PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**IMCIVREE®**

setmelanotide injection

Solution, 10 mg/mL setmelanotide (as setmelanotide acetate), Subcutaneous

Sterile

Anti-obesity Agent

Manufacturer:

Rhythm Pharmaceuticals, Inc.
222 Berkeley Street
Suite 1200
Boston, MA 02116
United States

Imported and Distributed By:

Q&C Services
2000 Argentia Road Plaza 2
Suite 220
Mississauga, ON L5N 1V8
Canada

Date of Initial Authorization:
May 5, 2023

Submission Control Number: 268412

RECENT MAJOR LABEL CHANGES

None at time of authorization.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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)
- 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

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

1.1 Pediatrics

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.

Pediatrics (6 to 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of IMCIVREE in pediatric patients (6 to 17 years of age) have been established. Therefore, Health Canada has authorized an indication for pediatric use (see 1 INDICATIONS).

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 7 WARNINGS AND PRECAUTIONS).

1.2 Geriatrics

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

2 CONTRAINDICATIONS

IMCIVREE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 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 (see 14 CLINICAL TRIALS).
- 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.
- In pediatric patients, evaluate the impact of weight loss on growth and maturation.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Patients 18 years of age and older

- 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.

Patients from 6 to 17 years of age

- The starting dose of setmelanotide is 0.5 mg (0.05 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 2.0 mg daily.
- If the starting dose is not tolerated, IMCIVREE should be discontinued.

Dosage Adjustment

Mild to Moderate Renal Impairment

No dose adjustments are needed for patients with mild (estimated glomerular filtration rate [eGFR] of 60-89 mL/min/1.73 m^2) or moderate (eGFR of 30 to 59 mL/min/1.73 m^2) renal impairment.

Severe Renal Impairment

Adults and Pediatric Patients 12 Years of Age and Older

For patients with eGFR 15 to 29 mL/min/1.73 m^2:

- 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.

The use of IMCIVREE in pediatric patients from 6 to 11 years of age with severe renal impairment is not recommended.

Hepatic impairment

Data are not available in patients with any degree of hepatic impairment. IMCIVREE is not recommended in these patients.

4.4 Administration

- Prior to initiation of IMCIVREE, train patients or their caregivers on proper injection technique. Instruct patients to use a 1-mL syringe with a 28- or 29-gauge needle appropriate for subcutaneous injection for doses 0.5 mg to 3 mg.
- Remove IMCIVREE from the refrigerator approximately 15 minutes prior to administration. Alternatively, warm IMCIVREE prior to administration by rolling the vial gently between the palms of the hands for 60 seconds.
- Inspect IMCIVREE visually before use. It should appear clear to slightly opalescent, colorless to slightly yellow. Do not use if particulate matter or discoloration is seen.
- Administer IMCIVREE once daily, at the beginning of the day, without regard to meals.
- Inject IMCIVREE subcutaneously in the abdomen each day. Do not administer IMCIVREE intravenously or intramuscularly.
- See detailed Instructions for Use at the end of the Patient Medication Information.

4.5 Missed Dose

If a dose is missed, resume the once daily regimen as prescribed with the next scheduled dose.

5 OVERDOSAGE

In the event of overdose, appropriate supportive treatment (e.g., monitoring of heart rate and blood pressure) should be initiated according to the patient's clinical signs and symptoms.

While data on overdosage is limited, it is expected that symptoms of setmelanotide overdose would be consistent with adverse events observed in patients in the clinical trials (see 8 ADVERSE REACTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution, 10 mg/mL setmelanotide (as setmelanotide acetate) in a 1 mL multiple-dose vial.	**Benzyl alcohol** (preservative), carboxymethylcellulose sodium, edetate disodium dihydrate (EDTA), mannitol, mPEG-2000-DSPE, nitrogen, phenol (preservative), water for injection. May contain hydrochloric acid and sodium hydroxide to adjust pH.

7 WARNINGS AND PRECAUTIONS

General

IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including IMCIVREE. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (IMCIVREE contains 10 mg of benzyl alcohol per mL).

Psychiatric

Depression and suicidal ideation

IMCIVREE may cause depression or suicidal ideation. Depression and suicidal ideation occurred in adults and pediatric patients in IMCIVREE clinical studies (see 8 ADVERSE REACTIONS). Some cases of depression and suicidal ideation or behaviour that occurred in clinical studies were serious. 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.

Reproductive Health:

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 (see 8 ADVERSE REACTIONS).

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

Skin pigmentation and darkening of nevi

Generalized increased skin pigmentation occurred in the majority of patients treated with IMCIVREE in clinical trials (see 8 ADVERSE REACTIONS). IMCIVREE may also cause darkening of pre-existing nevi due to its pharmacologic effect. Melanocytic nevi were observed in all pivotal studies (30% of patients in Study 1 and Study 2 combined and 14% of patients in Study 3). 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.

7.1 Special Populations

7.1.1 Pregnant Women

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.

Patients who are pregnant should also be advised of the potential risk from the preservative benzyl alcohol.

Benzyl alcohol is rapidly metabolized by a pregnant woman, thus benzyl alcohol exposure in the fetus is unlikely. However, its metabolite benzoic acid might accumulate over time and cause metabolic acidosis. Adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs (see 7 WARNINGS AND PRECAUTIONS).

In animal reproductive studies, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-fetal effects. Setmelanotide was not teratogenic in two species (rats and rabbits) (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

Treatment with IMCIVREE is not recommended while breastfeeding.

IMCIVREE from multiple-dose vials contains the preservative benzyl alcohol. Because benzyl alcohol is rapidly metabolized by a lactating woman, benzyl alcohol exposure in the breastfed infant is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs (see 7 WARNINGS AND PRECAUTIONS).

There is no information on the presence of setmelanotide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. However, setmelanotide was present in the milk of female rats (see 16 NON-CLINICAL TOXICOLOGY). It is therefore likely that the drug will be present in human milk.

7.1.3 Pediatrics

IMCIVREE has been approved for use in pediatric patients aged 6 to 17 years of age (see 1 INDICATIONS, 1.1 Pediatrics).

The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 6 years old.

Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and low birth weight infants who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (IMCIVREE contains 10 mg of benzyl alcohol) (7 WARNINGS AND PRECAUTIONS).

7.1.4 Geriatrics

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

7.1.5 Renal Impairment

The recommended dosage in patients with mild (eGFR of 60-89 mL/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 mL/min/1.73 m^2) is the same as those with normal kidney function (see 4.2 Recommended Dose and Dosage Adjustment and 10 CLINICAL PHARMACOLOGY).

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 patient 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) (see 4.2 Recommended Dose and Dosage Adjustment and 10 CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the pivotal studies, the most common adverse reactions (≥ 10%) among setmelanotide-treated patients were injection site reactions, skin hyperpigmentation, spontaneous penile erection, nausea, headache, diarrhea, abdominal pain, vomiting, melanocytic nevus, back pain, fatigue, depression, asthenia, dizziness, and dry mouth.

