CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213793Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMCIVREE safely and effectively. See full prescribing information for IMCIVREE.
IMCIVREE (setmelanotide) injection, for subcutaneous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS). (1)

Limitations of Use:

IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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 (1)
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity (1)

DOSAGE AND ADMINISTRATION

- Select patients for treatment who have genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR. (2.1)
- Treat patients with variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) in the clinical context of the patient. (2.1)
- Evaluate weight loss after 12-16 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. (2.4)
- See the Full Prescribing Information for administration instructions. (2.5)

Dosage in Adult and Pediatric Patients 12 years of age or older

- The starting dose is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for gastrointestinal (GI) adverse reactions. (2.2)
- If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 1 mg once daily dose is tolerated and additional weight loss is desired, titrate to 2 mg (0.2 mL) once daily. (2 2)
- If the 2 mg daily dose is tolerated, increase the dose to 3 mg (0.3 mL) once daily. If the 3 mg once daily dose is not tolerated, maintain administration of 2 mg (0.2 mL) once daily. (2.2)

Dosage in Pediatric Patients 6 to less than 12 years of age

- The starting dose is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for GI adverse reactions. (2.3)
- If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily dose. If the 0.5 mg once daily dose is tolerated and additional weight loss is desired, titrate to 1 mg (0.1 mL) once daily. (2.3)
- If the 1 mg dose is tolerated, increase the dose to 2 mg (0.2 mL) once daily. (2.3)
- If the 2 mg once daily dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 2 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg (0.3 mL) once daily. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL solution in a 1 mL multiple-dose vial

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- *Disturbance in sexual arousal* Spontaneous penile erections in males and sexual adverse reactions in females occurred 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. (5.1)
- *Depression and suicidal ideation* Depression and suicidal ideation have occurred with IMCIVREE. Monitor patients for new onset or worsening depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors. (5.2)
- *Skin Pigmentation and Darkening of Pre-Existing Nevi* IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions. (5.3)
- *Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in neonates and low birth weight infants* _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. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- *Lactation* not recommended when breastfeeding (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

Limitations of Use:

IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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, including obesity associated with other genetic syndromes and general (polygenic) obesity

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

- Select patients for treatment with IMCIVREE who have genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR *[see Clinical Studies (14)]*.
- Treat patients with variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) in the clinical context of the patient *[see Clinical Studies (14)]*.
- Currently available tests for the detection of variants in the *POMC*, *PCSK1*, or *LEPR* genes have not been approved or cleared by the FDA.

2.2 Dosage in Adults and Pediatric Patients 12 Years of Age and Older

- The starting dose of IMCIVREE is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for gastrointestinal (GI) adverse reactions *[see Adverse Reactions (6.1)]*.
- If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 1 mg once daily dose is tolerated and additional weight loss is desired, titrate to 2 mg (0.2 mL) once daily.
- If the 2 mg daily dose is tolerated and additional weight loss is desired, increase the dose to 3 mg (0.3 mL) once daily. If the 3 mg once daily dose is not tolerated, maintain administration of 2 mg (0.2 mL) once daily.

2.3 Dosage in Pediatric Patients 6 to less than 12 Years of Age

- For pediatric patients aged 6 to less than 12 years, the starting dose of IMCIVREE is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for GI adverse reactions *[see Adverse Reactions (6.1)]*.
- If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily. If the 0.5 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 1 mg (0.1 mL) once daily.
- If the 1 mg dose is tolerated, increase the dose to 2 mg (0.2 mL) once daily.
- If the 2 mg once daily dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 2 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg (0.3 mL) once daily.

2.4 Monitoring

- Periodically assess response to IMCIVREE therapy. In pediatric patients, evaluate the impact of weight loss on growth and maturation.
- Evaluate weight loss after 12-16 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.

2.5 Administration Instructions

- Prior to initiation of IMCIVREE, train patients on proper injection technique. Instruct patients to use a 1-mL syringe with a 28- or 29-gauge needle appropriate for subcutaneous injection.
- 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.
- 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.
- Administer IMCIVREE once daily, at the beginning of the day, without regard to meals.
- Inject IMCIVREE subcutaneously in the abdomen, thigh, or arm, rotating to a different site each day. Do not administer IMCIVREE intravenously or intramuscularly.
- If a dose is missed, resume the once daily regimen as prescribed with the next scheduled dose.

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL, clear to slightly opalescent, colorless to slightly yellow solution in a 1-mL multiple-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Disturbance in Sexual Arousal

Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males (23%) and sexual adverse reactions in females (7% in IMCIVREE-treated patients and 0% in placebo-treated patients from an unapproved population) occurred in clinical studies with IMCIVREE *[see Adverse Reactions (6.1)]*.

Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

5.2 Depression and Suicidal Ideation

Some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Patients with a history of severe depression were excluded from IMCIVREE clinical studies. Depression (26%) and suicidal ideation (11%) occurred in IMCIVREE clinical studies *[see Adverse Reactions (6.1)]*.

Monitor patients for new onset or worsening of depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

5.3 Skin Pigmentation and Darkening of Pre-Existing Nevi

IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect. Skin hyperpigmentation occurred in 21 patients (78%) of patients treated with IMCIVREE *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.1)]*. This effect is 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.

5.4 Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants

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. 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) *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Spontaneous Penile Erection *[see Warnings and Precautions (5.1)]*
- Depression and Suicidal Ideation *[see Warnings and Precautions (5.2)]*
- Skin Pigmentation and Darkening of Pre-Existing Nevi *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IMCIVREE was evaluated in two 52-week, open-label clinical studies of 27 patients with obesity due to POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance *[see Clinical Studies (14)]*.

Table 1 summarizes the adverse reactions that occurred in the open-label studies during the first 52 weeks of treatment in 3 or more patients treated with IMCIVREE.

