

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

RECENT MAJOR CHANGES

Indications and Usage (1)	03/2026
Dosage and Administration (2.1, 2.2, 2.4)	03/2026
Warnings and Precautions (5.5, 5.6)	03/2026

INDICATIONS AND USAGE

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated to reduce excess body weight and maintain reduction long term in adults and pediatric patients aged (1):

- 4 years and older with acquired hypothalamic obesity (HO).
- 2 years and older with Bardet-Biedl syndrome (BBS).
- 2 years and older with pro-opiomelanocortin (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. (1)
- Other types of obesity not related to acquired HO, BBS, or 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 a clinical diagnosis of acquired HO or BBS or who have genetically determined or suspected deficiency of POMC, PCSK1, or LEPR. (2.1)
- Recommended starting dosage injected subcutaneously for:
 - Adults and pediatric patients aged 4 years and older with acquired HO is 0.5 mg (0.05 mL) once daily for 2 weeks. (2.2)
 - Adults and pediatric patients aged 12 years and older with BBS or POMC, PCSK1, or LEPR deficiency is 2 mg (0.2 mL) once daily for 2 weeks. (2.3)
 - Pediatric patients aged 6 to less than 12 years with BBS or POMC, PCSK1, or LEPR deficiency is 1 mg (0.1 mL) once daily for 2 weeks. (2.3)
 - Pediatric patients aged 2 to less than 6 years with BBS or POMC, PCSK1, or LEPR deficiency is 0.5 mg (0.05 mL) once daily for 2 weeks. (2.3)
- Recommended maintenance dosage for adults and pediatric patients aged 6 years and older for all indications is 3 mg (0.3 mL) injected subcutaneously once daily. (2.2, 2.3)
- Recommended maintenance dose for pediatric patients with acquired HO aged 4 years to less than 6 years and for pediatric patients with BBS or

POMC, PCSK1, or LEPR deficiency aged 2 to less than 6 years is determined by body weight. (2.2, 2.3)

- For recommended dosage in patients with renal impairment, see Full Prescribing Information. (2.4)
- For titration and administration recommendations, see Full Prescribing Information. (2.2, 2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL solution in a 1 mL multiple-dose vial (3)

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE (4)

WARNINGS AND PRECAUTIONS

- **Disturbance in Sexual Arousal:** Spontaneous penile erections in males and sexual adverse reactions in females have occurred. 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. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur. (5.2)
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE. (5.3)
- **Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi:** Generalized increased skin pigmentation, darkening of pre-existing nevi, and development of new nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions. (5.4)
- **Acute Adrenal Insufficiency in Patients with Acquired HO:** Monitor patients for signs of acute adrenal insufficiency. (5.5)
- **Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus:** Monitor patients for signs and symptoms of hyponatremia and hypernatremia. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 20\%$ in at least 1 indication) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, 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 and FDA-approved patient labeling.

Revised: 03/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMCIVREE is indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged [see *Dosage and Administration (2.1)*]:

- 4 years and older with acquired hypothalamic obesity (HO)
- 2 years and older with syndromic or monogenic obesity due to:
 - Bardet-Biedl syndrome (BBS)
 - Pro-opiomelanocortin (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).

1.1 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.
- Other types of obesity not related to acquired HO, BBS, or POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Acquired HO

- Select patients for treatment with IMCIVREE who have acquired HO [see *Clinical Studies (14.1)*].

BBS

- Select patients for treatment with IMCIVREE who have a clinical diagnosis of BBS [see *Clinical Studies (14.2, 14.4)*]. Consider genetic confirmation in pediatric patients aged <6 years.

POMC, PCSK1, or LEPR Deficiency

- Select patients for treatment with IMCIVREE who have genetically determined or suspected deficiency of POMC, PCSK1, or LEPR [see *Clinical Studies (14.3, 14.4)*].

- 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 (14.3, 14.4)*].
- An FDA-approved test for the detection of variants in the *POMC*, *PCSK1*, or *LEPR* genes is not available.