Subjects in the pivotal studies experienced serious adverse reactions of depression and suicidal ideation.

One patient discontinued setmelanotide treatment in the pivotal studies due to an occurrence of Grade 1 eosinophilia.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

POMC, PCSK1, and LEPR Deficiency

The safety of IMCIVREE was evaluated in two 52-week, open-label clinical studies of 30 patients with obesity due to POMC, PCSK1, or LEPR deficiency (Study 1 and Study 2) (see 14 CLINICAL TRIALS).

Table 2 summarizes the adverse reactions that occurred in the open-label studies during the first 52 weeks of treatment in more than 10% of patients treated with IMCIVREE.

Table 2: Adverse Reactions Occurring in ≥ 5% of IMCIVREE-Treated Patients with Obesity due to POMC, PCSK1, or LEPR Deficiency in Open-Label Clinical Studies of 52-Week Duration (Study 1 and Study 2)

System Organ Class Preferred Term	IMCIVREE n = 30 n (%)
Ear and labyrinth disorders	
Vertigo	4 (13)
Gastrointestinal disorders	
Nausea	16 (53)
Abdominal pain[1]	10 (33)
Vomiting	10 (33)
Diarrhea	6 (40)
Dry mouth	4 (13)
General disorders and administrative site conditions	
Injection site reaction[2]	27 (90)
Fatigue	8 (27)
Asthenia	7 (23)
Chills	3 (10)
Musculoskeletal and connective tissue disorders	
Back pain	9 (30)
Nervous system disorders	
Headache	15 (50)

System Organ Class Preferred Term	IMCIVREE n = 30 n (%)
Dizziness	5 (17)
Psychiatric disorders	
Depression[3]	7 (23)
Anxiety	3 (10)
Reproductive system and breast disorders	
Spontaneous penile erection[4]	6 (40)
Skin and subcutaneous tissue disorders	
Skin hyperpigmentation[5]	17 (57)
Melanocytic nevus	9 (30)
Alopecia	3 (10)
Erythema	2 (7)
Hyperhidrosis	2 (7)
Rash papular	2 (7)

[1] Includes abdominal pain and upper abdominal pain
[2] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration
[3] Includes depression and depressed mood
[4] n = 15 male patients
[5] Includes skin hyperpigmentation and pigmentation disorders

Bardet-Biedl Syndrome

The safety of IMCIVREE was evaluated in a clinical study, which included a 14-week, randomized, double-blind, placebo-controlled period followed by a 52-week open-label, treatment period, in 44 patients with obesity and a clinical diagnosis of BBS (Study 3) (see 14 CLINICAL TRIALS). The study duration was 66 weeks.

During the 14-week placebo-controlled period in Study 3, the most common reported adverse reactions in IMCIVREE-treated patients when compared to placebo-treated patients were hyperpigmentation disorders (67% vs 0%, respectively) and vomiting (11% vs 0%, respectively).

Adverse reactions were also evaluated during the 52-week active-treatment period, defined as the period from randomization to Week 52 in patients initially randomized to IMCIVREE, and from Week 14 to Week 66 in patients initially randomized to placebo. Table 3 summarizes the adverse reactions that occurred in 2 or more IMCIVREE-treated patients in Study 3 during the 52-week active treatment period.

Table 3: Adverse Reactions Occurring in ≥ 5% of IMCIVREE-Treated Patients with Obesity and a Clinical Diagnosis of BBS During the 52-week Active-Treatment Period from the Start of IMCIVREE Treatment (Study 3)

System Organ Class Preferred Term	IMCIVREE n = 43[1] n (%)
Gastrointestinal disorders	
Nausea	11 (26)
Vomiting	8 (19)
Diarrhea	6 (14)
General disorders and administrative site conditions	
Injection Site Reactions[2]	22 (51)
Fatigue	2 (5)
Nervous system disorders	
Headache	3 (7)
Psychiatric disorders	
Aggression	2 (5)
Reproductive system and breast disorders	
Spontaneous penile erection[3]	5 (25)
Skin and subcutaneous tissue disorders	
Hyperpigmentation Disorders[4]	27 (63)
Melanocytic nevus	6 (14)
Skin striae	3 (7)

[1] 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
[2] Includes injection site erythema, pruritis, induration, pain, bruising, edema, reaction, hemorrhage, irritation, mass
[3] n = 20 male patients
[4] Includes skin hyperpigmentation, hair color changes, melanoderma

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatric patients were included in the pivotal studies with setmelanotide. The observed safety profile is consistent in children and adults.

8.3 Less Common Clinical Trial Adverse Reactions

POMC, PCSK1, and LEPR Deficiency (occurring in <5% of Patients in Study 1 and Study 2)

Blood and Lymphatic System Disorders: eosinophilia
Cardiac Disorders: cardiac flutter

Gastrointestinal Disorders: abdominal discomfort, gingival discolouration
General Disorders and Administration Site Conditions: malaise, oedema temperature intolerance, xerosis
Hepatobiliary Disorders: cholelithiasis, cholestasis, hepatocellular injury
Injury, Poisoning and Procedural Complications: accidental overdose, ligament sprain
Investigations: blood bilirubin increased, blood luteinising hormone increased, blood uric acid increased, insulin tolerance test abnormal
Metabolism and Nutrition Disorders: decreased appetite, vitamin A deficiency, vitamin D deficiency
Musculoskeletal and Connective Tissue Disorders: muscle spasms, musculoskeletal chest pain, musculoskeletal pain, neck pain
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): eye naevus
Nervous System Disorders: parosmia, sciatica, sleep paralysis, syncope
Psychiatric Disorders: affect lability, fear of injection, insomnia, restlessness, suicidal ideation
Renal and Urinary Disorders: haematuria, renal colic, renal failure
Reproductive System and Breast Disorders: dysmenorrhea, erection increased, metrorrhagia, vaginal haemorrhage
Skin and Subcutaneous Tissue Disorders: lentigo, lipodystrophy acquired, skin hypopigmentation, skin striae, urticaria
Vascular Disorders: flushing

Bardet-Biedl Syndrome (occurring in <5% of Patients in Study 3)

Cardiac Disorders: bradycardia
Endocrine Disorders: precocious puberty
Eye Disorders: Visual Impairment
Gastrointestinal Disorders: abdominal pain, gastroesophageal reflux disease
Investigations: blood creatine increased, eosinophil count increased
Metabolism and Nutrition Disorders: decreased appetite, hunger, increased appetite
Musculoskeletal and connective tissue disorders: muscle spasms, myalgia, pain in extremity
Neoplasms benign, malignant and unspecified (incl cysts and polyps): melanocytic naevus
Nervous System Disorders: disturbance in attention, dizziness, hyperaesthesia, hypokinesia, tremor
Psychiatric Disorders: disturbance in sexual arousal, libido increased, sexually inappropriate behaviour
Reproductive and Breast Disorders: Menorrhagia
Skin and Subcutaneous Tissue Disorders: dry skin, eczema, hair colour changes, melanoderma, rash
Vascular Disorders: hot flush

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Pediatric patients were included in the pivotal studies with setmelanotide. The observed safety profile is consistent in children and adults.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

No clinically relevant changes in laboratory findings were observed.