Table 1: Adverse Reactions Occurring in 3 or More Patients Treated with IMCIVREE in Open Label Clinical Studies of 52-week Duration

	IMCIVREE-treated Patients N = 27 %
Injection site reaction [a]	96
Skin hyperpigmentation [b]	78
Nausea	56
Headache	41
Diarrhea	37
Abdominal pain [c]	33
Back pain	33
Fatigue	30
Vomiting	30
Depression [d]	26
Upper respiratory tract infection	26
Spontaneous penile erection [e]	23
Arthralgia	19
Asthenia	19
Dizziness	15
Dry mouth	15
Dry skin	15
Insomnia	15
Vertigo	15
Alopecia	11
Chills	11
Constipation	11
Influenza-like illness	11

	IMCIVREE-treated Patients N = 27 %
Muscle spasm	11
Pain in extremity	11
Rash	11
Suicidal ideation	11

[a] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration
[b] Includes skin hyperpigmentation, pigmentation disorders, skin discoloration
[c] Includes abdominal pain and upper abdominal pain
[d] Includes depressed mood
[e] n = 13 male patients

In a 12-week, placebo-controlled clinical study in an unapproved population, 4 female patients (7%) treated with IMCIVREE experienced sexual adverse reactions compared to 0 patients in the placebo group; 3 experienced a disturbance in sexual arousal and one experienced hypersensitivity of the labia.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 61% of adult and pediatric patients with POMC- or LEPR-deficiency who received IMCIVREE (N=28) screened positive for antibodies to IMCIVREE, and 39% screened negative. The 61% of patients who screened positive for antibodies to IMCIVREE were inconclusive for antibodies to IMCIVREE in the confirmatory assay. There was no observation of a rapid decline in IMCIVREE concentrations to suggest the presence of anti-drug antibodies.

Approximately 13% of adult and pediatric patients with LEPR-deficiency (3 patients) confirmed positive for antibodies to alpha-MSH that were classified as low-titer and non-persistent. Of these 3 patients (13%), 2 tested positive post- IMCIVREE treatment and 1 was positive pre-treatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

IMCIVREE contains the preservative benzyl alcohol. Because benzyl alcohol is rapidly metabolized by a pregnant woman, benzyl alcohol exposure in the fetus is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.4)].*

There are no available data with IMCIVREE in pregnant women to inform a drug-associated risk for major birth defects and miscarriage, or adverse maternal or fetal outcomes. For the general US population, weight loss offers no potential benefit to a pregnant woman and may result in fetal harm *(see Clinical Considerations).* In animal reproduction studies, setmelanotide subcutaneously administered to pregnant rats from before mating to the end of organogenesis was not teratogenic at doses 11 times the maximum recommended human dose (MRHD) of 3 mg. Setmelanotide subcutaneously administered to pregnant rabbits during the period of organogenesis was not teratogenic at clinical doses. Setmelanotide administered subcutaneously to pregnant rats during organogenesis through lactation did not result in adverse developmental effects at doses 7 times the MRHD (*see Data*).

The estimated background risk of birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal obesity increases the risk for congenital malformations, including neural tube defects, cardiac malformations, oral clefts, and limb reduction defects. In addition, weight loss during pregnancy may result in fetal harm including increased risk of small for gestational age. Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

Embryo-fetal development was evaluated in female rats administered setmelanotide subcutaneously during mating to end of major organogenesis (14 days prior to mating to gestation day 17) at doses of 0.5, 3, and 5 mg/kg/day, resulting in exposures up to 11 times the human exposure at MRHD of 3 mg, based on AUC. Dose-related decreases in maternal food intake and body weight gain were observed during the premating period but not during gestation. No evidence of embryo-fetal toxicity was observed.

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

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

8.2 Lactation

Risk Summary

Treatment with IMCIVREE is not recommended for use 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 Warnings and Precautions (5.4) and Use in Specific Populations (8.4)]*.

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 is present in the milk of rats (*see Data*). When a drug is present in rat milk, it is likely that the drug will be present in human milk.

Data

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.

8.4 Pediatric Use

The safety and effectiveness of IMCIVREE for obesity due to POMC, PCSK1, or LEPR deficiency have been established in pediatric patients aged 6 years and older. Use of IMCIVREE for this indication is supported by evidence from 2 open-label studies that included 9 pediatric patients *[see Clinical Studies (14)]*.

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

IMCIVREE is not approved for use in neonates or infants. Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and low birth weight infants in the neonatal intensive care unit 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) *[see Warnings and Precautions (5.4)].*

8.5 Geriatric Use

Clinical studies of IMCIVREE did not include patients aged 65 and over. It is not known whether they respond differently from younger patients.

8.6 Renal Impairment

Population pharmacokinetic analysis suggests decreased clearance in patients with renal impairment. The majority of patients in the clinical studies had normal renal function.

No dose adjustments for patients with mild renal impairment (estimated glomerular filtration rate (eGFR) of 60-89 mL/min/1.73 m^2) are needed. IMCIVREE is not recommended for use in patients with moderate (eGFR 30-59 mL/min/1.73 m^2) and severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) and end stage renal disease (eGFR less than 15 mL/min/1.73 m^2).

10 OVERDOSAGE

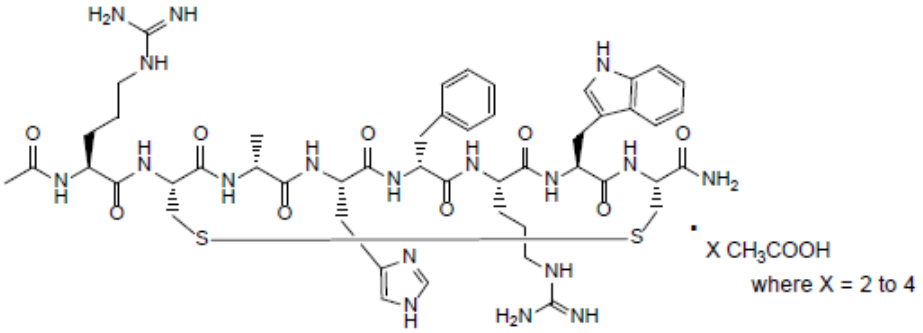
In the event of an overdose initiate appropriate supportive treatment according to the patient's clinical signs and symptoms.

11 DESCRIPTION

IMCIVREE contains setmelanotide acetate, a melanocortin 4 (MC4) receptor agonist. Setmelanotide is an 8 amino acid cyclic peptide analog of endogenous melanocortin peptide α-MSH (alpha-melanocyte stimulating hormone).