2.2 Recommended Dosage in Patients with Acquired HO

- Monitor patients for gastrointestinal (GI) adverse reactions during dosage initiation and titration [see *Adverse Reactions (6.1)*].
- If the starting dosage is:
 - Not tolerated, discontinue the product.
 - Tolerated for 2 weeks, increase the dosage as presented in Table 1 or Table 2.

Adults and Pediatric Patients Aged 6 Years and Older

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks.

Table 1: Recommended Dosage in Adults and Pediatric Patients Aged 6 Years and Older with Acquired HO

Week	Daily dose	Volume to be injected
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Weeks 3-4	1 mg once daily	0.1 ml once daily
Weeks 5-6	2 mg once daily	0.2 ml once daily
Weeks 7 and onward	3 mg once daily	0.3 ml once daily

Pediatric Patients Aged 4 to Less Than 6 Years

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks.

Table 2: Recommended Dosage Based on Baseline Body Weight in Pediatric Patients Aged 4 to Less Than 6 Years with Acquired HO

Patient Weight/Treatment Week	Daily Dose	Volume to be Injected
15 kg to less than 20 kg		
Week 1 and onward	0.5 mg once daily	0.05 mL once daily
20 kg to less than 30 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3 and onward	1 mg once daily	0.1 mL once daily
30 kg to less than 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Weeks 5 and onward	1.5 mg once daily	0.15 mL once daily
Greater than or equal to 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Weeks 5-6	1.5 mg once daily	0.15 mL once daily
Weeks 7 and onward	2 mg once daily	0.2 mL once daily

2.3 Recommended Dosage in Patients with BBS or POMC, PCSK1, or LEPR Deficiency

Adults and Pediatric Patients Aged 12 Years and Older

- The recommended starting dosage is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks in adults and pediatric patients aged 12 years and older.
- Monitor patients for GI adverse reactions during dosage initiation and titration [*see Adverse Reactions (6.1)*].
- If the starting dosage is:
 - Not tolerated, reduce the dosage to 1 mg (0.1 mL) once daily. If the 1 mg once daily dosage is tolerated for at least 1 week, increase the dosage to 2 mg (0.2 mL) once daily.
 - Tolerated for 2 weeks, increase the dosage to 3 mg (0.3 mL) once daily. If the 3 mg once daily dosage is not tolerated, decrease the dosage to 2 mg (0.2 mL) once daily.
- The recommended maintenance dosage is 3 mg (0.3 mL) injected subcutaneously once daily.

Pediatric Patients Aged 6 to Less Than 12 Years

- The recommended starting dosage is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 6 to less than 12 years.
- Monitor patients for GI adverse reactions during dosage initiation and titration [*see Adverse Reactions (6.1)*].
- If the starting dosage is:
 - Not tolerated, reduce the dosage to 0.5 mg (0.05 mL) once daily. If the 0.5 mg once daily dosage is tolerated for at least 1 week, increase the dosage to 1 mg (0.1 mL) once daily.
 - Tolerated for 2 weeks, increase the dosage to 2 mg (0.2 mL) once daily. If the 2 mg daily dosage is:
 - Not tolerated, reduce the dosage to 1 mg (0.1 mL) once daily.
 - Tolerated, increase the dosage to 3 mg (0.3 mL) once daily.
- The recommended maintenance dosage is 3 mg (0.3 mL) injected subcutaneously once daily.

Pediatric Patients Aged 2 to Less Than 6 Years

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 2 to less than 6 years.
- Monitor patients for GI adverse reactions during dosage initiation and titration [*see Adverse Reactions (6.1)*].

- If the starting dosage is:
 - Not tolerated, discontinue the product.
 - Tolerated for 2 weeks, increase the dosage based on baseline body weight, as presented in Table 3.