Post-Market Findings

Not applicable.

8.5 Post-Market Adverse Reactions

No significant new safety findings which alter the characterization of previously recognized important identified risks, important potential risks, or missing information have been identified.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No clinical studies evaluating the drug-drug interaction potential of setmelanotide have been conducted.

9.4 Drug-Drug Interactions

Setmelanotide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and transporters. Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Setmelanotide is a MC4 receptor agonist. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity related to the Leptin-Melanocortin pathway associated with insufficient activation of the MC4 receptor, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

10.2 Pharmacodynamics

Skin Hyperpigmentation

Setmelanotide is a MC4 receptor agonist with off-target activity at the melanocortin 1 (MC1) and melanocortin 3 (MC3) receptors. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light. Setmelanotide activates the MC1 receptor and potentially causes skin hyperpigmentation.

10.3 Pharmacokinetics

The mean steady state setmelanotide $C_{max,ss}$, AUC_{tau}, and trough concentration for a 3-mg dose administered once daily by subcutaneous injection to otherwise healthy subject with obesity (N=6) was 37.9 ng/mL, 495 h*ng/mL, and 6.77 ng/mL, respectively. Steady-state plasma concentrations of setmelanotide were achieved within 2 days with daily dosing of 1-3 mg setmelanotide. The accumulation of setmelanotide in the systemic circulation during once-daily dosing over 12 weeks was approximately 30%. Setmelanotide AUC and C_{max} increased dose-proportionally following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

Table 4: Summary of Setmelanotide Pharmacokinetic Parameters in Otherwise Healthy Subjects with Obesity

Dose	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng*h/mL)	$t_{½}$ (h)	C_{trough} (ng/mL)
3.0 mg QD	37.9 (14.0)	8.00 (3.00-9.00)	495 (16.8)	7.11 (14.1)	6.77 (38.0)

Note: Values are presented as mean (CV%) except t_{max}, which is presented as median (min, max).

Absorption

After subcutaneous injection of IMCIVREE, steady-state plasma concentrations of setmelanotide increased slowly and reached maximum concentrations at a median t_{max} of 8 h after dosing. The absolute bioavailability following subcutaneous injection of setmelanotide has not been investigated in humans.

Distribution

The mean apparent volume of distribution of setmelanotide after subcutaneous injection of IMCIVREE 3 mg once daily was estimated from the population pharmacokinetics model to be 48.7 L. Protein binding of setmelanotide is 79%.

In vitro experiments indicate that setmelanotide is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. In vitro data indicate that setmelanotide is very unlikely a P-gp or BCRP substrate.

Metabolism

Setmelanotide did not appear to be metabolised by rat, monkey, or human hepatic microsomes or hepatocytes, or kidney microsomes. Setmelanotide is stable in human, rat, and monkey hepatocytes. Setmelanotide is expected to be metabolized into small peptides by catabolic pathways.

Elimination

The effective elimination half-life ($t_{½}$) of setmelanotide was approximately 11 hours. The total apparent steady state clearance of setmelanotide following subcutaneous injection of IMCIVREE 3 mg once daily was estimated from the population PK model to be 4.86 L/h.

Excretion

Approximately 39% of the administered setmelanotide dose was excreted unchanged in urine during the 24-hour dosing interval following subcutaneous injection of 3 mg once daily in otherwise healthy obese subjects.

Special Populations and Conditions

No clinically significant differences in the pharmacokinetics of setmelanotide were observed based on sex or disease. The effect of age 65 years or older, pregnancy, or hepatic impairment on the pharmacokinetics of setmelanotide is unknown.

- **Pediatrics** IMCIVREE has been evaluated in pediatric patients aged 6 to less than 12 years and aged 12 to less than 17 years. Simulations from the population pharmacokinetic analyses suggest that AUC and C_{max} are 100% and 92% higher in pediatric patients 6 to less than 12 years as compared to patients greater than or equal to 17 years. For patients aged 12 to less than 17 years, the setmelanotide AUC and C_{max} were 44% and 37% higher, respectively as compared to patients greater than or equal to 17 years.

- **Renal Insufficiency** Exposure parameters, AUC0-t and AUC0-inf, were approximately 13%-15%, 34%-35%, and 86%-96% higher for patients with mild, moderate, and severe renal impairment, respectively, as compared to patients with normal renal function. Pharmacokinetic analysis showed a 12%, 26%, and 49% lower clearance (CL/F) of setmelanotide in patients with mild, moderate, and severe renal impairment, respectively, as compared to patients with normal renal function.

  Renal impairment did not appear to affect plasma protein binding. The average fraction unbound (f_u) was approximately 0.21 and was independent of renal function status.

11 STORAGE, STABILITY AND DISPOSAL

IMCIVREE injection is supplied as:

- 10 mg/mL, clear to slightly opalescent, colorless to slightly yellow solution in a 1-mL multiple-dose vial
- Package of 1 multiple-dose vial

Store unopened IMCIVREE vials in the refrigerator at 2°C to 8°C in the original carton. After removal from the refrigerator, vials may be kept at temperatures ranging from refrigerated to room temperature (2°C to 30°C) for up to 30 days. After the vial is punctured (opened), discard after 30 days. See Table 5 for a summary of storage conditions for IMCIVREE. Store vials in the original carton.

Table 5: Recommended Storage for IMCIVREE Vials

Storage Condition	Unopened Vial	Opened Vial
2°C to 8°C	Until the expiration date	Up to 30 days, OR Until the expiration date (whichever is earlier)
2°C to 30°C[1]	Up to 30 days, OR Until the expiration date (whichever is earlier)	Up to 30 days, OR Until the expiration date (whichever is earlier)
>30°C	Discard and do not use	Discard and do not use

[1] If necessary, IMCIVREE may be stored at room temperature (≤30°C) and then returned to refrigerated conditions

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

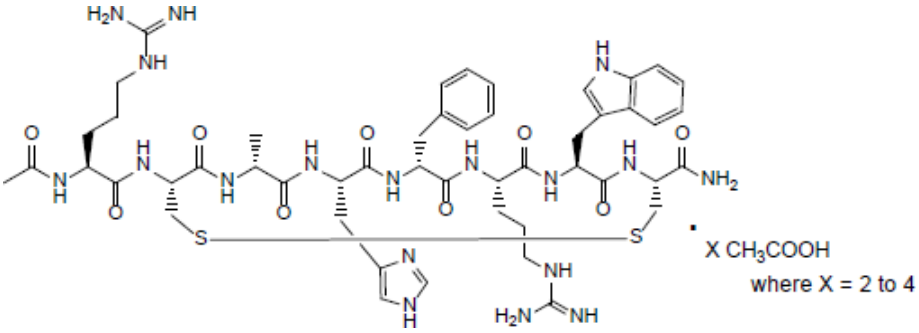
Drug Substance

Proper/common name: setmelanotide acetate

Chemical name: acetyl-L-arginyl-L-cysteinyl-D-alanyl-L- histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-cysteinamide cyclic (2→8)-disulfide acetate

