Pr IMCIVREE®
setmelanotide injection

IMCIVREE (setmelanotide solution for subcutaneous injection) is indicated for weight management in adult and pediatric patients 6 years of age and older with obesity due to Bardet-Biedl syndrome (BBS).[1]

IMCIVREE

The **first and only** treatment to target an impaired MC4R pathway, a root cause of genetic obesity in people with **Bardet-Biedl Syndrome (BBS)** aged 6 and older.[1]

IDENTIFYING OBESITY DUE TO BBS IN YOUR PATIENTS

BARDET-BIEDL SYNDROME (BBS) IS A RARE GENETIC DISEASE[2]

IT AFFECTS ABOUT 1 IN 140,000-160,000 CANADIANS[3]

COGNITIVE IMPAIRMENT (>50%)[4]

VISUAL IMPAIRMENT (93%)[2,4]

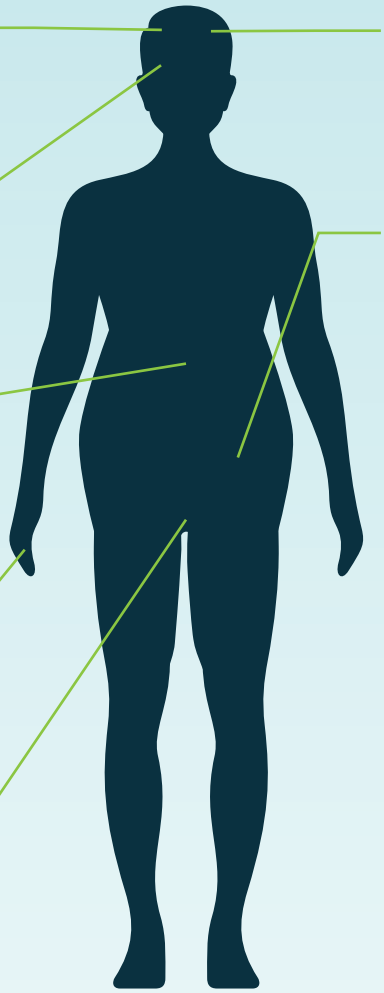
- Onset of rod-cone dystrophy presenting as atypical retinitis pigmentosa, usually between 5 and 10 years of age

OBESITY (72%-92%)[4-6]

- Typically early onset by age 5

POSTAXIAL POLYDACTYLY (63%-81%)[4]

HYPOGONADISM (59%-98%)[2]



HYPERPHAGIA (INSATIABLE HUNGER)[7]

- Severe preoccupation with food
- Excessive food-seeking behaviour

RENAL ANOMALIES (53%)[2,4,8]

- Generally involves cystic tubular disease and anatomical malformations
- Renal disease is often detectable before the age of 10, and in some cases before age 1

Additional clinical features of BBS may include:[2,9]

- Speech delay
- Developmental delay
- Diabetes mellitus
- Congenital heart disease
- Dental anomalies
- Brachydactyly/syndactyly
- Ataxia/poor coordination
- Anosmia/hyposmia

BBS HAS A HIGHLY VARIABLE PHENOTYPE WITH COMMON FEATURES THAT EVOLVE OVER TIME[2,10,11]

	Birth	First years of life (0-5 years)	Early childhood (>5 years)
Renal anomalies[2,9,12]	Anatomical malformations	Progressive kidney disease	Polyuria/polydipsia
Visual impairment[2,13]			Progressive vision loss Night blindness
Postaxial polydactyly[2,9,14-16]	Extra digits (postaxial)	Typically surgically removed	
Obesity[2,6,7]	Normal birth weight	Rapid weight gain Unusual food seeking	Severe obesity Behaviours persist
Cognitive impairment[2,17]		Developmental delay	Learning difficulties

