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:[1]

- Bardet-Biedl syndrome (BBS).
- Genetically confirmed biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency due to variants interpreted as pathogenic, likely pathogenic, or of uncertain significance.

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), POMC, PCSK1 and LEPR deficiencies** aged 6 and older.[1]

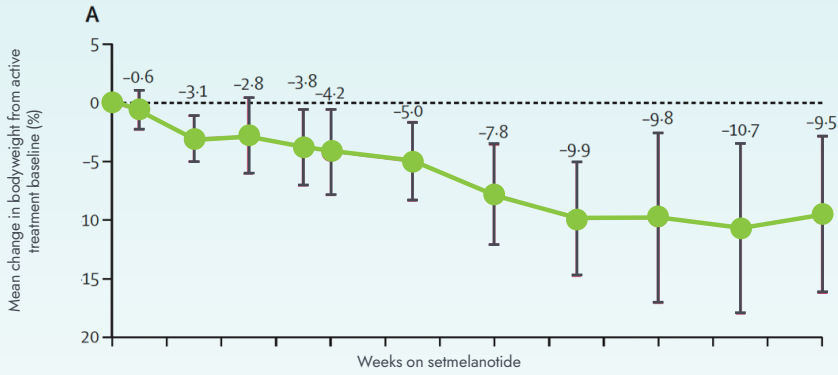
FIRST-EVER PHASE 3 CLINICAL TRIAL MEASURING WEIGHT REDUCTION IN PATIENTS WITH BBS

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)[2†]

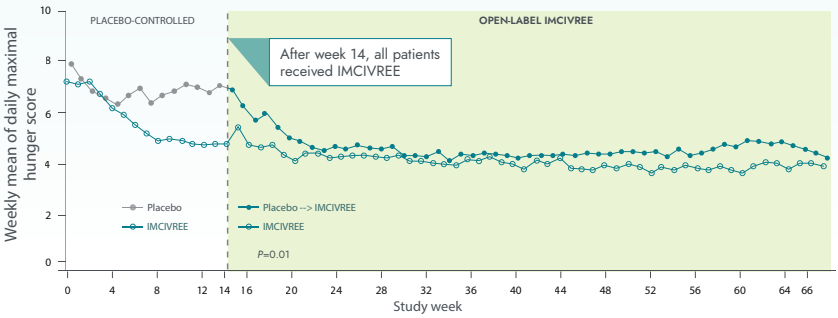
* 95% CI:‡ 18.6, 55.9. † Standard deviation 6.8. ‡ Estimated % and 95% CI are based on Rubin's Rule.
CI = confidence interval.

Key secondary endpoint: Mean percentage change in body weight in patients aged ≥18 with BBS[2*†‡] (-9.5%, SD 6.7, 95% CI [-13.7, -5.2]; p=0.0002)



* Active treatment baseline is defined as the last measurement before the first dose of IMCIVREE, i.e., week 0 for IMCIVREE group and week 14 for placebo group.[2]
† Data shown include only patients who received 52 weeks of IMCIVREE at the time of the analysis.[2]
‡ For patients aged 18 years or older, population sizes ranged from 7 to 15, with n=12 at 52 weeks on active treatment. Error bars are the standard deviation (SD).[2]

Key secondary endpoint: Hunger scores in the 14-week placebo-controlled and 52-week open-label periods[2*]



2.1-POINT REDUCTION
in mean hunger score at week 52[3]

* 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]

IN PATIENTS AGED ≥6 WITH POMC, PCSK1, OR LEPR DEFICIENCIES,

A SIGNIFICANT PROPORTION OF PATIENTS ACHIEVED ≥10% WEIGHT LOSS AT WEEK 52[1]

85.7% of POMC or PCSK1 patients achieved at least 10% weight loss from baseline at week 52 (n=14)[1*]

53.3% of LEPR patients achieved at least 10% weight loss from baseline at week 52 (n=15)[1†]

IN PATIENTS AGED ≥12 WITH POMC, PCSK1, OR LEPR DEFICIENCIES,

IMCIVREE DELIVERED IMPROVEMENT IN HUNGER SCORES FROM BASELINE AT 1 YEAR[4]

27.1% mean reduction in hunger score in patients with POMC or PCSK1 deficiencies (n=7)[4]

43.7% mean reduction in hunger score in patients with LEPR deficiency (n=7)[4]

* 90% CI:‡ 61.46, 97.40; p<0.0001.
† 90% CI:‡ 30.00, 75.63; p<0.0001.
‡ Two-sided confidence interval (CI) obtained using Clopper-Pearson method and one-sided p-value obtained from exact binomial test, testing that at least 5% of patients in the population of interest would achieve 10% weight loss.[1]