Molecular formula and molecular mass: $C_{49}H_{68}N_{18}O_9S_2$ (anhydrous, free-base), 1117.3 Daltons (anhydrous, free-base)

Structural formula:



Physicochemical properties:

Physical form and appearance: Amorphous white to off-white powder

Hygroscopicity: Hygroscopic when assessed using dynamic vapor sorption with evidence of deliquescent behavior at humidity >70%RH

UV Absorption: Maximum absorption at 220 nm with smaller absorption peak centred at 279 nm

logD (octanol/PBS buffer pH 7.4): -0.8 ± 0.2 (temperature = 22°C)

Solubility: 19.6 mg/mL (WFI at 24 hours)

Stereochemistry:

The drug substance is chiral with the octapeptide consisting of the following L and D amino acids:

Ac-L Arg^1-L Cys^2-D Ala^3-L His^4-D Phe^5-L Arg^6-L Trp^7-L Cys^8-NH_2

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

POMC, PCSK1, and LEPR Deficiency

Table 6: Summary of patient demographics for clinical trials in POMC, PCSK1, and LEPR Deficiency

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1 (POMC or PCSK1)	Open label with 8-week double blind placebo- controlled withdrawal period; Placebo	Setmelanotide; Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg in adult patients and 2.5 mg in pediatric patients) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose; SC injection	Total: 15 Pivotal: 10 Supplemental: 5	17.2 (7 to 30 years)	9 males / 6 females

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 2 (LEPR)	Open label with 8-week double blind placebo- controlled withdrawal period; Placebo	Setmelanotide; Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg in adult patients and 2.5 mg in pediatric patients) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose; SC injection	Total: 15 Pivotal: 11 Supplemental: 4	21.67 (8 to 37 years)	6 males / 9 females

The safety and efficacy of IMCIVREE for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period.

- Study 1 enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency.
- Study 2 enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency.

The studies enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or variants of unknown significance for either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). In both studies, the local genetic testing results were centrally confirmed using Sanger sequencing. Patients with double heterozygous variants in 2 different genes were not eligible for treatment with IMCIVREE. In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m^2. Weight in pediatric patients was ≥95th percentile using growth chart assessments.

IMCIVREE dose titration occurred over a 2- to 12-week period, followed by a 10-week, open- label treatment period with IMCIVREE. Patients who achieved at least a 5-kilogram weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the open-label treatment period continued into a double-blind withdrawal period lasting 8 weeks, including 4 weeks of IMCIVREE followed by 4 weeks of placebo (investigators and patients were blinded to this sequence). Following the withdrawal sequence, patients re-initiated treatment with IMCIVREE at their therapeutic dose for up to 32 weeks.

Use of IMCIVREE in children 6 to <18 years of age included 9 patients with POMC, PCSK1, or LEPR deficiency.

Primary efficacy analyses were conducted in pivotal patients only (10 in Study 1 and 11 in Study 2), with supportive data from supplemental patients.

Of the patients included in the efficacy analysis in Studies 1 and 2, 12 patients (57%) were adults, 7 patients (33%) were ≥12 to < 18 years of age, and 2 patients (10%) were from 7 to <12 years of age.

- In Study 1, 50.0% of pivotal patients were female, 70.0% were White, and the mean BMI was 40.41 kg/m^2 (range: 26.6-53.3) at baseline.
- In Study 2, 72.7% of pivotal patients were female, 90.9% were White, and the mean BMI was 48.17 kg/m^2 (range: 35.8-64.6) at baseline.

Table 7: Results of Study 1 in POMC and PCSK1 Deficiency

Primary Endpoint	Statistics	Pivotal (N=10)	Supplemental (N=4)	Total (Pivotal + Supplemental) (N=14)
Patients Achieving at Least 10% Weight Loss from Baseline at Week 52	n (%)	8 (80.0)	4 (100.0)	12 (85.7)
	90 % CI[a]	(49.31, 96.32)	(47.29, 100.00)	(61.46, 97.40)
	p-value	<0.0001	<0.0001	<0.0001

[a] 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.

Table 8: Results of Study 2 in LEPR Deficiency

Primary Endpoint	Statistics	Pivotal (N=11)	Supplemental (N=4)	Total (Pivotal + Supplemental) (N=15)
Patients Achieving at Least 10% Weight Loss from Baseline at Week 52	n (%)	5 (45.5)	3 (75.0)	8 (53.3)
	90 % CI[a]	(19.96, 72.88)	(24.86, 98.73)	(30.00, 75.63)
	p-value	<0.0001	<0.0001	<0.0001

[a] 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.

Bardet-Biedl Syndrome

Table 9: Summary of patient demographics for clinical trials in Bardet-Biedl Syndrome

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 3 (BBS)	Randomized Double-blind, Placebo-controlled followed by an open-label treatment period.	Setmelanotide or placebo; QD via SC injection for the first 14 weeks. Starting dose 2 mg with increase to 3 mg for patients ≥16 years Starting dose 1 mg with increase to 2 mg for patients ≥ 6 to <16 years of age). After the 14-week double-blind treatment period, all patients received open label setmelanotide QD via SC injection for 38 weeks; SC injection	44 (32 pivotal; 12 supplemental)	20 (6 to 46 years)	20 males / 24 females

The safety and efficacy of IMCIVREE for chronic weight management in adult and pediatric patients aged 6 years and older with obesity and a clinical diagnosis of Bardet-Biedl syndrome (BBS) were assessed in a 66-week clinical study, which included a 14-week randomized, double- blind, placebo-controlled period and a 52-week open-label period (Study 3).

The study enrolled patients aged 6 years and above with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of ≥30 kg/m^2 and pediatric patients had weight ≥97th percentile using growth chart assessments.

In Study 3, eligible patients entered a 14-week, randomized, double-blind, placebo-controlled treatment period (Period 1) in which patients received IMCIVREE or placebo, followed by a 52-week open-label treatment period (Period 2) in which all patients received IMCIVREE. To maintain the blind during Period 1, dose titration to a fixed dose of 3 mg given subcutaneously once daily was performed during the first 2 weeks of both Period 1 and Period 2.

The primary efficacy analysis in Study 3 included 2 different populations of patients ≥ 12 years of age, of which 28 pivotal patients had BBS. Of these, 15 patients (54%) were adults and 13 patients (46%)

were from ≥12 to <18 years of age. Overall, 14 (50%) of patients were female, 24 (86%) were white, and the mean BMI was 42.4 kg/m^2 (range: 24.4-61.3 kg/m^2) at baseline.

An ad-hoc analysis was conducted in the subgroup of patients with BBS.

In Study 3, 35.7% of patients with BBS aged ≥12 years met the primary endpoint of ≥10% weight loss after 1 year of treatment with setmelanotide (Table 10).