Most common clinical features	Clinical manifestations	
Renal anomalies[2,8,12,17-19] Renal anomalies can be a major cause of morbidity and mortality in BBS, and chronic kidney disease (CKD) may present in patients <10 years of age.	• Cystic tubular disease • Anatomical malformations • Urinary tract abnormalities • Hypertension • Chronic renal failure • Transplantation • Polyuria/polydipsia	• Chronic tubulointerstitial nephritis • Glomerular defects • Urinary concentrating defects • Anatomical malformations at birth, including parenchymal cysts, calyceal cysts, calyceal clubbing and blunting, horseshoe kidney, fetal lobulation, scarring, unilateral renal agenesis, dysplastic kidneys, bladder obstruction, hydronephrosis, ectopic kidney, renal calculi, and vesicoureteral reflux
Visual impairment[2,17,20,21] Symptoms usually develop in the first decade of life, and most patients are legally blind by the second/third decade.	• Rod-cone dystrophy/retinitis pigmentosa (RP) • Night blindness – Photophobia – Legal blindness – Diminution of colour • Optic atrophy	• Overall loss of visual acuity – Strabismus – Astigmatism – Cataracts – Colour blindness – Macular edema and degeneration
Hyperphagia[7,22,23] Presents at <5 years of age.	• Pathological, insatiable hunger • Long time to satiation • Shorter duration of satiation	• Prolonged feeling of hunger • Severe preoccupation with food and distress if denied food
Obesity[2,24-27] Presents at <5 years of age.	• Early-onset truncal obesity • Normal birth weight, followed by rapid weight gain	
Cognitive impairment[9,17] Learning difficulties and developmental delays present in school-aged patients.	• Developmental delay (gross motor, fine motor, speech/language) • Mild to moderate learning difficulties • Speech delays, poor articulation, poor language interpretation	• Behavioural problems (immaturity, frustration, obsessive/compulsive nature, poor concentration/hyperactivity) • Gaze avoidance • Lack of abstract thought
Limb abnormalities[2,14,16] Extra fingers and/or toes can be seen at birth and are typically surgically removed in early childhood (>5 years of age).	• Postaxial polydactyly • Brachydactyly • Syndactyly	
Genitourinary abnormalities[2,9,17,20] May be apparent at puberty.	**In males:** • Hypogonadism • Micropenis, small-volume testes, maldescent of testes, cryptorchidism, hypogonadotropic hypogonadism, delayed puberty, infertility	**In females:** • Uterine, fallopian, ovarian, or vaginal hypoplasia or atresia • Low fertility rates

FIRST-EVER PHASE 3 CLINICAL TRIAL MEASURING WEIGHT REDUCTION IN PATIENTS WITH BBS

In patients aged ≥12, 35.7% of patients achieved at least 10% body weight reduction at 52 weeks[1*]

In patients aged ≥18 years, there was a ~9.1% mean percent change in BMI after 1 year (n=15)[28‡]

In patients aged 6 to <18 years, there was a 9.5% mean percent change in BMI after 1 year (n=16)[28†]

Key secondary endpoint: there was a 2.1 point reduction in mean hunger score at week 52[29§]

In patients aged <18 with BBS, IMCIVREE was associated with early, significant, and sustained reduction in BMI Z-score (exploratory endpoint).[28]

* 95% CI:¶ 18.6, 55.9. † Standard deviation 6.4. ‡ Standard deviation 6.8. § Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible").[2] ¶ Estimated % and 95% CI are based on Rubin's Rule. CI = confidence interval.

SAFETY INFORMATION

Clinical Use:

Limitations of Use: Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign.
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, or BBS including obesity associated with other genetic syndromes and general (polygenic) obesity.

Geriatrics: Clinical studies of IMCIVREE in the approved indications did not include patients aged 65 and over. It is not known whether geriatric patients would respond differently than younger adult patients.

Pediatrics (<6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric patients below 6 years of age. IMCIVREE contains the preservative benzyl alcohol, which has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants (see most serious warnings and precautions).

Contraindications:

Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Most serious warnings and precautions:

- **Depression or suicidal ideation:** Patients with a history of depression or suicidal ideation may be at increased risk for recurrent episodes while taking IMCIVREE. Monitor patients for new onset or worsening of depression, suicidal thoughts or behaviour, or any unusual changes in mood or behaviour. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviours or if clinically significant or persistent depression symptoms occur.
- **Disturbance in sexual arousal:** Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with IMCIVREE. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.
- **Skin pigmentation and darkening of nevi:** Generalized increased skin pigmentation occurred in the majority of patients treated with IMCIVREE in clinical trials. This effect is generally reversible upon discontinuation of the drug. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions. IMCIVREE should not be used in patients with a personal medical history or a family history of melanoma or pre-melanoma skin lesions.
- **Pediatrics:** IMCIVREE is not approved for use in neonates or infants. IMCIVREE contains the preservative benzyl alcohol, which has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants.