ONCE-DAILY, SUBCUTANEOUS INJECTION THAT CAN BE ADMINISTERED AT HOME[1]

Titrate IMCIVREE to the recommended dose

In patients aged ≥18 years:

- The starting dose of setmelanotide is 1 mg (0.1 mL) injected subcutaneously (SC) once daily (QD) for 2 weeks.
- Monitor patients for gastrointestinal (GI) adverse reactions to adjust dosage.
- The dose may be increased by 0.5 mg daily every 2 weeks if tolerated to a maximum dose of 3.0 mg daily.
- If the starting dose is not tolerated, IMCIVREE should be discontinued.

IMCIVREE should be administered once daily, at the beginning of the day, without regard to meals – there is no food requirement for administration.[1]

No dose adjustments are needed for patients with mild to moderate renal impairment.[1]

For adults and pediatric patients 12 years of age and older with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2):[1]

- The starting dose of setmelanotide is 0.5 mg (0.05 mL) injected subcutaneously QD for 2 weeks. Monitor patients for GI adverse reactions.
- The dose may be increased by 0.5 mg daily every 2 weeks if tolerated to a maximum of 1.5 mg daily.
- If the starting dose is not tolerated, IMCIVREE should be discontinued.

IMCIVREE is not recommended for use in pediatric patient 6 to < 12 years of age with severe renal impairment or for use in patients with end stage renal disease.[1]

Dosing considerations:

- IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic aetiology.
- IMCIVREE should be administered once daily, at the beginning of the day, without regard to meals.
- Select patients for treatment with IMCIVREE who have genetically determined deficiency of POMC, PCSK1, or LEPR or clinical diagnosis of BBS.
- Assess response to IMCIVREE therapy regularly.
- **In patients with BBS,** evaluate weight loss after 22 weeks of treatment. If a patient has not lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential, discontinue IMCIVREE as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
- **In patients with POMC, PCSK1, or LEPR deficiency,** evaluate weight loss after 12 to 16 weeks of treatment. If a patient has not lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential, discontinue IMCIVREE as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

WELL ESTABLISHED SAFETY AND TOLERABILITY PROFILE

Adverse reactions occurring in ≥5% of IMCIVREE-treated patients in the BBS clinical trial[1]

	IMCIVREE (n=43)*
Hyperpigmentation disorders†	63%
Injection site reactions‡	51%
Nausea	26%
Spontaneous penile erection§	25%
Vomiting	19%
Diarrhea	14%
Melanocytic naevus	14%
Headache	7%
Skin striae	7%
Aggression	5%
Fatigue	5%

* 43 patients were treated with at least 1 dose of IMCIVREE; 1 patient initially randomized to placebo withdrew from the study prior to receiving IMCIVREE and is not included.
† Includes skin hyperpigmentation, hair colour changes, melanoderma, melanocytic nevus.
‡ Includes injection site erythema, pruritus, induration, pain, bruising, edema, reaction, hemorrhage, irritation, mass.
§ n = 20 male patients.

Adverse reactions occurring in ≥5% of IMCIVREE-treated patients in the POMC, PCSK1, and LEPR deficiency clinical trials[1]

	IMCIVREE (n=30)*
Injection site reaction*	90%
Skin hyperpigmentation†	57%
Nausea	53%
Headache	50%
Diarrhea	40%
Spontaneous penile erection‡	40%
Abdominal pain§	33%
Vomiting	33%
Back pain	30%
Melanocytic naevus	30%
Fatigue	27%
Depression‖	23%
Asthenia	23%
Dizziness	17%
Vertigo	13%
Dry mouth	13%
Chills	10%
Anxiety	10%
Alopecia	10%
Erythema	7%
Hyperhidrosis	7%
Rash papular	7%

* Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discolouration.
† Includes skin hyperpigmentation, melanocytic naevus, and pigmentation disorders.
‡ n = 15 male patients.
§ Includes abdominal pain and upper abdominal pain.
‖ Includes depression and depressed mood.

Scan here to view IMCIVREE Product Monograph.

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. Haqq AM et al. Lancet Diabetes Endocrinol. 2022;10(12):859-868. 3. Data on file. Rhythm Pharmaceuticals Inc. 4. Clément K et al. Lancet Diabetes Endocrinol. 2020;8(12):960-970.

Rhythm® PHARMACEUTICALS

PrIMCIVREE® setmelanotide injection