Table 10: Proportion of Patients Who Achieved ≥10% Reduction in Body Weight from Active Treatment Baseline After 52 Weeks of Active Treatment Among Patients ≥12 Years Old with BBS (Study 3)

Primary Endpoint	Statistics	Patients ≥ 12 years
>10% Reduction in Body Weight from ATB After 52 Weeks of Active Treatment	N	28
	Estimated %	35.7
	95 % CI[a]	(18.6, 55.9)

[a] Estimated % and 95% CI are based on Rubin's Rule.

14.4 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of setmelanotide or of other setmelanotide products.

One paediatric patient with BBS aged ≥12 years was confirmed positive to setmelanotide anti-drug antibodies with a very low titre.

In patients with POMC, PCSK1, or LEPR deficiency or in patients with BBS, there is insufficient information to characterize the ADA response to setmelanotide and the effects of ADA on pharmacokinetics, pharmacodynamics, safety, or effectiveness of setmelanotide products.

Patients with POMC, PCSK1, or LEPR deficiency or patients with BBS were assessed for antibodies to alpha-MSH. No patients with POMC or PSCK1 deficiency were positive for antibodies to alpha-MSH. Two adult patients with LEPR deficiency tested positive for antibodies to alpha-MSH at a single timepoint post-dose. Three adult BBS patients tested positive for antibodies to alpha-MSH prior to treatment.

Because of the limited sample size, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of setmelanotide products or consequences from these antibodies against endogenous alpha-MSH could not be determined. None of the IMCIVREE-treated patients with POMC-deficiency developed antibodies to alpha-MSH.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In repeat-dose studies, setmelanotide in mPEG-DSPE formulation was injected subcutaneously in rats (both sexes) for 26 weeks at daily doses of 3 mg/kg (up to 10-fold the MRHD of 3 mg based on AUC), and in monkeys (both sexes) for 39 weeks at doses of 3 or 1 mg/kg (up to 31-fold the MRHD based on AUC). In both species, decreased body weight correlated with decreased BW gain, which were considered related to the pharmacological activity of the drug. No notable changes in food intake were observed. Minimal vacuolation of choroid plexus epithelial cells and minimal aggregation of vacuolated macrophages were observed in the choroid plexus of rats and monkeys, respectively. These changes were considered nonadverse, adaptive responses to mPEG-DSPE. Inflammatory injection site reactions observed in both species were attributed primarily to mPEG-DSPE with possible involvement of setmelanotide at high doses. Hyperpigmentation was noted in all setmelanotide-treated groups with no microscopic changes indicative of melanocyte proliferation.

During a four-week recovery phase, in both species, rapid body weight gain was observed in the first week and was higher in setmelanotide-treated groups compared to control groups by the end of the recovery phase. The body weight gain possibly resulted from the removal of agonist activity at MC4 receptor. Vacuolation and aggregation of macrophages, mixed-cell infiltration and skin hyperpigmentation were partially resolved in the high dose groups of both species.

Special Toxicology

Interspecies discordance was observed for cardiovascular effects. Increases in heart rate and blood pressure were observed in rats and minipigs but not in primates.

Carcinogenicity: Setmelanotide in preserved mPEG-DSPE formulation was not carcinogenic in both sexes of Tg.rasH2 mice at daily doses of 10 mg/kg (up to 19-fold the MRHD of 3 mg based on AUC) when injected subcutaneously for 26 weeks. Due to lack of pro-carcinogenic concern based on non-clinical studies, a 2-year carcinogenicity study in rats was not performed.

Genotoxicity: Setmelanotide was not genotoxic at maximum tested limits. Setmelanotide was not mutagenic in an in vitro bacterial reverse mutation assay in five bacteria strains. Setmelanotide was not clastogenic in an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes, nor in an in vivo micronucleus assay in rat bone marrow after a continuous subcutaneous infusion at doses up to 200 mg/kg for 2 days.

Reproductive and Developmental Toxicology:

Fertility

In a 26-week repeat-dose study, there were no effects on the fertility of male rats following administration of setmelanotide in mPEG-DSPE formulation injected subcutaneously at daily doses of 3.0 mg/kg (up to 10-fold the daily MRHD of 3 mg based on AUC).

In a fertility and embryo-fetal development study, no effects on the fertility of female rats were observed with subcutaneous administration at daily doses of 5 mg/kg/day (up to 13-fold the daily MRHD of 3 mg based on AUC).

Embryo-fetal Development

Embryo-fetal development was evaluated in female rats administered setmelanotide subcutaneously during mating to the end of major organogenesis (14 days prior to mating to gestation day 17) at daily

doses of 0.5, 3, and 5 mg/kg (exposure up to 13-fold the daily MRHD of 3 mg based on AUC). Dose-related decreases in maternal food intake and body weight gain were observed during the premating period and during gestation. No evidence of embryo-fetal toxicity was observed.

Embryo-fetal development was evaluated in pregnant rabbits administered setmelanotide subcutaneously during organogenesis (gestation days 7 to 19) at daily doses of 0.05, 0.1 and 0.2 mg/kg resulting in clinically relevant exposures at the daily MRHD of 3 mg doses based on AUC. Increases in embryo-fetal resorptions and post-implantation losses were observed at daily doses ≥0.1 mg/kg (exposure ~0.5 fold the daily MRHD of 3 mg based on AUC) in the presence of significant maternal toxicity, and fetal body weights were 7% lower than controls at daily doses of 0.2 mg/kg.

Pre- and Postnatal Development

Pre- and post-natal development was evaluated in rats administered setmelanotide subcutaneously during organogenesis and continuing to weaning (gestation day 6 to lactation day 21) at daily doses of 0.5, 3.0 and 5.0 mg/kg (exposures up to 7-fold the human exposures at the MRHD based on AUC). Pup body weights at birth were 9% lower than controls at daily doses of 3.0 and 5.0 mg/kg (exposure ≥4-fold the daily MRHD of 3 mg based on AUC). These findings were consistent with reduced maternal body weight gain and food consumption during gestation. No adverse setmelanotide-related effects on pup survival, growth, maturation, visual function, neurobehavioural performance, or reproductive performance were observed up to the highest dose.

Dose-related setmelanotide concentrations were observed in milk 2 hours after subcutaneous injection in the preweaning phase of a pre- and post-natal development study in rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups on post- natal Day 11.

Juvenile Toxicity:
In a juvenile rat toxicity study, setmelanotide was injected subcutaneously at daily doses of 0.5, 1.5 and 3 mg/kg in mPEG-DSPE and at a dose of 15 mg/kg in saline from 7 to 55 days of age. Reduced food consumption and decreased body weight gain were considered pharmacological effects of setmelanotide. Inflammatory injection site reactions were similar to those observed in adult rats. Injection site observations included hemorrhage, mixed inflammatory cell infiltrates and myofiber degeneration/regeneration and were partially reversible following a 4-week recovery period. No systemic toxicity was observed at any dose, including no effects on sexual maturation, growth parameters, behavioral performance, learning and memory, or reproductive performance, ophthalmology, or systemic organ histopathology at doses up to 7- and 33-fold the MRHD of 3 mg for setmelanotide in mPEG-DSPE and setmelanotide in saline, respectively, based on AUC. During the recovery period, all setmelanotide-treated groups had statistically significantly higher body weight gains than controls.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrIMCIVREE®

Setmelanotide injection

Read this carefully before you start taking **IMCIVREE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMCIVREE**.

