

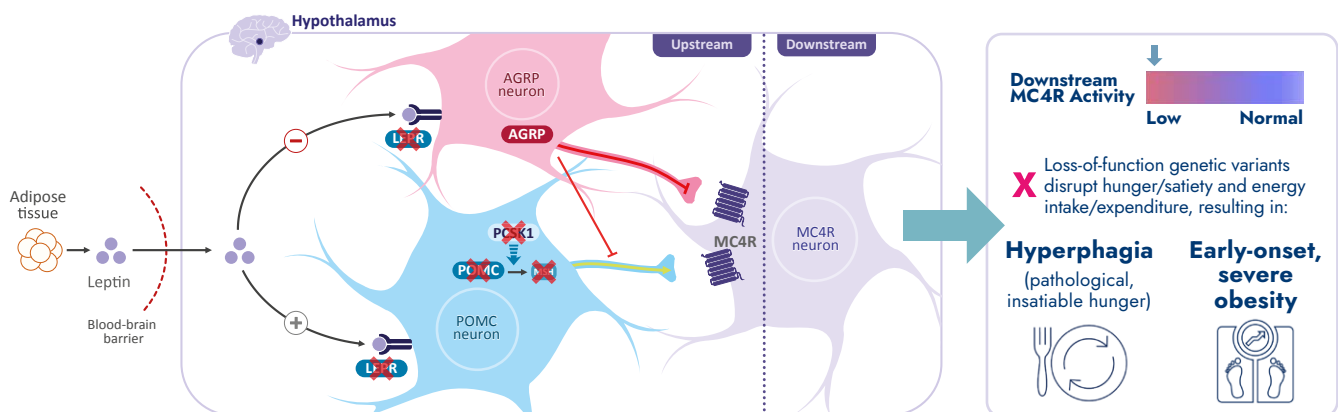
# Leptin receptor deficiency and proopiomelanocortin deficiency

Leptin receptor (LEPR) deficiency and proopiomelanocortin (POMC) deficiency are caused by rare genetic variants within the melanocortin-4 receptor (MC4R) pathway - a key pathway responsible for regulating hunger.<sup>1-3</sup>

They are autosomal recessive diseases caused by variants of the *LEPR* or *POMC* genes.<sup>1</sup>



## Impaired MC4R pathway<sup>1-3</sup>



### Abbreviations:

**AGRP**, agouti-related protein; **LEPR**, leptin receptor; **MC4R**, melanocortin-4 receptor; **MSH**, melanocyte-stimulating hormone; **PCSK1**, proprotein convertase subtilisin/kexin type 1; **POMC**, proopiomelanocortin.

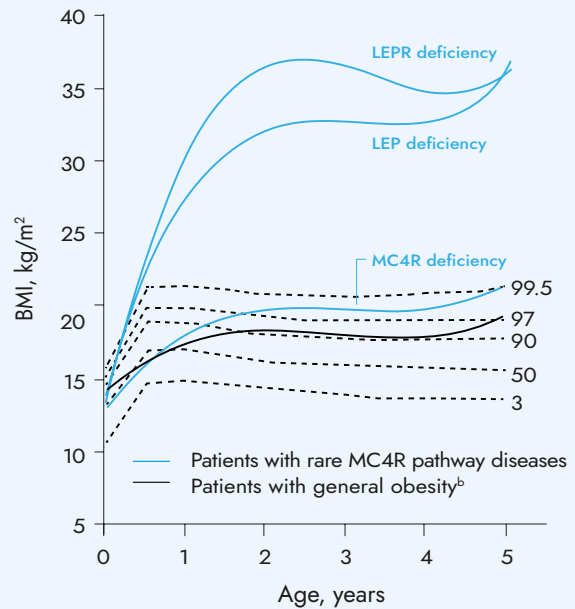
## Primary cardinal symptoms of LEPR and POMC deficiency

### Hyperphagia<sup>4</sup>

Characteristics and behaviours include:

-  Heightened and prolonged hunger
-  Longer time to reach satiety
-  Shorter duration of satiety
-  Severe preoccupation with food (hyperphagic drive)
-  Food-seeking behaviours (sneaking and stealing food)
-  Distress and inappropriate behavioural response if denied food