Table 3: Recommended Maintenance Dosage Based on Baseline Body Weight in Pediatric Patients Aged 2 to Less Than 6 Years with BBS or POMC, PCSK1, or LEPR Deficiency

Patient Weight/Treatment Week	Daily Dose	Volume to be Injected
15 kg to less than 20 kg		
Week 1 and onward	0.5 mg once daily	0.05 mL once daily
20 kg to less than 30 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3 and onward	1 mg once daily	0.1 mL once daily
30 kg to less than 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Weeks 5 and onward	1.5 mg once daily	0.15 mL once daily
Greater than or equal to 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3-4	1 mg once daily	0.1 mL once daily
Weeks 5-6	1.5 mg once daily	0.15 mL once daily
Weeks 7 and onward	2 mg once daily	0.2 mL once daily

2.4 Recommended Dosage in Patients with Renal Impairment

Recommended Dosage in Patients with End Stage Renal Disease [estimated glomerular filtration (eGFR) less than 15 mL/min/1.73 m²]

IMCIVREE is not recommended for use in patients with end stage renal disease.

Recommended Dosage in Patients with Severe Renal Impairment (eGFR of 15 to 29 mL/min/1.73 m²)

Adults and Pediatric Patients Aged 4 Years and Older with Acquired HO

IMCIVREE is not recommended for use in adults and pediatric patients aged 4 years and older with acquired HO and severe renal impairment.

Adults and Pediatric Patients Aged 12 Years and Older with BBS or POMC, PCSK1, or LEPR Deficiency

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in adults and pediatric patients aged 12 years and older with severe renal impairment.
- Monitor patients for GI adverse reactions during dosage initiation and titration [see *Adverse Reactions (6.1)*].
- If the recommended starting dosage is [see *Use in Specific Populations (8.6)*]:
 - Not tolerated, discontinue IMCIVREE.

- Tolerated for 2 weeks, increase the dosage to 1 mg (0.1 mL) once daily. If the 1 mg daily dosage is tolerated for at least 1 week, increase the dosage to 1.5 mg (0.15 mL) once daily. The recommended maintenance dosage is 1.5 mg (0.15 mL) injected subcutaneously once daily [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Pediatric Patients Ages 6 Years to Less Than 12 Years with BBS or POMC, PCSK1, or LEPR Deficiency

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 6 to less than 12 years with severe renal impairment.
- Monitor patients for GI adverse reactions during dosage initiation and titration [*see Adverse Reactions (6.1)*].
- If the recommended starting dosage is [*see Use in Specific Populations (8.6)*]:
 - Not tolerated, discontinue IMCIVREE.
 - Tolerated for 2 weeks, increase the dosage to 1 mg (0.1 mL) injected subcutaneously once daily. The recommended maintenance dosage is 1 mg (0.1 mL) injected subcutaneously once daily [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Pediatric Patients Aged 2 to Less Than 6 Years Weighing at Least 20 kg with BBS or POMC, PCSK1, or LEPR Deficiency

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 2 to less than 6 years with severe renal impairment and weight of at least 20 kg.
 - The use of IMCIVREE in pediatric patients aged 2 to less than 6 years with weight less than 20 kg and severe renal impairment is not recommended [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].
- Monitor patients for GI adverse reactions during dosage initiation and titration [*see Adverse Reactions (6.1)*].
- If the recommended starting dosage is [*see Use in Specific Populations (8.6)*]:
 - Not tolerated, discontinue IMCIVREE.
 - Tolerated for 2 weeks, increase the dosage based on baseline body weight, as presented in Table 4 [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Table 4: Recommended Maintenance Dosage Based on Baseline Body Weight in Pediatric Patients with BBS or POMC, PCSK1, or LEPR Deficiency and Severe Renal Impairment Aged 2 to Less Than 6 Years of Age Weighing at Least 20 kg

Patient Weight/Treatment Week	Daily Dose	Volume to be Injected
20 kg to less than 30 kg		
Week 1 and onward	0.5 mg once daily	0.05 mL once daily
30 kg to less than 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3 and onward	1 mg once daily	0.1 mL once daily
Greater than or equal to 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Weeks 3 and onward	1 mg once daily	0.1 mL once daily

- The recommended maintenance dosage is 1 mg (0.1 mL) injected subcutaneously once daily [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]. Monitor patients for adverse reactions [see *Adverse Reactions (6.1)*].