What is IMCIVREE used for?

IMCIVREE is used to manage weight in adults and children 6 years of age or older with obesity due to one of the following inherited (genetic) conditions:

- Bardet-Biedl syndrome (BBS)
- Biallelic Pro-opiomelanocortin (POMC)
- Proprotein convertase subtilisin/kexin type 1 (PCSK1)
- Leptin receptor (LEPR) deficiency

Your healthcare professional will order a genetic test to confirm POMC, PCSK1, or LEPR deficiency before you start using IMCIVREE.

How does IMCIVREE work?

Setmelanotide, the medicine in IMCIVREE is in a class of medicines called melanocortin 4 (MC4) receptor agonists. It works in the brain to promote weight loss.

What are the ingredients in IMCIVREE?

Medicinal ingredient: Setmelanotide (as setmelanotide acetate)

Non-medicinal ingredients: **Benzyl alcohol** (preservative), carboxymethylcellulose sodium, edetate disodium dihydrate (EDTA), mannitol, mPEG-2000-DSPE, nitrogen, phenol (preservative), water for injection. May contain hydrochloric acid and sodium hydroxide to adjust pH.

IMCIVREE comes in the following dosage forms:

solution: 10 mg/mL

Do not use IMCIVREE if:

- You are allergic to setmelanotide or any other ingredients in IMCIVREE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMCIVREE. Talk about any health conditions or problems you may have, including if you:

- have or have had any of the following conditions:
    - areas of darkened skin, including skin discoloration (hyperpigmentation).
    - depression, mood problems, suicidal thoughts or behaviour problems.
    - kidney or liver problems.

- are pregnant or planning to become pregnant. Losing weight while pregnant will harm your unborn baby. Your healthcare professional will stop your treatment with IMCIVREE if you become pregnant. Tell your healthcare professional if you become pregnant or think you might be pregnant during treatment with IMCIVREE.
- are breastfeeding or plan to breastfeed. It is not known if IMCIVREE passes into your breastmilk. You should not breastfeed during treatment with IMCIVREE.

Other warnings you should know about:

IMCIVREE may cause serious side effects, including:

- **sexual problems:** IMCIVREE can cause unwanted sexual reactions in both men and women. Men had erections at times other than sex (spontaneous penile erection) with IMCIVREE. If you have an erection lasting more than 4 hours, **get medical help right away.**
- **mental health problems**: IMCIVREE may cause new or worsening symptoms of depression, suicidal thoughts or behaviors, or any unusual changes in your mood or behavior. Call your healthcare professional right away if your mental health changes in unexpected ways, and if you become suicidal (think about harming or killing yourself or plan or try to do so).
- **skin problems**: IMCIVREE may change your skin color. This includes darkening of your skin or skin lesions (moles or spots on the skin), you already have. These changes happen because of how IMCIVREE works in the body and will usually go away when you stop using IMCIVREE. Your healthcare professional will check your skin before starting and during your treatment with IMCIVREE.
- See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Children:

- **do not** give IMCIVREE to children younger than 6 years old since IMCIVREE has NOT been approved for use in children below this age.
- Benzyl alcohol is a preservative in IMCIVREE. Benzyl alcohol can cause serious side effects, including death, in premature and low-birth weight infants who have received medicines that contain benzyl alcohol. **Do not** give IMCIVREE to a newborn or infant.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IMCIVREE:

No relevant drug-drug interactions are known. Inform your healthcare professional of any other medications you are taking.

How to take IMCIVREE:

Before you use **IMCIVREE**:

- use IMCIVREE exactly as prescribed by your healthcare professional.
- children should have regular growth checks to monitor weight loss and growth.
- your healthcare professional will regularly check how well IMCIVREE is working and may adjust your dose if necessary.
- If you have POMC, PCSK1, or LEPR deficiency, your healthcare professional may tell you to stop using IMCIVREE if you have not lost a certain amount of weight after 12 to 16 weeks of treatment.

- If you have BBS, your healthcare professional may tell you to stop using IMCIVREE if you have not lost a certain amount of weight after 22 weeks of treatment.

How to inject IMCIVREE:

- see the detailed instructions for use below to learn how to prepare and inject IMCIVREE.
- IMCIVREE is for injection under the skin (subcutaneous injection)
- IMCIVREE may be given by your healthcare professional, yourself or your caregiver. If you will be giving yourself the shot, your healthcare professional will teach you how to prepare and inject your dose of IMCIVREE for the first time. **Do not** try to inject IMCIVREE unless you have been trained by a healthcare professional.
- inject IMCIVREE 1 time each day when you first wake up.
- inject IMCIVREE under the skin of your belly (stomach) area.
- change the site where you give the shot each day.
- give IMCIVREE with or without food.
- only use the syringes and needles recommended by your healthcare professional for use with IMCIVREE.
- always use a new syringe and needle for each injection to prevent contamination.
- throw away used syringes and needles in a puncture-resistant, disposable sharps container as soon as you finish giving the injection.
- **do not** reuse or share your needles with other people.
- **do not** recap the needle. Recapping the needle can lead to a needle stick injury.
- keep IMCIVREE, needles, syringes, and all medicines out of the reach of children.

Usual dose:

Your healthcare professional will advise you on the right dose to inject.

Overdose:

If you, or a person you are caring for, have taken or received too much IMCIVREE, you may experience the side effects described in the below section "**What are possible side effects from using IMCIVREE?**".

If you think you, or a person you are caring for, have taken too much IMCIVREE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of IMCIVREE, inject your next dose at the regularly scheduled time the next day.

What are possible side effects from using IMCIVREE?

These are not all the possible side effects you may have when taking **IMCIVREE**. If you experience any side effects not listed here, tell your healthcare professional.

- injection site reaction (pain, redness, irritation, swelling or other problems where the shot was given)
- nausea, diarrhea, stomach (belly) pain, throwing up
- headache
- back pain
- fatigue
- weakness

- dizziness
- dry mouth

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Increased skin pigmentation or darkening of pre-existing skin lesions (mole)		X	
Depression (sad mood that won't go away) or suicidal thoughts or actions: difficulty sleeping or sleeping too much, feelings of worthlessness, guilt, helplessness or hopelessness, withdrawal from social situations, reduced libido (sex drive) and thoughts of harming or killing yourself or plan or try to do so			X
Erections lasting more than 4 hours			X
Unwanted sexual reaction (changes in sexual arousal that happen without any sexual activity)		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

unopened and **opened** vials of IMCIVREE:

- keep out of reach and sight of children.
- **do not** use after the expiry date which is stated on the carton or the vial.
- keep vials in the original carton.
- store in the refrigerator between 2°C to 8°C. If needed, unopened and opened vials may be removed from the refrigerator and stored at temperatures ranging from refrigerated to room temperature (2°C to 30°C) for up to 30 days. unopened and opened vials may be returned to the refrigerator.
- throw away:
    - **opened** vials 30 days after first opening, even if some medicine is still left. Write the date on the carton when you first open the vial.
    - **unopened** vials of IMCIVREE if it has been more than 30 days since the vial was first removed from the refrigerator.