The chemical name for setmelanotide acetate is acetyl-L-arginyl-L-cysteinyl-D-alanyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-cysteinamide cyclic (2→8)-disulfide acetate. Its molecular formula is $C_{49}H_{68}N_{18}O_9S_2$ (anhydrous, free-base), and molecular mass is 1117.3 Daltons (anhydrous, free-base).

The chemical structure of setmelanotide is:



IMCIVREE injection is a sterile clear to slightly opalescent, colorless to slightly yellow solution. Each 1 mL of IMCIVREE contains 10 mg of setmelanotide provided as setmelanotide acetate, which is a salt with 2 to 4 molar equivalents of acetate, and the following inactive ingredients: 100 mg N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt, 8 mg carboxymethylcellulose sodium (average MWt 90,500), 11 mg mannitol, 5 mg phenol, 10 mg benzyl alcohol, 1 mg edetate disodium dihydrate, and Water for Injection. The pH of IMCIVREE is 5 to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure. Nonclinical evidence shows that MC4 receptors are important for setmelanotide-regulated appetite and weight loss. 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 *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

12.2 Pharmacodynamics

Energy Expenditure

Short-term administration of IMCIVREE in 12 healthy obese patients increased resting energy expenditure and shifted substrate oxidation to fat.

Blood Pressure and Heart Rate

No clinically significant increases in blood pressure (BP) or heart rate (HR) were observed following administration of IMCIVREE to healthy obese patients or patients with monogenic obesity.

12.3 Pharmacokinetics

The mean steady state setmelanotide $C_{max,ss}$, AUC_{tau}, and trough concentration for a 3-mg dose administered subcutaneously once daily 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 proportionally following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

Absorption

After subcutaneous injection of IMCIVREE, plasma concentrations of setmelanotide reached maximum concentrations at a median t_{max} of 8 h after dosing.

Distribution

The mean apparent volume of distribution of setmelanotide after subcutaneous administration of IMCIVREE 3 mg once daily was estimated from the population pharmacokinetics model to be 48.7 L. Protein binding of setmelanotide is 79.1%.

Elimination

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

Metabolism

Setmelanotide is expected to be metabolized into small peptides by catabolic pathways.

Excretion

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

Specific Populations

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

Pediatric Patients

IMCIVREE has been evaluated in pediatric patients aged 6 to less than 12 years and aged 12 to 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 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. [*see Dosage and Administration (2.2)*].

Patients with Renal Impairment

Population pharmacokinetic analysis suggests a 19% higher setmelanotide AUC in patients with mild renal impairment as compared to patients with normal renal function *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In vitro assessment of drug-drug interactions

Setmelanotide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP), transporters and plasma protein binding.

In vivo assessment of drug-drug interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential of setmelanotide.

Setmelanotide was not mutagenic or clastogenic in a bacterial reverse mutation test, an *in vitro* chromosome aberration test in human lymphocyte cultures, or an *in vivo* bone marrow micronucleus study in rats.

There were no effects on the fertility of male rats subcutaneously administered up to 3.0 mg/kg/day setmelanotide, which represents 9 times the MRHD of 3 mg, based on AUC. No effects on the fertility of female rats were observed with subcutaneous administration up to 5 mg/kg/day setmelanotide, which represents 11 times the MRHD of 3 mg, based on AUC.

14 CLINICAL STUDIES

The safety and efficacy of IMCIVREE for chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03287960) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency. In both studies, the local genetic testing results were centrally confirmed using Sanger sequencing. The studies enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for either the *POMC* or *PCSK1* genes (Study 1) or the *LEPR* gene (Study 2). 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.

Dose titration occurred over a 2- to 12-week period, followed by a 10-week, open-label treatment period. 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 active treatment with IMCIVREE at the therapeutic dose for up to 32 weeks.

Efficacy analyses were conducted in 21 patients (10 in Study 1 and 11 in Study 2) who had completed at least 1 year of treatment at the time of a prespecified data cutoff. Six additional patients enrolled in the studies (4 in Study 1 and 2 in Study 2) who had not yet completed 1 year of treatment at the time of the cutoff were not included the efficacy analyses.

Of the 21 patients included in the efficacy analysis in Studies 1 and 2, 62% were adults and 38% were aged 16 years or younger. In Study 1, 50% of patients were female, 70% were White, and the median BMI was 40.0 kg/m^2 (range: 26.6-53.3) at baseline. In Study 2, 73% of patients were female, 91% were White, and the median BMI was 46.6 kg/m^2 (range: 35.8-64.6) at baseline.

Effect of IMCIVREE on Body Weight

In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a ≥10% weight loss after 1 year of treatment with IMCIVREE. In Study 2, 46% of patients with obesity due to LEPR deficiency achieved a ≥10% weight loss after 1 year of treatment with IMCIVREE (Table 2).

Table 2: Body Weight (kg) – Proportion of Patients Achieving at Least 10% Weight Loss from Baseline at 1 Year in Study 1 and Study 2

Parameter	Statistic	Study 1 (POMC) (N=10)	Study 2 (LEPR) (N=11)
Patients Achieving at Least 10% Weight Loss at Year 1	n (%)	8 (80.0%)	5 (45.5%)
	95% CI[1]	(44.4%, 97.5%)	(16.8%, 76.6%)
	P-value[2]	<0.0001	0.0002

Note: The analysis set includes patients who received at least 1 dose of study drug and had at least 1 baseline assessment.
1 From the Clopper-Pearson (exact) method
2 Testing the null hypothesis: Proportion =5%