Other relevant warnings and precautions:

- **Pregnancy:** There are no available data with IMCIVREE in pregnant women. It is not recommended to use IMCIVREE when pregnant or while trying to get pregnant, as it has not been studied in pregnant women. Weight loss during pregnancy may harm the baby.
- **Breast-feeding:** Treatment with IMCIVREE is not recommended while breast-feeding.
- **Severe renal impairment:** Patients with severe renal impairment have a higher exposure of setmelanotide relative to patients with normal kidney function. IMCIVREE is not recommended for use in pediatric patients 6 to <12 years of age with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) or for use in patients with end stage renal disease (eGFR less than 15 mL/min/1.73 m^2). Reduce the recommended starting and target dosage of IMCIVREE in adults and pediatric patients 12 years of age and older with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2).

For more information:

Please consult the product monograph at www.rhythmtx.ca for important information relating to adverse reactions, drug interactions, and dosing information which has not been discussed in this piece. The product monograph is also available by calling us at 1-833-789-6337.

References:

1. IMCIVREE Product Monograph. Rhythm Pharmaceuticals Inc. May 4, 2023. 2. Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. 3. Bardet-Biedl Syndrome. Fighting Blindness Canada. Accessed March 31, 2023. https://www.fightingblindness.ca/eyehealth/eye-diseases/bardet-biedl-syndrome/. 4. Forsythe E et al. *Front Pediatr*. 2018. doi:10.3389/fped.2018.00023. 5. Pigeyre M et al. *Clin Sci (Lond)*. 2016;130(12):943-986. 6. Pomeroy J et al. *Pediatr Obes*. 2021;16(2):e12703. 7. Sherafat-Kazemzadeh R et al. *Pediatr Obes*. 2013;8(5):e64-e67. 8. Forsythe E et al. *J Am Soc Nephrol*. 2017;28(3):963-970. 9. Forsyth R, Gunay-Aygun M. GeneReviews®. July 14, 2003. Updated July 23, 2020. Accessed May 3, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1363. 10. Castro-Sanchez S et al. *J Med Genet*. 2015;52(8):503-513. 11. Katsanis N et al. *Hum Mol Genet*. 2001;10(20):2293-2299. 12. Putoux A et al. *Pediatr Nephrol*. 2012;27(1):7-15. 13. Weihbrecht K et al. *Med Res Arch*. 2017. doi:10.18103/mra.v5i9.1526. 14. Khan OA et al. *Cureus*. 2019;11(2):e4114. 15. Agrawal H et al. *Pediatr Rev*. 2018;39(5):e21-e23. 16. Vlahovic AM, Haxhija EQ. Pediatric and Adolescent Plastic Surgery for the Clinician. Springer; 2017:89-105. 17. Beales PL et al. *J Med Genet*. 1999;36(6):437-446. 18. Panny A et al. *J Dent Res*. 2017;96(12):1361-1369. doi:10.1177/0022034517716913. 19. Sandilands EA et al. *Br J Clin Pharmacol*. 2013;76(4):504-515. 20. Florea L et al. *Genes (Basel)*. 2021;12(9):1353. doi:10.3390/genes12091353. 21. Meng X et al. *Front Cell Dev Biol*. 2021;9:635216. doi:10.3389/fcell.2021.635216. 22. Eneli I et al. *Appl Clin Genet*. 2019;12:87-93. 23. Heymsfield SB et al. *Obesity (Silver Spring)*. 2014;22(01):S1-S17. 24. Hampl SE et al. *Pediatrics*. 2023;151(2):e202206064. 25. Styne DM et al. *J Clin Endocrinol Metab*. 2017;102(3):709-757. 26. Defining childhood weight status. Centers for Disease Control and Prevention. Accessed January 30, 2023. https://www.cdc.gov/obesity/basics/childhood-defining.html. 27. Obesity and overweight. World Health Organization. Published June 9, 2021. Accessed January 30, 2023. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. 28. Haqq AM et al. *Lancet Diabetes Endocrinol*. 2022;10(12):859-868. 29. Data on file. Rhythm Pharmaceuticals Inc.

Scan here to view IMCIVREE Product Monograph.

Rhythm® PHARMACEUTICALS

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