If you want more information about IMCIVREE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.rhythmtx.ca, or by calling 1-833-789-6337.

This leaflet was prepared by Rhythm Pharmaceuticals Inc.

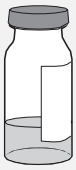
Last Revised May 5, 2023

Instructions For Use

Calculate the number of doses of IMCIVREE in each vial:

- Each unopened IMCIVREE vial contains 10 milligrams (mg) of medicine in 1 milliliter (mL) of solution.
- The vial will contain both medicine and air. Most of the vial will be filled with air.
- Your healthcare professional will determine your dose of medicine in milligrams (mg).
- The IMCIVREE vial may be used to give more than 1 dose of medicine (multiple-dose vial).
- Use Table 11 to see how many times you may use each vial based on your prescribed dose.
- **Do not** use more doses from a single vial than listed in Table 11.

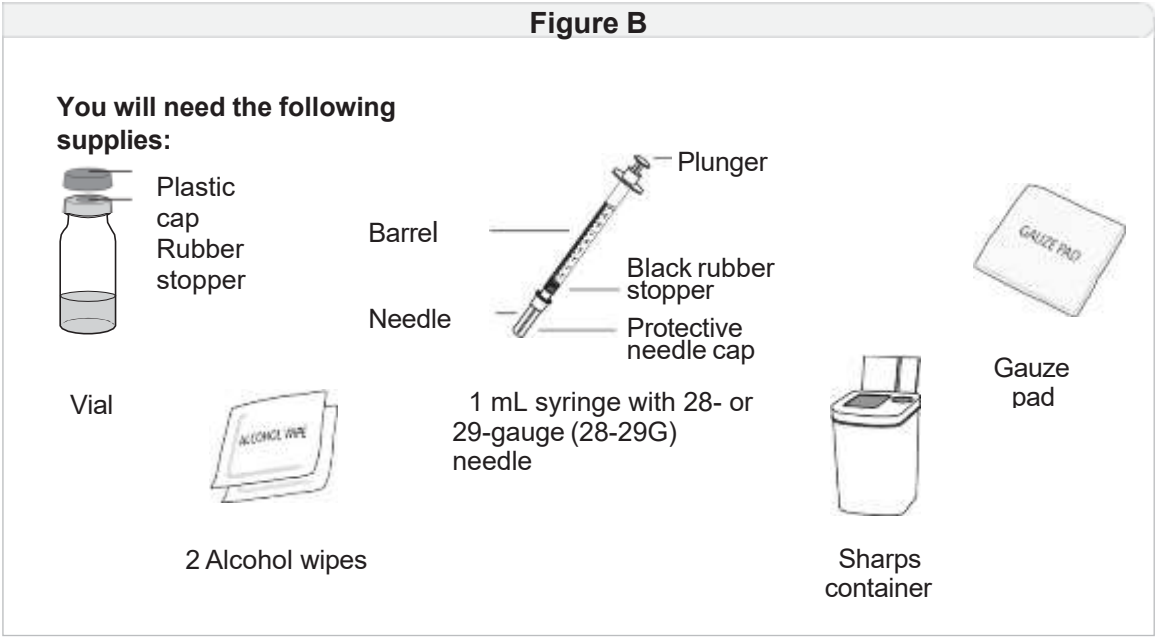
Table 11: Dose Calculation

		Prescribed dose (mg)	Prescribed dose (mL)	Number of doses per vial
Figure A 	10 mg/mL multiple dose vial	0.5 mg	0.05 mL	20
		1 mg	0.1 mL	10
		1.5 mg	0.15 mL	6
		2 mg	0.2 mL	5
		2.5 mg	0.25 mL	4
		3 mg	0.3 mL	3

Step 1 **Gather Your Supplies**

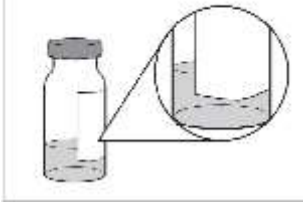
- Gather the supplies you will need for your injection (**Figure B**).
- Place your supplies on a clean, flat work surface.

Figure B



Step 2 **Check your IMCIVREE vial**

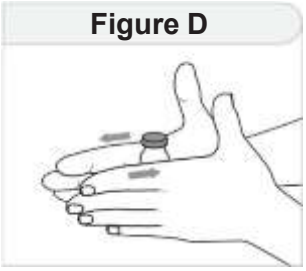
Figure C



- Check the expiration (Exp) date on the vial label (**Figure C**).
- Check the liquid. The liquid should look clear to almost clear and colorless to slightly yellow. The liquid should be free of particles.
- **Do not** use if:
  - The expiration (Exp) date has passed.
  - The liquid is cloudy.
  - There are particles floating in the vial.
  - The plastic cap on a new vial is broken or missing.

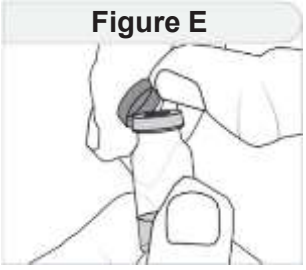
Step 3 **Prepare your IMCIVREE vial**

Figure D



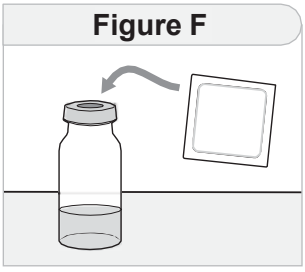
- Allow the vial to reach room temperature.
  - Remove the vial from the refrigerator 15 minutes before injection.
  - You can also warm the vial by rolling it gently between the palms of your hands for 60 seconds (**Figure D**).
- **Do not** try to warm the vial by using a heat source such as hot water or a microwave.
- **Do not** shake the vial.
- Wash your hands with soap and warm water.

Figure E



- If using a new vial, remove the plastic cap (**Figure E**) and throw away this plastic cap in the trash. Do not put the plastic cap back on the vial.

Figure F



- Clean the top of the vial rubber stopper with 1 alcohol wipe (**Figure F**). Throw away the alcohol wipe in the trash.
- **Do not** remove the vial rubber stopper.

Step 4 **Prepare the syringe**

- When measuring your dose, be sure to read the markings starting from the end closest to the black rubber stopper (**Figure G**).

FIGURE G

Use a 1 ml syringe with 0.01 ml dosing increments and a 28 to 29 gauge needle with a 6 to 13 mm needle length, suitable for injection under the skin.