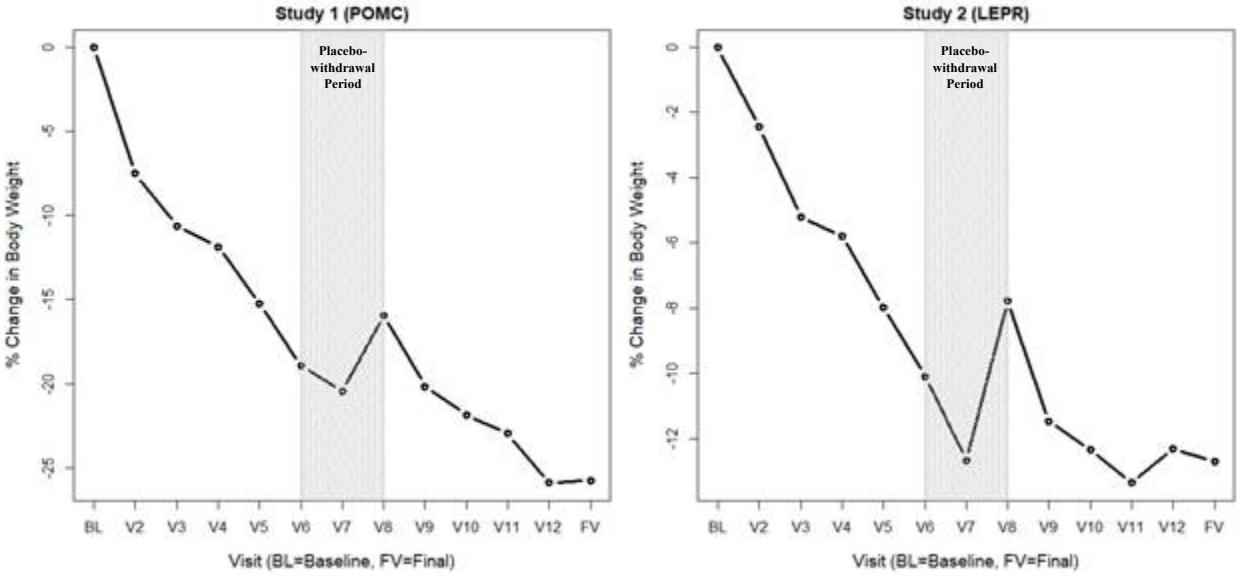
When treatment with IMCIVREE was withdrawn in the 16 patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was <100 kg) during the 10-week open-label period, these patients gained an average of 5.5 kg in Study 1 and 5.0 kg in Study 2 over 4 weeks. Re-initiation of treatment with IMCIVREE resulted in subsequent weight loss (see Figure 1).

Table 3: Percent Change from Baseline in Weight at 1 Year in Studies 1 and 2 (Full Analysis Set)

Parameter	Statistic	Study 1 (POMC) (N=10)	Study 2 (LEPR) (N=11)
Baseline Body Weight (kg)	Mean (SD)	118.7 (37.5)	133.3 (26.0)
	Median	115.0	132.3
	Min, Max	55.9, 186.7	89.4, 170.4
1-Year Body Weight (kg)	Mean (SD)	89.8 (29.4)	119.2 (27.0)
	Median	84.1	120.3
	Min, Max	54.5, 150.5	81.7, 149.9
Percent Change from Baseline to 1 Year (%)	Mean (SD)	-23.1 (12.1)	-9.7 (8.8)
	Median	-26.7	-9.8
	Min, Max	-35.6, -1.2	-23.3, 0.1
	LS Mean[1]	-23.12	-9.65
	95% CI[1]	(-31.9, -14.4)	(-16.0, -3.3)
	P-value[2]	0.0003	0.0074

Note: This analysis includes patients who received at least 1 dose of study drug, had at least 1 baseline assessment.
1 ANCOVA model containing baseline body weight as a covariate
2 Testing the null hypothesis: mean percent change=0

Figure 1: Mean Percent Change in Body Weight from Baseline by Visit (Study 1 [N=9] and Study 2 [N=7])



BL=Baseline (day of first dose)
V2 to V3 = variable dose titration period (2 to 12 weeks)
V3 to V6 = 10-week open-label treatment period
V6 to V8 = 8-week placebo withdrawal period (4 weeks active, 4 weeks placebo)
V8 to V12 = 32-week open-label treatment period
FV = Final visit; time point for primary efficacy analysis

Note: This figure includes patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was <100 kg) during the 10-week open-label period.

Effect of IMCIVREE on Hunger

Patients 12 years and older self-reported their daily maximal hunger in a diary, 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"). Weekly means of daily hunger scores at Baseline and Week 52 are summarized in Table 4.

Table 4: Daily Hunger Scores – Change from Baseline at 1 Year in Subjects Aged ≥12 Years in Study 1 and Study 2 with Available Hunger Data

Parameter	Statistic	Hunger in 24 Hours	
		Study 1 (N=8)	Study 2 (N=11)
Baseline Hunger Score	Median	7.9	7.0
	Min, Max	7, 9	5, 8
1-Year Hunger Score	Median	5.5	4.4
	Min, Max	3, 8	2, 8
Change from Baseline to 1 Year	Median	-2.0	-3.0
	Min, Max	-7, -0	-5, -1

Note: This analysis includes patients aged 12 years and older who received at least 1 dose of study drug and had available data. One patient in Study 2 had missing hunger data at Week 52.

Hunger score was captured in a daily diary and was averaged to calculate a weekly score for analysis. Hunger ranged from 0 to 10 on an 11-point scale where 0 = "not hungry at all" and 10 = "hungriest possible."

Hunger scores generally worsened during the double-blind, placebo withdrawal period among those patients who had experienced an improvement from baseline, and scores improved when IMCIVREE was reinitiated.

Supportive of IMCIVREE's effect on weight loss, there were general numeric improvements in cardiometabolic parameters, such as blood pressure, lipids, glycemic parameters, and waist circumference. However, because of the limited number of patients studied and the lack of a control group, the treatment effects on these parameters could not be accurately quantified.

16 HOW SUPPLIED/STORAGE AND HANDLING

IMCIVREE injection: 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: NDC 72829-010-01

Store unopened IMCIVREE vials in the refrigerator at 2°C to 8°C (36°F to 46°F). After removal from the refrigerator, vials may be kept at temperatures ranging from refrigerated to room temperature (2°C to 25°C (36°F to 77°F)) for up to 30 days with brief excursions up to 30°C (86°F). 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: IMCIVREE Recommended Storage for IMCIVREE Vials

Storage Condition	Unopened Vial	Opened Vial
2°C to 8°C (36°F to 46°F)	Until the expiration date	Up to 30 days, OR Until the expiration date (whichever is earlier)
2°C to 25°C (36°F to 77°F) with excursions permitted up to 30°C (86°F)[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 (>86°F)	Discard and do not use	Discard and do not use

[1] If necessary, IMCIVREE may be stored at room temperature (≤30 C [≤86 F]) and then returned to refrigerated conditions

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (*Instructions for Use*).