### Early-onset, severe obesity<sup>5,6,a</sup>

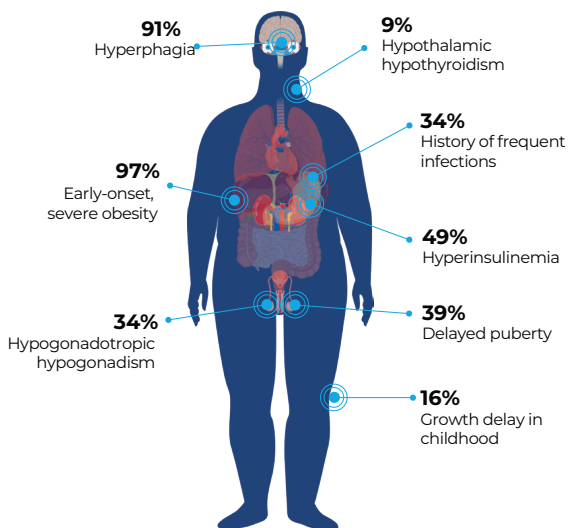


a) Defined as having a BMI  $\geq 120\%$  of the 95th percentile and onset before the age of 5.

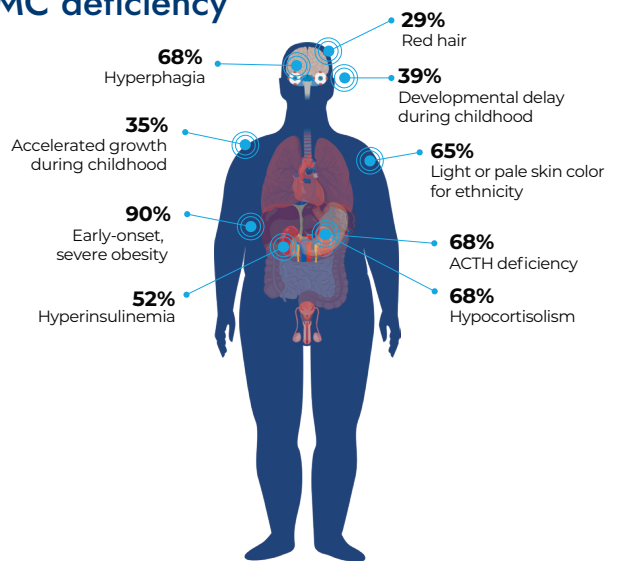
b) Patients with general obesity have a BMI  $>30$  kg/m<sup>2</sup> by age 14-16 years and do not have a variant in *LEPR*, *LEP*, or *MC4R*. Reprinted with permissions from Springer Nature from Kohlsdorf K, et al. *Int J Obes (Lond)*. 2018;42(9):1602–1609.

## Clinical characteristics of LEPR and POMC deficiency<sup>7,c</sup>

### LEPR deficiency



### POMC deficiency



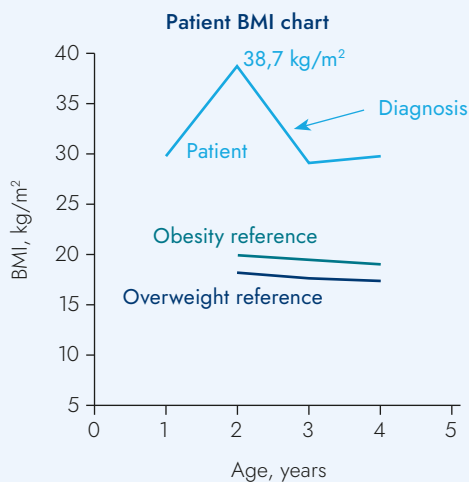
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