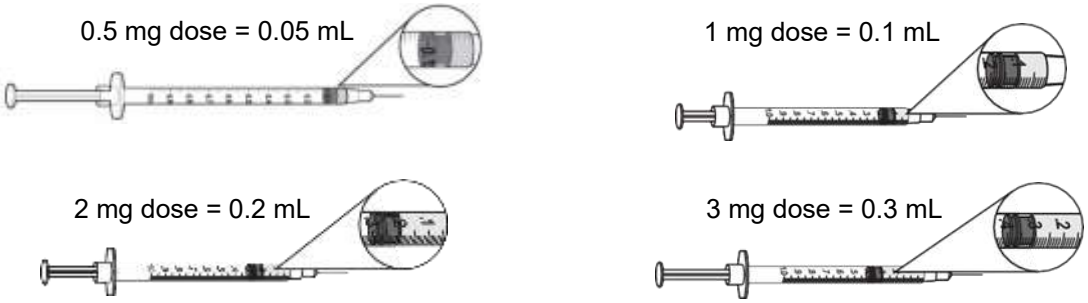
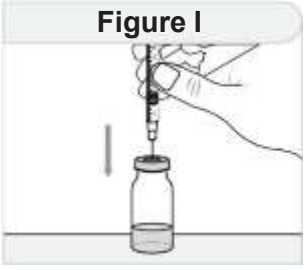


Figure H

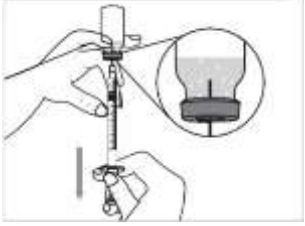
- Fill the syringe with air.
  - Keep the protective needle cap on the syringe.
  - Pull back on the plunger until the end of the black rubber stopper stops at your dose. Read the units starting from the end closest to the black rubber stopper. Fill the syringe with air equal to the amount of the medicine to be given (**Figure H**).
- Remove the protective needle cap from the syringe.
  - Remove the protective needle cap by pulling it straight off and away from your body.

Figure I



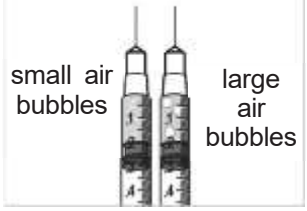
- Insert the needle.
  - Place the vial on the clean, flat work surface.
  - With the vial in the upright position, place the syringe directly over the vial and insert the needle straight down into the center of the vial rubber stopper (**Figure I**).
  - Push the air from the syringe into the vial.

Figure J



- Fill the syringe with IMCIVREE.
  - Keep the needle in the vial and slowly turn the vial upside down.
  - Make sure to keep the tip of the needle in the medicine (**Figure J**).
- Slowly pull back on the plunger to fill the syringe with the amount of IMCIVREE needed for your prescribed dose.
- Be careful not to pull the plunger out of the syringe.
- **Do not** use more than 1 vial of IMCIVREE to give a single dose. Use a new vial that has enough medicine for your prescribed dose.

Figure K



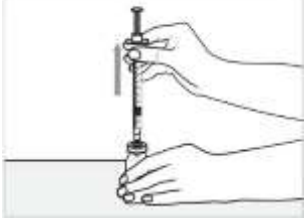
- Check for large air bubbles (**Figure K**).
  - Keep the needle in the vial and check the syringe for large air bubbles.

What to do if you see large air bubbles:

Large air bubbles can reduce the dose of medicine you receive. To remove large air bubbles:

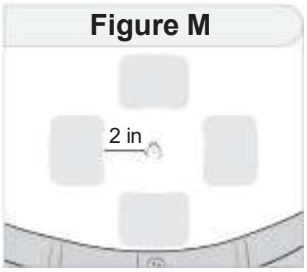
- Gently tap the side of the syringe with your finger to move the air bubbles to the top of the syringe.
- Move the tip of the needle above the medicine and slowly push the plunger up to push the large air bubbles back into the vial.
- After the large air bubbles are removed, pull back on the plunger again (more slowly this time) to fill the syringe with your prescribed dose of medicine.

Figure L



- Withdraw the needle
  - Return the vial to an upright position and place it on the clean, flat work surface.
  - While holding the vial with 1 hand and the barrel of the syringe between the fingertips of your other hand, pull the needle straight out of the vial (**Figure L**).
  - Set the syringe down on the clean, flat work surface.
- Make sure the needle does not touch the surface.
- **Do not** recap the needle

Step 5 **Prepare your injection site**



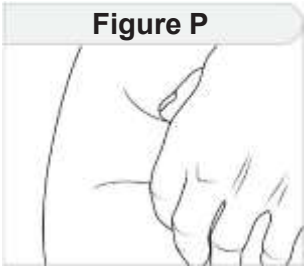
- Choose the area on the belly (abdomen) where you will give the injection (**Figure M**).
- Be sure to choose an area on the belly (abdomen) at least 2 inches from the belly button.
- **Do not** inject into the belly button, ribs, and hip bones, as well as scars or moles.
- **Do not** inject in an area that is red, swollen, or irritated.

- Clean the injection site with the second alcohol wipe using a circular motion.
- **Do not** touch, fan, or blow on the cleaned area.
- Allow the skin to dry for about 10 seconds.

Rotate your injection site each day.

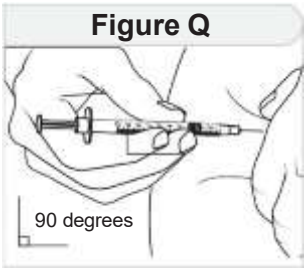
You should use a different injection site each time you give an injection, at least 1 inch away from the area you used for your previous injection. You may want to use a calendar or diary to record your injection sites.

Step 6 **Place your hands for the injection**

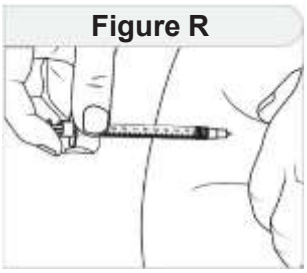


- With 1 hand, pinch about 2 inches of skin at the injection site between your thumb and index (pointer) finger (**Figure P**). Pinching the skin is important to help make sure that you inject the medicine under the skin (into fatty tissue) but not any deeper (into the muscle).

Step 7 **Inject and release**



- With your other hand, place the syringe between the thumb and index (pointer) finger.
- Hold the middle of the syringe (where the markings are printed) at a 90-degree angle to your body and push the needle straight into the injection site (**Figure Q**). Make sure that you push the needle all the way into the skin.
- **Do not** hold or push on the plunger while inserting the needle.



- Slowly push the plunger down to inject the medicine (**Figure R**)
- Keep the needle in your skin and count to 5 to make sure that all the medicine is given.
- Let go of the pinched skin and remove the needle.
- Use the gauze pad to gently apply pressure to the injection site.
- **Do not** recap the needle.

Tips for giving injections to children

When giving a child an injection, it can help to have the child do other things. Have the child:

- squeeze something soft like a ball or stuffed animal.
- slowly breathe in and out.
- sing a song, count, or name favorite colors or animals.

Last Revised May 5, 2023