Spontaneous Penile Erection

Inform male patients that spontaneous erection may occur with IMCIVREE treatment. Advise patients to seek appropriate medical treatment if an erection lasts longer than 4 hours *[see Warnings and Precautions (5.1)]*.

Depression and Suicidal Ideation

Inform patients or caregivers that some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Advise patients or caregivers to report any new or worsening symptoms of depression *[see Warnings and Precautions (5.2)]*.

Skin Pigmentation and Darkening of Pre-Existing Nevi

Inform patients or caregivers that skin darkening occurs in the majority of patients treated with IMCIVREE because of its mechanism of action. This change is reversable upon discontinuation of IMCIVREE. Inform patients or caregivers that they should have a full body skin examination before starting and during treatment with IMCIVREE to monitor these changes *[see Warnings and Precautions (5.3)]*.

Pregnancy

Advise patients who may become pregnant to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that treatment with IMCIVREE is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*.

Administration

Instruct patients and caregivers how to prepare and administer the correct dose of IMCIVREE and assess their ability to inject subcutaneously to ensure the proper administration of IMCIVREE. Instruct patients to use a 1 mL syringe with a 28- or 29-gauge needle appropriate for subcutaneous injection.

Manufactured for:

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

PATIENT INFORMATION
IMCIVREE™ [im-SIV-ree]
(setmelanotide)
injection, for subcutaneous use

What is IMCIVREE?

- IMCIVREE is a prescription medicine used in adults and children 6 years of age and older with obesity due to the genetic conditions proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency, to help them lose weight and keep the weight off.
- Your healthcare provider should order a genetic test to confirm POMC, PCSK1, or LEPR deficiency before you start using IMCIVREE.
- IMCIVREE is not for use in people with the following conditions because it may not work:
  - Obesity due to suspected POMC, PCSK1, or LEPR deficiency not confirmed by genetic testing (benign or likely benign result).
  - Other types of obesity not related to POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic conditions and general obesity.

It is not known if IMCIVREE is safe and effective in children under 6 years of age.

Before using IMCIVREE, tell your healthcare provider about all your medical conditions, including if you:

- have or have had areas of darkened skin, including skin discoloration (hyperpigmentation).
- have or have had depression, or suicidal thoughts or behavior.
- have kidney problems.
- are pregnant or planning to become pregnant. Losing weight while pregnant may harm your unborn baby. Your healthcare provider may stop your treatment with IMCIVREE if you become pregnant. Tell your healthcare provider 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.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use IMCIVREE?

- See the detailed Instructions for Use to learn how to prepare and inject IMCIVREE.
- IMCIVREE is given as an injection under your skin (subcutaneous) by you or a caregiver.
- A healthcare provider should show you or your caregiver how to prepare and inject your dose of IMCIVREE before injecting for the first time. Do not try to inject IMCIVREE unless you have been trained by a healthcare provider.
- Use IMCIVREE exactly as prescribed by your healthcare provider.
- Your healthcare provider may tell you to stop using IMCIVREE if you have not lost a certain amount of weight after 12 to 16 weeks of treatment.
- IMCIVREE should be injected 1 time each day when you first wake up. IMCIVREE can be given with or without food.
- If you miss a dose of IMCIVREE, inject your next dose at the regularly scheduled time the next day.

What are the possible side effects of IMCIVREE?
IMCIVREE may cause serious side effects, including:

- **Male and female sexual function problems.** IMCIVREE can cause an erection that happens without any sexual activity in males (spontaneous penile erection) and unwanted sexual reactions (changes in sexual arousal that happen without any sexual activity) in females. If you have an erection lasting longer than 4 hours, get emergency medical help right away.
- **Depression and suicidal thoughts or actions.** You or a caregiver should call your healthcare provider right away if you have any new or worsening symptoms of depression.
- **Increased skin pigmentation and darkening of skin lesions (moles or nevi) you already have.** These changes happen because of how IMCIVREE works in the body and will go away when you stop using IMCIVREE. You should have a full body skin exam before starting and during treatment with IMCIVREE to check for skin changes.
- **Benzyl alcohol toxicity**. 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. IMCIVREE should not be used in premature and low-birth weight infants.

The most common side effects of IMCIVREE include:

- injection site reactions
- darkening of the skin
- nausea
- headache
- diarrhea
- abdominal pain
- back pain
- fatigue
- vomiting
- depression
- upper respiratory tract infection
- erection that happens without any sexual activity in males

These are not all the possible side effects of IMCIVREE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Rhythm Pharmaceuticals at 1-833-789-6337.

General information about the safe and effective use of IMCIVREE.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IMCIVREE for a condition for which it was not prescribed. Do not give IMCIVREE to other people, even if they have the

same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMCIVREE that is written for health professionals.
What are the ingredients in IMCIVREE? **Active ingredient:** setmelanotide **Inactive ingredients:** N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl- glycero-3-phosphoethanolamine sodium salt, carboxymethylcellulose sodium, mannitol, phenol, benzyl alcohol, edetate disodium dihydrate, and water for injection.

INSTRUCTIONS FOR USE
IMCIVREE™ [im-SIV-ree]
(setmelanotide)
injection, for subcutaneous use

This Instructions for Use contains information on how to inject IMCIVREE. Read and follow these instructions before injecting IMCIVREE.

Important Information You Need to Know Before Injecting IMCIVREE

- **IMCIVREE is for injection under the skin only (subcutaneous injection). Do not** inject IMCIVREE into a vein or muscle.
- Inject IMCIVREE 1 time each day when you first wake up.
- Take IMCIVREE with or without food.
- IMCIVREE is given by you or a caregiver. A healthcare provider will show you or your caregiver how to inject your dose of IMCIVREE before you inject for the first time. Ask your healthcare provider or call IMCIVREE Guidance, Partnership, Support (GPS) at 1-844-YOUR-GPS (1-844-968-7477) if you have questions.
- Store opened vials of IMCIVREE in the refrigerator between 36°F to 46°F (2°C to 8°C). If needed, vials may be removed from the refrigerator and stored at temperatures ranging from refrigerated to room temperature (36°F to 77°F (2°C to 25°C)), and vials may be returned to the refrigerator. Brief temperature excursions up to 86°F (30°C) are permitted. Throw away all opened vials 30 days after first opening, even if some medicine is still left.
- Unopened vials of IMCIVREE may be stored in the refrigerator between 36°F to 46°F (2°C to 8°C) until the expiration date. If needed, unopened vials may also be removed from the refrigerator and stored at temperatures ranging from refrigerated to room temperature (36°F to 77°F (2°C to 25°C)) for up to 30 days. Vials may be returned to the refrigerator. Brief storage temperature excursions up to 86°F (30°C) are permitted. Throw away IMCIVREE if it has been more than 30 days since the vial was first removed from the refrigerator.
- If necessary, vials may be stored at room temperature below 86°F (30° C) and may be returned to refrigerated conditions. Write the date on the carton when you first open the vial.
- Throw away IMCIVREE that has been stored above 86°F (30° C).