### Prevalence:

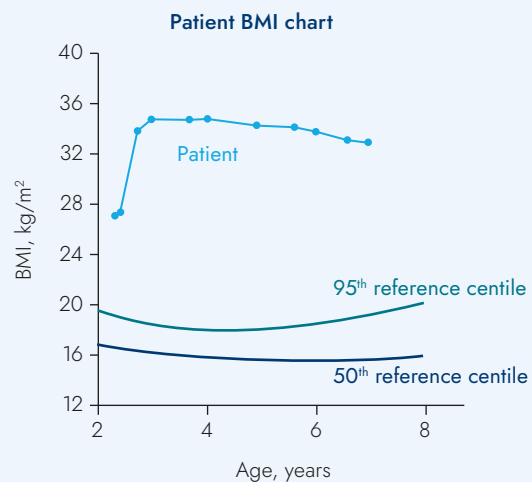
**LEPR:** 1.34 per million people<sup>8</sup>

**POMC/PCSK1:** fewer than 50 cases described worldwide for both indications<sup>9</sup>

## Example BMI chart: LEPR deficiency<sup>10</sup>



## Example BMI chart: POMC deficiency<sup>11</sup>



## How are LEPR and POMC deficiency diagnosed?

Diagnosis of LEPR and POMC deficiency may be suspected on the basis of clinical manifestations and is confirmed by genetic testing.<sup>10,12</sup>



### Paediatric patients

Genetic testing is recommended in paediatric patients with:<sup>4,10,12</sup>

- Early-onset, severe obesity
- Family history of severe obesity
- Features of syndromic obesity
- History of food-seeking behaviours
- Hyperphagia
- Neurodevelopmental abnormalities



### Adult patients

Characteristics of patients diagnosed in adulthood include:<sup>12-14</sup>

- Endocrine abnormalities
- History of early-onset, severe obesity
- Hyperphagia from early age
- Resistant to obesity management approaches
- Red hair

Clinical characteristics can vary on an individual basis and between gene variants. It's therefore important to:<sup>10,12,13</sup>

- Take a detailed clinical history
- Record family history, if available
- Monitor resistance to traditional obesity management strategies

### References:

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UK-DSE-2300016 | Date of preparation February 2024

Prescribing information and adverse event reporting information can be found on page 4

# Prescribing Information

▼ **IMCIVREE® (setmelanotide)** 10mg/ml solution for injection. **Active ingredient:** Setmelanotide. **Presentation:** Each vial contains 10mg setmelanotide in 1ml solution for subcutaneous injection.

**Indications:** 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. **Dosage and method of administration:** IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic aetiology. **POMC, including PCSK1, deficiency and LEPR deficiency:** *Adults and children 12 to 17 years of age:* 1mg daily for 2 weeks. If well-tolerated, dose can be increased to 2mg daily. If dose escalation is not tolerated, dose can be maintained at 1mg daily. If additional weight loss is desired in adults, and if weight remains above the 90<sup>th</sup> percentile in children 12 to 17 years of age, dose can be increased to 2.5mg with a maximum dose of 3mg daily. *Children aged 6 to <12 years:* 0.5mg daily for 2 weeks. If tolerated after 2 weeks, dose can be increased to 1mg daily. If dose escalation is not tolerated, dose can be maintained at 0.5mg daily. If 1mg is tolerated after 2 weeks, dose can be increased to 2mg daily. If weight remains above the 90<sup>th</sup> percentile and additional weight loss is desired, dose may be increased to 2.5mg daily. **BBS:** *Adults and children more than 16 years of age:* 2mg daily for 2 weeks. If well-tolerated, dose can be increased to 3mg daily. If 2mg starting dose is not tolerated, reduce to 1mg daily. If 1mg daily is tolerated, continue dose titration. Following starting dose, if a subsequent dose is not tolerated, reduce to previous level dose. If reduced dose is tolerated, continue dose titration. *Children aged 6 to <16 years:* 1mg daily for 1 week. If well-tolerated, dose can be increased to 2mg daily. If well-tolerated, dose can be increased to 3mg daily. If 1mg starting dose is not tolerated, reduce to 0.5mg daily. If 0.5mg dose is tolerated, continue dose titration. Following starting dose, if a subsequent dose is not tolerated, reduce to previous level dose. If reduced dose is tolerated, continue dose titration. **Renal impairment:** *Mild-to-moderate:* no dose adjustments are necessary. *Severe: POMC, including PCSK1, deficiency and LEPR deficiency (adults and children 12 to 17 years of age) and BBS (adults and children 16 to 17 years of age):* 0.5mg daily for 2 weeks. If well-tolerated, dose can be increased to 1mg daily. If well-tolerated and clinical response is insufficient, increase to 2mg daily. If well-tolerated and clinical response is insufficient, increase to 2.5mg daily. If well-tolerated and clinical response is insufficient, increase to 3mg daily. If 0.5mg dose is not tolerated, reduce to 0.25mg daily. If 0.25mg dose is tolerated, continue dose titration. Following starting dose, if a subsequent dose is not tolerated, reduce to previous level dose. If reduced dose is tolerated, continue dose titration. *POMC, including PCSK1, deficiency and LEPR deficiency (children aged 6 to <12 years) and BBS (children 6 to <16 years of age):* 0.25mg daily for 2 weeks. If not tolerated, discontinue treatment. If well-tolerated, dose can be increased to 0.5mg daily for 3 weeks. If well-tolerated, increase to 1mg daily. If well-tolerated and clinical response is insufficient, increase to 2mg daily. Following the starting dose, if a subsequent dose is not tolerated, reduce