Recommended Dosage in Patients with Mild (eGFR of 60 to 89 mL/min/1.73 m²) or Moderate (eGFR of 30 to 59 mL/min/1.73 m²) Renal Impairment

The recommended dosage in patients with acquired HO, BBS, or POMC, PCSK1, or LEPR Deficiency and mild or moderate renal impairment is the same as in those with normal kidney function [see *Dosage and Administration (2.2, 2.3)*].

2.5 Administration Instructions

- Prior to initiation of IMCIVREE, train patients and their caregivers on proper injection technique. Instruct them to use a 1-mL syringe with a 28-gauge or 29-gauge needle appropriate for subcutaneous injection.
- 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, 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

IMCIVREE is contraindicated in patients with a prior serious hypersensitivity reaction to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions have included anaphylaxis [*see Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Disturbance in Sexual Arousal

Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections and increased frequency of penile erections in males occurred in clinical trials 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 [*see Adverse Reactions (6.1)*]. 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 behavior, or any unusual changes in mood or behavior. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors or if clinically significant or persistent depression symptoms occur.

5.3 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with IMCIVREE. These reactions generally occurred within minutes to hours after injecting IMCIVREE [*see Adverse Reactions (6.2)*]. If hypersensitivity reactions occur, advise patients to promptly seek medical attention and discontinue use of IMCIVREE. IMCIVREE is contraindicated in patients with a prior serious hypersensitivity reaction to setmelanotide or any of the excipients in IMCIVREE.

5.4 Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi

Generalized or focal increases in skin pigmentation occurred in the majority of IMCIVREE-treated patients in clinical trials [*see Adverse Reactions (6.1) and Clinical Pharmacology (12.1)*]. This effect is reversible upon discontinuation of the drug.

IMCIVREE may also cause the development of new melanocytic nevi or darkening of pre-existing nevi due to its pharmacologic effect.

Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmented lesions.

5.5 Acute Adrenal Insufficiency in Patients with Acquired HO

In a clinical trial of adults and pediatric patients aged 4 years and older with acquired HO and secondary adrenal insufficiency, serious adverse reactions related to acute adrenal insufficiency were reported by 5% of IMCIVREE-treated patients and no placebo-treated patients. In patients with secondary adrenal insufficiency, monitor for clinical signs of acute adrenal insufficiency.

5.6 Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus

In a clinical trial of adults and pediatric patients aged 4 years and older with acquired HO and concomitant central diabetes insipidus (DI)/arginine vasopressin (AVP) deficiency, hyponatremia was reported in 6% of IMCIVREE-treated patients and 2% of placebo-treated patients, and hypernatremia was reported in 5% of IMCIVREE-treated patients and 4% of placebo-treated patients.

In patients with acquired HO and concomitant DI/AVP deficiency, monitor serum sodium levels with changes in fluid intake and hydration status. Adjust the doses of concomitant therapies for DI/AVP deficiency as needed.

6 ADVERSE REACTIONS

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

- Disturbance in Sexual Arousal [*see Warnings and Precautions (5.1)*]
- Depression and Suicidal Ideation [*see Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.3)*]
- Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi [*see Warnings and Precautions (5.4)*]
- Acute Adrenal Insufficiency in Patients with Acquired HO [*see Warnings and Precautions (5.5)*]
- Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus [*see Warnings and Precautions (5.6)*]

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.

Acquired HO (Adults and Pediatric Patients Aged 4 Years and Older)

The safety of IMCIVREE was evaluated in a randomized, double-blind, placebo-controlled clinical trial which included a dose titration period of 4 to 8 weeks and a 52-week treatment period, in 142 patients aged 4 years and older with acquired HO (Trial 1) [*see Clinical Studies (14.1)*]. The trial duration was 56 to 60 weeks.