Important note:

- Only use the syringes and needles provided to you 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. See "**Disposing of IMCIVREE**" at the end of these instructions.
- **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.**

Understanding Your IMCIVREE Dose

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 provider 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 **Figure A** 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 **Figure A** .

Figure A

	Prescribed dose (mg)	Prescribed dose (mL)	Number of doses per vial
10 mg/1 mL multiple-dose vial	1 mg	0.1 mL	10
	2 mg	0.2 mL	5
	3 mg	0.3 mL	3

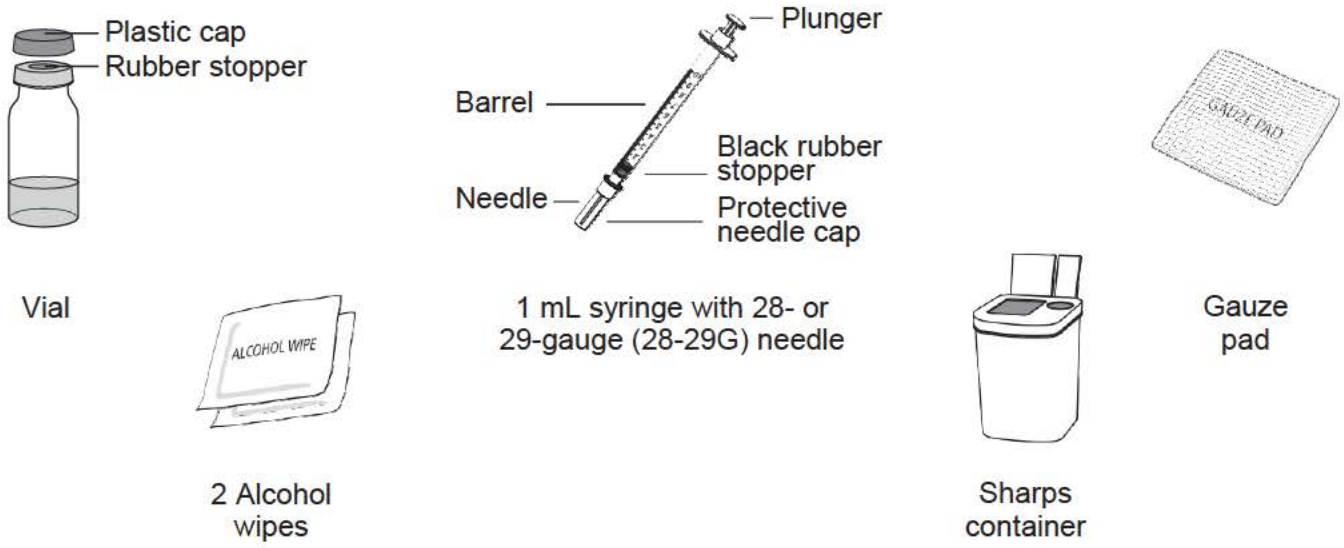
Preparing to Inject IMCIVREE

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.

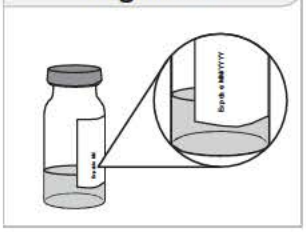
Figure B

You will need the following supplies:



Step 2 Check your IMCIVREE vial.

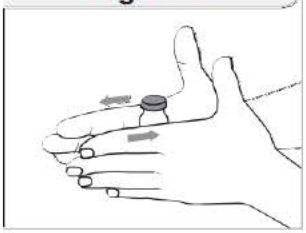
Figure C



- 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.

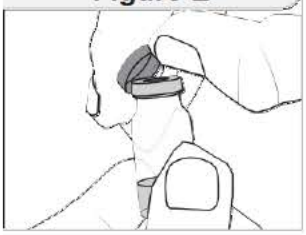
Step 3 Prepare your IMCIVREE vial.

Figure D



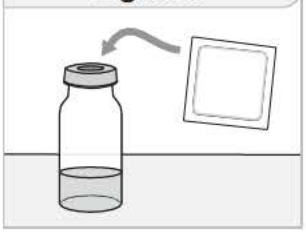
- Allow the vial to reach room temperature.
  - Remove the vial from the refrigerator 15 minutes before injection.
  - You can also warm the vial by rolling it gently between the palms of your hands for 60 seconds (**Figure D**).
- **Do not** try to warm the vial by using a heat source such as hot water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

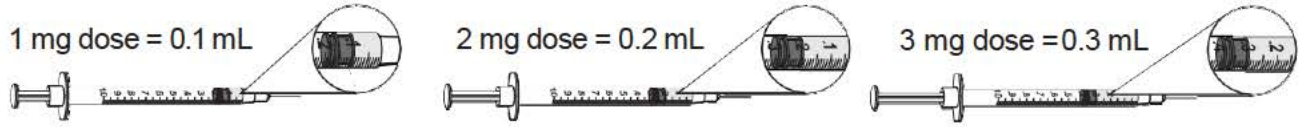
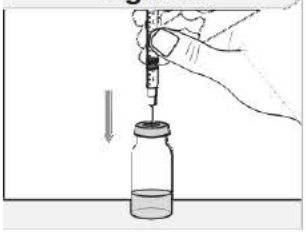


Figure H

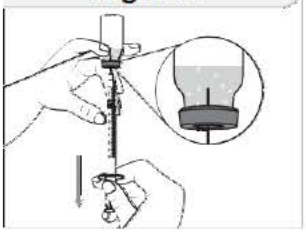
- Fill the syringe with air.
  - Keep the protective needle cap on the syringe.
  - Pull back on the plunger until the end of the black rubber stopper stops at your dose. Fill the syringe with air equal to the amount of the medicine to be given (**Figure H**).
- Remove the protective needle cap from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

Figure I



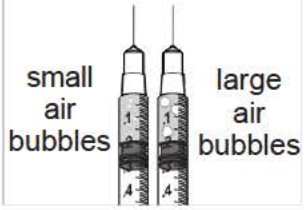
- Insert the needle.
  - Place the vial on the clean, flat work surface.
  - With the vial in the upright position, place the syringe directly over the vial and insert the needle straight down into the center of the vial rubber stopper (**Figure I**).
  - Push the air from the syringe into the vial.

