Rare melanocortin-4 receptor pathway diseases: Clinical features and genetic confirmation

Rare melanocortin-4 receptor (MC4R) pathway diseases can be caused by genetic variants within the pathway, which impair signalling that controls hunger.[1]

Hyperphagia (pathological, insatiable hunger) and **early-onset, severe obesity** are clinical features of a rare MC4R pathway disease.[1] If you see these features in your patients, **they may be living with a rare MC4R pathway disease**.[1]

Hyperphagia[2]

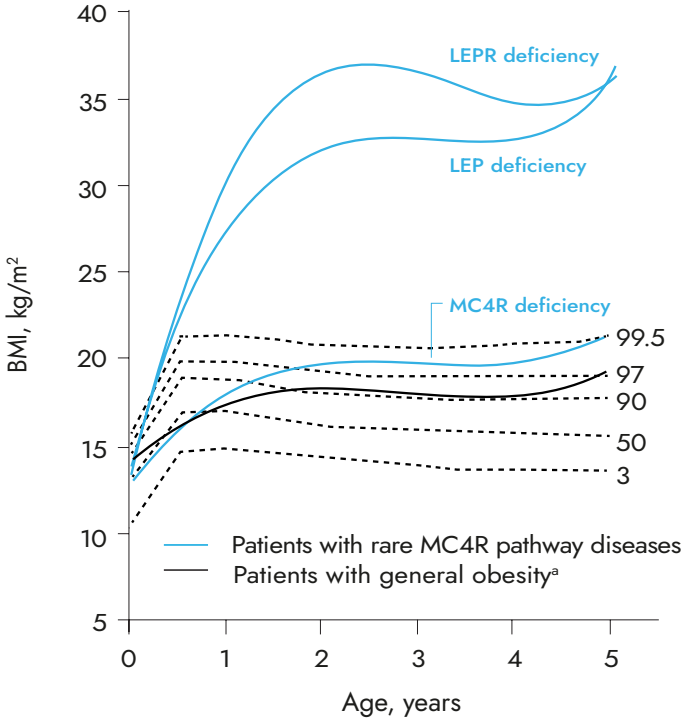
Also known as an abnormally strong sensation of hunger or desire to eat.

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 or stealing food)
- **Distress and functional impairment if denied food**

Early-onset, severe obesity[3]

Defined as having a BMI ≥120% of the 95th percentile and onset before the age of 5.[4]



a) Patients with general obesity have a BMI >30 kg/m² by age 14 to 16 years and do not have a variant in *LEP*, *LEPR*, or *MC4R*.

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Proactive identification of clinical features, and appropriate referral for genetic confirmation using correct gene panels can help move children living with a rare MC4R pathway disease onto their most appropriate care path.[5]

Access to appropriate tools means genetic variants that cause rare MC4R pathway diseases can be diagnosed early.[5]

The diagnosis pathway[5]

- Patient visits HCP to discuss symptoms
- HCP identifies clinical features
- HCP refers patient for genetic testing
- Genetic testing results confirm if the patient has a rare MC4R pathway disease

Through a correct referral, children with genetic variants that cause rare MC4R pathway diseases can be screened, and appropriately cared for

Current genetic screening allows many more rare diseases to be identified – rare MC4R pathway diseases can now be part of this

If you need more information on genetic confirmation or locating expert centres in your country, please contact us: EU_Medinfo@rhythmtx.com

References:
1. Loos, RJF and Yeo, GSH. Nat Rev Gens. 2022;23:120–133. **2.** Heymsfield SB, et al. Obesity (Silver Spring). 2014;22(suppl 1):S1–S17 **3.** Kohlsdorf K, et al. Int J Obes (Lond). 2018;42(9):1602–1609 **4.** Hampl SE, et al. Pediatrics. 2023;151(2):e2022060640 **5.** Styne DM, et al. J Clin Endocrinol Metab. 2017;102(3):709–757

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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 90th 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 90th 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 pigmentary 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 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
Ireland: HPRA Pharmacovigilance, www.hpra.ie
Adverse events should also be reported to Rhythm Pharmaceuticals Netherlands B.V., Radarweg 29, 1043NX Amsterdam, Netherlands.
Tel: +31 20 8546071.

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