Report IMCIVREE® Setmelanotide

Product Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: setmelanotide **Brand Name:** Imcivree® **Originator/licensee:** Rhythm Pharmaceuticals Inc **Classification:** NCE **ATC code:** A08AA12 **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** Setmelanotide is an 8-amino acid cyclic peptide analogue of naturally occurring alpha-melanocyte stimulating hormone (a-MSH). Setmelanotide is a selective MC4 receptor agonist and is claimed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss [1].	**Authorized Indication:** **EMA:** setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above [1]. **Route of administration:** subcutaneous injection **Licensing status** **EU CHMP P.O. date:** 21.05.2021 **FDA M.A. date:** 25.11.2020 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **AE:** adverse event; **LEPR:** leptin receptor; **LOF:** loss-of-function; **MC4**: Melanocortin-4-receptor **PBO:** placebo; **PCSK1:** Proprotein Convertase Subtilisin/Kexin Type 1; **POMC:** pro-opiomelanocortin	**Summary of clinical EFFICACY:** **Study RM-493-012 (Study 012) - NCT02896192** and **Study RM-493-015 (Study 015) - NCT03287960:** single arm, open-label, one-year phase-3 studies. **Study 012** enrolled pts aged ≥ 6 years with bi-allelic, homozygous or compound heterozygous genetic status for either the POMC or PCSK1 genes, with the LOF variant for each allele conferring a severe obesity phenotype. **Study 015** enrolled pts aged ≥ 6 years with bi-allelic, homozygous or compound heterozygous genetic status for the LEPR gene, with the LOF variant for each allele conferring a severe obesity phenotype. Key exclusion criteria included a recent diet or exercise regimen, or both, resulting in weight loss or stabilization and previous gastric bypass surgery resulting in more than 10% weight loss with no evidence of weight regain. In both studies pts entered a 2- to 12 week open-label dose titration phase. Setmelanotide was injected subcutaneously once daily at a starting dose of 1.0 mg for adults and 0.5 mg for paediatric participants. Doses were up-titrated every two weeks by 0.5 mg until reaching an individualised therapeutic dose. Pts with at least 5 kg weight loss (or ≥5% if weighing <100 kg at baseline) entered an 8-week double-blind period (including four weeks each of blinded setmelanotide and PBO treatment) followed by 32 additional weeks of open-label treatment. The primary endpoint of the studies was the proportion of participants with at least 10% weight loss compared with baseline at approximately 1 year. Between Feb 2017 and Sept 2018, 10 pts were enrolled in **Study 012**; 8 (80%) participants achieved at least 10% weight loss at approximately one year. In the same period, 11 participants were enrolled in **Study 015** and 5 (45%) pts achieved the primary endpoint. [2][3][4][5] **Summary of clinical SAFETY:** **Study RM-493-012 (Study 012) - NCT02896192** and **Study RM-493-015 (Study 015) - NCT03287960:** in **Study 012**, the most common AEs were injection site reaction and hyperpigmentation, which were reported in all 10 participants; nausea was reported in five participants and vomiting in three participants. In **Study 015**, the most commonly reported treatment-related AEs were injection site reaction in all 11 participants, skin disorders in five participants, and nausea in four participants. No serious treatment-related AEs occurred in both trials [3]. **Ongoing studies:** • **For the same indication:** Yes • **For other indications:** Yes **Discontinued studies (for the same indication):** No --- **References:** [1]. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-imcivree_en.pdf [2]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000SumR.pdf [3]. Clément, Karine et al. "Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials." The lancet. Diabetes & endocrinology vol. 8,12 (2020): 960-970. doi:10.1016/S2213-8587(20)30364-8 [4]. https://clinicaltrials.gov/ct2/show/record/NCT02896192?term=NCT02896192&draw=2&rank=1 [5]. https://clinicaltrials.gov/ct2/show/record/NCT03287960?term=NCT03287960&draw=2&rank=1 [6]. https://www.empr.com/drug/imcivree/ [7]. https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=11020&MISSING%20CONTENT=Obesity-due-to-pro-opiomelanocortin-deficiency&search=Disease_Search_Simple&title=Obesity%20due%20to%20pro-opiomelanocortin%20deficiency [8]. European Medicines Agency. Public summary of opinion on orphan designation: Setmelanotide for the treatment of leptin receptor deficiency. 2019 [9]. European Medicines Agency. Public summary of opinion on orphan designation: Setmelanotide for the treatment of pro-opiomelanocortin receptor deficiency. 2016 [10].https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=Setmelanotide&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=	**Economic impact:** 1 mL vial (10mg/mL) costs approximately $3,296 [6]. Price per year at the maximum dose of 3 mg/day is $360,912 **Epidemiology:** Obesity due to POMC deficiency has been described in less than 10 patients. Prevalence is <1/1,000,000 [7]. In November 2018, LEPR deficiency affected approximately 0.1 in 10,000 people in the EU, which was equivalent to a total of around 5,000 people [8]. --- **POSSIBLE PLACE IN THERAPY:** **POMC deficiency:** no satisfactory methods are authorised in the EU for the treatment of POMC deficiency. Pts are treated with the weight loss medicines orlistat and methylcellulose [9]. **LEPR deficiency:** no satisfactory treatments are authorised in the EU for LEPR deficiency. Pts are managed with medicines for general weight control or by surgery [8]. **OTHER INDICATIONS IN DEVELOPMENT:** Bardet-Biedl Syndrome; Alström Syndrome; Smith-Magenis Syndrome; obesity due to MC4 deficiency [10]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** / **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** / *Service reorganization: No *Possible off label use: Yes

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