Table 5 summarizes the adverse reactions that occurred in 5% or more of the IMCIVREE-treated patients and more frequently than placebo-treated patients in Trial 1.

Table 5: Adverse Reactions (≥5% and more frequently than placebo) in IMCIVREE-Treated Patients Aged 4 Years and Older with Acquired HO (Trial 1)

Adverse Reaction	IMCIVREE (N=94) %	Placebo (N=48) %
Skin hyperpigmentation ¹	58	10
Nausea	55	25
Vomiting	38	19
Headache ²	37	31
Melanocytic naevus ³	15	6
Constipation	12	6
Dizziness	12	4
Oropharyngeal pain	11	4
Gastroenteritis	9	2
Ear infection	5	0
¹ Includes skin hyperpigmentation, skin discoloration, nail pigmentation, freckles, pigmentation disorder		
² Includes headache and migraine		
³ Development of new melanocytic nevi and darkening or increase in size of existing melanocytic nevi		

Other Adverse Reactions in Patients Aged 4 Years and Older with Acquired HO

Disturbance in Sexual Arousal

Spontaneous penile erections and increased frequency of penile erections were reported in 7% of IMCIVREE-treated patients and 4% of placebo-treated patients.

Acute Adrenal Insufficiency

Serious adverse reactions related to acute adrenal insufficiency were reported by 5% of IMCIVREE-treated patients and no placebo-treated patients.

Sodium Imbalance

Among patients with acquired HO and concomitant central diabetes insipidus (DI)/arginine vasopressin (AVP) deficiency, hyponatremia was reported in 6% of IMCIVREE-treated patients and 2% of placebo-treated patients, and hypernatremia was reported in 5% of IMCIVREE-treated patients and 4% of placebo-treated patients.

Bardet-Biedl Syndrome (Adults and Pediatric Patients Aged 6 Years and Older)

The safety of IMCIVREE was evaluated in a clinical trial, which included a 14-week, randomized, double-blind, placebo-controlled period followed by a 52-week open-label treatment period, in 44 patients aged 6 years and older with obesity and a clinical diagnosis of BBS (Trial 2) [see *Clinical Studies (14.2)*]. The trial duration was 66 weeks.

During the 14-week placebo-controlled period in Trial 2, 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 6 summarizes the adverse reactions that occurred in 2 or more IMCIVREE-treated patients in Trial 2 during the 52-week active treatment period.

Table 6: Adverse Reactions Occurring in 2 or More IMCIVREE-Treated Patients Aged 6 Years and Older with Obesity and a Clinical Diagnosis of BBS During the 52-week Active-Treatment Period from the Start of IMCIVREE Treatment (Trial 2)

Adverse Reaction	IMCIVREE-treated Patients N = 43 ¹ %
Skin hyperpigmentation ²	63
Injection site reactions ³	51
Nausea	26
Spontaneous penile erection ⁴	25
Vomiting	19
Diarrhea	14
Melanocytic nevus ⁵	14
Headache	7
Skin striae	7
Aggression	5
Fatigue	5

¹ 43 patients were treated with at least 1 dose of IMCIVREE; 1 patient initially randomized to placebo withdrew from the trial prior to receiving IMCIVREE and is not included

² Includes skin hyperpigmentation, hair color changes, melanoderma

³ Includes injection site erythema, pruritis, induration, pain, bruising, edema, reaction, hemorrhage, irritation, mass

⁴ n = 20 male patients

⁵ Includes new melanocytic nevus formation, increased melanocytic nevus size, and darkening of pre-existing melanocytic nevus

POMC, PCSK1, and LEPR Deficiency (Adults and Pediatric Patients Aged 6 Years and Older)

The safety of IMCIVREE was evaluated in two 52-week, open-label clinical trials of 27 patients aged 6 years and older 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 (Trial 3 and Trial 4) [see *Clinical Studies (14.3)*].