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



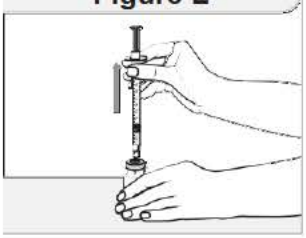
- Check for large air bubbles (**Figure K**).
  - Keep the needle in the vial and check the syringe for large air bubbles.

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

Injecting IMCIVREE

Step 5 Prepare your injection site.

Figure M

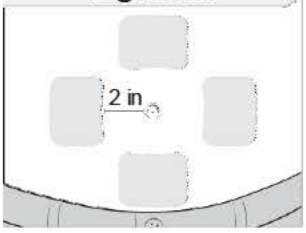


Figure N

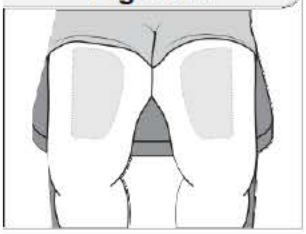
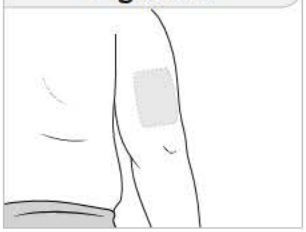


Figure O



- Choose the area where you will give the injection. Choose from the following recommended injection sites:
  - belly (abdomen) (**Figure M**)
  - front of the middle thighs (**Figure N**)
  - back of the upper arm (**Figure O**)
- 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

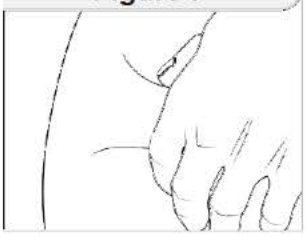
- Clean the injection site with the second alcohol wipe using a circular motion.
- **Do not** touch, fan, or blow on the cleaned area.
- Allow the skin to dry for about 10 seconds.

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.

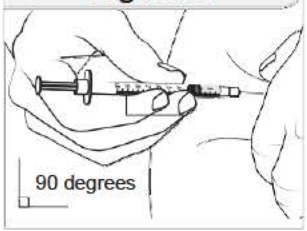
Figure P



- 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).

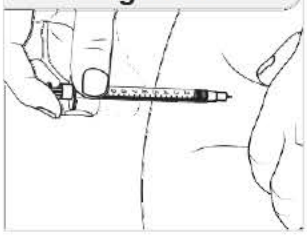
Step 7 Inject and release.

Figure Q



- 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.

Figure R



- 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.

Storing IMCIVREE

- Store unopened and opened vials in the original carton to protect them from light.
- Store opened vials of IMCIVREE in the refrigerator between 36°F to 46°F (2°C to 8°C). If needed, vials may be removed from the refrigerator and stored at temperatures ranging from refrigerated to room temperature (36°F to 77°F (2°C to 25°C)), and vials may be returned to the refrigerator. Brief temperature excursions up to 86°F (30°C) are permitted. Throw away all opened vials 30 days after first opening, even if some medicine is still left in the vial.
- Unopened vials of IMCIVREE may be stored in the refrigerator between 36°F to 46°F (2°C to 8°C) until the expiration date. If needed, unopened vials may also be removed from the refrigerator and stored at temperatures ranging from refrigerated to room temperature (36°F to 77°F (2°C to 25°C)) for up to 30 days. Vials may be returned to the refrigerator. Brief storage temperature excursions up to 86°F (30°C) are permitted. Throw away IMCIVREE if it has been more than 30 days since the vial was first removed from the refrigerator.
- If necessary, vials may be stored at room temperature below 86°F (30° C) and may be returned to refrigerated conditions. Write the date on the carton when you first open the vial.
- Throw away IMCIVREE that has been stored above 86°F (30°C).
- **Keep IMCIVREE, needles, syringes, and all medicines out of the reach of children.**

Disposing of IMCIVREE

Figure S

- Alcohol wipes, used gauze pads, and vials can be thrown away in the trash. Throw away (dispose of) used syringes and needles in a puncture-resistant container, such as an FDA-cleared sharps disposal container immediately after use (**Figure S**).

  Do not throw away (dispose of) syringes and needles in your household trash.

  If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.

  When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.
- Do not recycle your used sharps disposal container.

Note: Keep your sharps disposal container out of the reach of children and pets.

For more information about IMCIVREE, including how to inject IMCIVREE, go to www.IMCIVREE.com or call 1-844-YOUR-GPS (1-844-968-7477).

