 30 kg/m² (obesity), or • ≥ 27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea. Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight. Adolescents (≥ 12 years) Saxenda can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with: • obesity (BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points)* and • body weight above 60 kg. Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z-score after 12 weeks on the 3.0 mg/day or maximum tolerated dose. * IOTF BMI cut-off points for obesity by sex between 12-18 years, in accordance with study design of the Trial 4180.
Mounjaro (tirzepatide)	Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of • ≥ 30 kg/m^2 (obesity) or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).
Mysimba (naltrexone and bupropion)	Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of • ≥ 30 kg/m^2 (obese), or

Name	Indication
	• ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension) Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see section 5.1).
Xenical (orlistat)	Xenical is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI > 28 kg/m²) with associated risk factors. Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5 % of the body weight as measured at the start of therapy.

At time of initial orphan designation, authorized products for the treatment of for general obesity have previously been considered as satisfactory methods by the COMP. Now, at time of orphan review, the COMP assesses the applicability of satisfactory methods based on the authorized indication wording of Imcivree for the treatment of aHO: "*IMCIVREE is indicated for the treatment of obesity and control of hunger in adults and **children aged 4 years of age** and above with acquired hypothalamic obesity (aHO) due to hypothalamic injury or impairment*".

Considering that Imcivree is covering a broader age range (i.e. from 4 years of age) as compared to any of the authorized therapies listed above in Table 2, the COMP does not consider that any of these medicinal products for the treatment of general obesity or overweight are satisfactory methods, for the purpose of this procedure.

Significant benefit

Not applicable.

4. COMP list of issues

Prevalence

Septo-optic dysplasia (SOD) was used by the sponsor as a proxy population for determining epidemiological estimates of acquired hypothalamic obesity (aHO) due to anatomic defects. The prevalence of SOD was reported to be between 1.9 and 2.5 per 100,000 births. However, two recent review papers (Pasca L. et al, 2025, Cullingford DJ, et al. 2025) have both quoted a prevalence of 1 in 10,000 live births, and a higher obesity rate in SOD of 44% compared to the 30% used in the prevalence calculation of aHO by the sponsor. The sponsor is asked to discuss the relevance of these two recent data sources and potentially recalculate the prevalence of aHO accordingly.

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

Comments on sponsor's response to the COMP list of issues

In their written responses the sponsor explains that while a prevalence estimate for SOD of 1 in 10,000 births is provided in both Pasca et al. 2025 and Cullingford et al. 2025, both papers cite older

sources and/or include reports of geographical clustering outside of the EU for the basis of these estimates and do not represent the prevalence of SOD at the time the application was made or new information compared to the Orphan Maintenance Request submitted in September 2025. Therefore, the Sponsor believes that the Anatomic defect aHO (or the proxy of SOD_obese) prevalence estimate of 0.03 per 10,000 and the Total aHO prevalence estimate of 0.32 per 10,000 provided in the Orphan Maintenance Request are appropriate.

The COMP considers that the most reliable epidemiologic data for SOD for Europe is described in the article by Garne and colleagues (2018) who report a prevalence of 2.51 in 100,000 births (95% CI 1,6-3.58). Calculating the population prevalence based on the upper limit of the 95% CI of 3.58 in 100.000 births and accounting for the 44% of SOD patients who are reported to be obese/overweight (Cullingford 2025), the COMP accepted a contribution of Anatomic defect aHO (or the proxy of SOD_obese) to the overall prevalence of aHO of approximately 0.11 in 10,000 total EU population, assuming the following:

- A birth prevalence (SOD_obese) of 0.16 (0.358x0.44) per 10.000 births (Grant et al., 2018)
- EU births/year: ~4,000,000 -> 64 cases/year
- Average lifespan: ~80 years -> 5,120 people expected to live with the condition (SOD_obese) in EU
- EU population: ~450,000,000 -> translating to a rate of 0.11 in 10,000 total EU population.

The sum of the following four prevalence values results in a total population prevalence of aHO of approximately 0.4 in 10,000 total EU population:

- 0.15 in 10,000 (Tumour treatment related aHO, TTR-aHO) +
- 0.06 in 10,000 (Traumatic brain injury aHO, TBI-aHO) +
- 0.08 in 10,000 (Unspecified microinjuries aHO, UM-aHO) +
- 0.11 in 10,000 (Anatomic defect aHO with septo-optic dysplasia (SOD) obesity rate as proxy).

The COMP accepted a total prevalence estimate for aHO of approximately 0.4 in 10,000 persons in the EU.

The COMP adopted a positive opinion.

5. COMP position adopted on 27 March 2026

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 acquired hypothalamic obesity (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.4 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 an increased risk of fatal cardiovascular events and chronically debilitating, due to severe obesity, hyperphagia, an increased risk to develop severe atherosclerotic disease and type 2 diabetes mellitus;
- no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Imcivree.

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 acquired hypothalamic obesity (EU/3/23/2833) is not removed from the Community Register of Orphan Medicinal Products.