to previous level dose. If reduced dose is tolerated, continue dose titration. **End-stage renal disease:** Setmelanotide should not be administered to patients with end-stage renal disease. **Hepatic impairment:** Setmelanotide should not be administered to patients with hepatic impairment. **Method of administration:** For subcutaneous use. **Contraindications:** Hypersensitivity to the active ingredient or any excipients. **Special warnings and precautions: Skin monitoring** – full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmented lesions before and during treatment with setmelanotide. **Heart rate and blood pressure monitoring** – monitor as part of standard clinical practice at each medical visit (at least every 6 months). **Prolonged penile erection** – patients experiencing penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment for priapism. **Depression** – patients with depression should be monitored at each medical visit during treatment and consideration should be given to discontinuing treatment if patients experience suicidal thoughts or behaviours. **Paediatric population** – prescribing physician should periodically assess response to setmelanotide therapy. Growing children should be monitored for height and weight using age- and sex-appropriate growth curves. **Excipients** – medicine contains benzyl alcohol and may cause allergic reactions. This medicine contains less than 1mmol sodium (23mg) per dose, that is to say essentially “sodium-free”. **Adverse reactions:** Based on observation from clinical studies: **Very common:** skin hyperpigmentation, injection site reactions, nausea, vomiting, headache, spontaneous penile erection. **Common:** pruritus, dry skin, hyperhidrosis, skin discolouration, skin lesion, alopecia, fatigue, asthenia, pain, diarrhoea, abdominal pain, dry mouth, dyspepsia, constipation, abdominal discomfort, dizziness, erection increased, disturbance in sexual arousal, libido increased, depression, insomnia, melanocytic naevus, back pain, myalgia, muscle spasms, pain in extremity, hot flush, vertigo. For more information on other adverse reactions, see Summary of Product Characteristics. **Legal category:** POM (subject to restricted medical prescription). **Marketing Authorisation Holder:** Rhythm Pharmaceuticals Netherlands B.V., Radarweg 29, 1043NX Amsterdam, Netherlands. Tel: +31 20 8546071. For any enquiries, contact [EU\\_Medinfo@Rhythmtx.com](mailto:EU_Medinfo@Rhythmtx.com) or use the following Toll-Free phone numbers: **In United Kingdom: +44 (0) 80 005 413 01.** **Marketing authorisation number: GB:** PLGB 55587/0001 **NI / EU:** EU/1/21/1564/0001. **Cost: GB / NI £2,376** per one 1ml vial. **Ireland, price on application. Additional information is available on request. Last revised:** February 2024.

## Adverse events should be reported.

Reporting forms and information can be found at:  
**UK:** [yellowcard.mhra.gov.uk](http://yellowcard.mhra.gov.uk)  
**Ireland:** **HPR**A Pharmacovigilance, [www.hpra.ie](http://www.hpra.ie)  
Adverse events should also be reported to Rhythm Pharmaceuticals Netherlands B.V., Radarweg 29, 1043NX Amsterdam, Netherlands.  
Tel: +31 20 8546071.