IMCIVREE is Manufactured for:
Rhythm Pharmaceuticals, Inc.
222 Berkeley Street, Suite 1200
Boston, MA 02116

Made in France

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

IMCIVREE is a trademark of Rhythm Pharmaceuticals, Inc.
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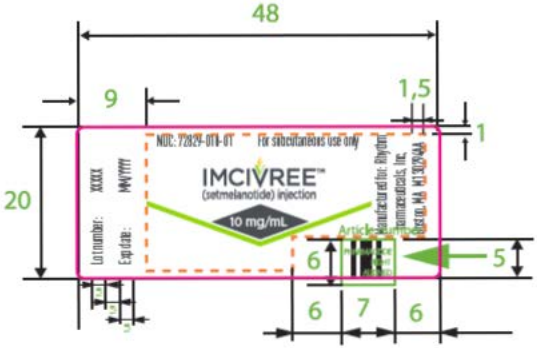
Approved [11/2020]


48
9
1,5
1
20
NDC: 72829-010-01
For subcutaneous use only
IMCIVREE™
(setmelanotide) injection
10 mg/mL
Lot number: XXXXX
Exp date: MM/YYYY
Manufactured for: Rhythm Pharmaceuticals, Inc.
Boston, MA 02210USA
Article number
6
5
6
7
6

NDC: 72829-010-01
For subcutaneous use only
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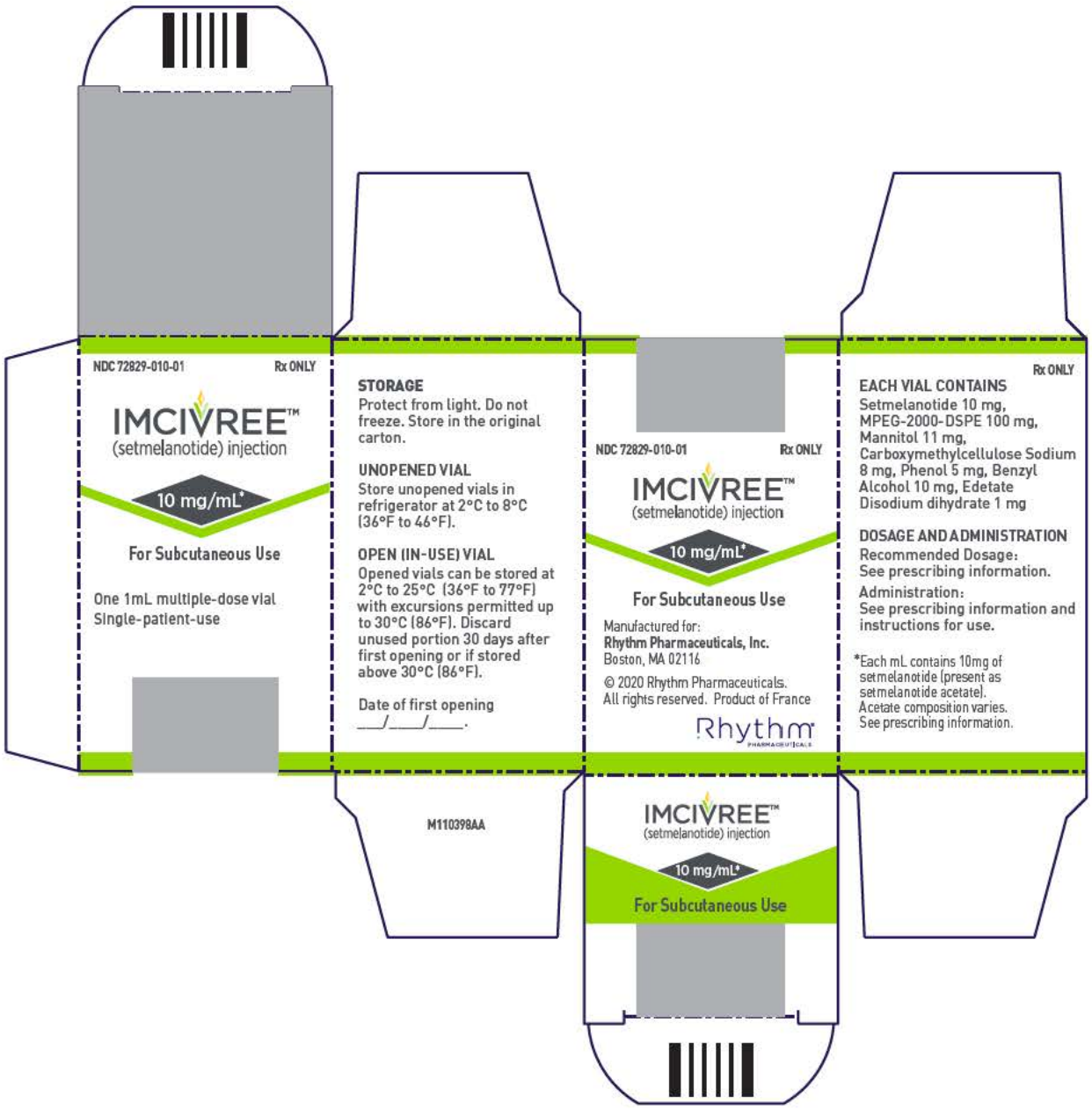
NDC 72829-010-01
Rx ONLY
IMCIVREE™
(setmelanotide) injection
10 mg/mL*
For Subcutaneous Use
One 1mL multiple-dose vial
Single-patient-use
STORAGE
Protect from light. Do not freeze. Store in the original carton.
UNOPENED VIAL
Store unopened vials in refrigerator at 2°C to 8°C (36°F to 46°F).
OPEN (IN-USE) VIAL
Opened vials can be stored at 2°C to 25°C (36°F to 77°F) with excursions permitted up to 30°C (86°F). Discard unused portion 30 days after first opening or if stored above 30°C (86°F).
Date of first opening
___/____/____.
M110398AA
NDC 72829-010-01
Rx ONLY
IMCIVREE™
(setmelanotide) injection
10 mg/mL*
For Subcutaneous Use
Manufactured for:
Rhythm Pharmaceuticals, Inc.
Boston, MA 02116
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All rights reserved. Product of France
Rhythm
PHARMACEUTICALS
Rx ONLY
EACH VIAL CONTAINS
Setmelanotide 10 mg, MPEG-2000-DSPE 100 mg, Mannitol 11 mg, Carboxymethylcellulose Sodium 8 mg, Phenol 5 mg, Benzyl Alcohol 10 mg, Edetate Disodium dihydrate 1 mg
DOSAGE AND ADMINISTRATION
Recommended Dosage:
See prescribing information.
Administration:
See prescribing information and instructions for use.
*Each mL contains 10mg of setmelanotide (present as setmelanotide acetate). Acetate composition varies. See prescribing information.
IMCIVREE™
(setmelanotide) injection
10 mg/mL*
For Subcutaneous Use
FRONT PANEL
RIGHT PANEL
BACK PANEL
LEFT PANEL

(b) (4)

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/s/

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11/25/2020 06:47:59 PM