Table 7 summarizes the adverse reactions that occurred in the open-label trials during the first 52 weeks of treatment in 3 or more patients treated with IMCIVREE.

Table 7: Adverse Reactions Occurring in 3 or More IMCIVREE-Treated Patients Aged 6 Years and Older with Obesity due to POMC, PCSK1, or LEPR Deficiency in Open-Label Clinical Trials of 52-Week Duration (Trial 3 and Trial 4)

Adverse Reaction	IMCIVREE-treated Patients N = 27 %
Injection site reaction ¹	96
Skin hyperpigmentation ²	78
Nausea	56
Headache	41
Diarrhea	37
Abdominal pain ³	33
Back pain	33
Fatigue	30
Vomiting	30
Depression ⁴	26
Upper respiratory tract infection	26
Spontaneous penile erection ⁵	23
Arthralgia	19
Asthenia	19
Melanocytic nevus ⁶	19
Dizziness	15
Dry mouth	15
Dry skin	15
Insomnia	15
Vertigo	15
Alopecia	11
Chills	11
Constipation	11
Influenza-like illness	11
Muscle spasm	11
Pain in extremity	11
Rash	11
Suicidal ideation	11
¹ Includes injection site erythema, pruritus, edema, pain, induration, bruising, injection site hypersensitivity, hematoma, nodule, and discoloration ² Includes skin hyperpigmentation, pigmentation disorders, skin discoloration, gingival discoloration ³ Includes abdominal pain and upper abdominal pain ⁴ Includes depressed mood ⁵ n = 13 male patients ⁶ Includes new melanocytic nevus formation, increased melanocytic nevus size, and darkening of pre-existing melanocytic nevus	

POMC, PCSK1, and LEPR Deficiency and BBS (Pediatric Patients Aged 2 to less than 6 Years)

The safety of IMCIVREE was evaluated in one 52-week, open-label clinical trial of 12 patients aged 2 to less than 6 years 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, or obesity due to BBS (Trial 5) [see *Clinical Studies (14.4)*]. No patients with PCSK1 were enrolled in the trial.

Table 8 summarizes the adverse reactions that occurred in the open-label trial during 52 weeks of treatment in 3 or more patients treated with IMCIVREE.

Table 8: Adverse Reactions Occurring in 3 or More IMCIVREE-Treated Patients Aged 2 to Less Than 6 Years with Obesity due to POMC or LEPR Deficiency or BBS in an Open-Label Clinical Trial of 52-Week Duration (Trial 5)

Adverse Reaction	IMCIVREE-treated Patients N = 12 %
Skin hyperpigmentation ¹	83
Injection site reactions ²	67
Vomiting	58
Nasopharyngitis	42
Melanocytic nevus ³	33
Fall	33
Fever	33
Upper respiratory tract infection	33
Cough	25
Diarrhea	25
¹ Includes skin hyperpigmentation, freckles, nail pigmentation, pigmentation lip, skin discoloration, gingival hyperpigmentation ² Includes injection site bruising, pruritus, discoloration, erythema, induration, oedema, pain, urticaria ³ Includes new melanocytic nevus formation, increased melanocytic nevus size, and darkening of pre-existing melanocytic nevus	

Other Adverse Reactions in Patients Aged 2 to less than 6 Years with Obesity due to POMC or LEPR Deficiency or BBS

Disturbance in Sexual Arousal

Spontaneous penile erections were reported in 8% of IMCIVREE-treated patients.

Depression

Depressed mood was reported in 8% of IMCIVREE-treated patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMCIVREE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity, including anaphylaxis

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.

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 have obesity, 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 until 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.

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 postnatal Day 11.

8.4 Pediatric Use

Acquired HO

The safety and effectiveness of IMCIVREE have been established to reduce excess body weight and maintain weight reduction long term in pediatric patients aged 4 years and older with acquired HO. Use of IMCIVREE for this indication is supported by evidence from a 56- to 60-week randomized, double-blind, placebo-controlled trial that included 76 pediatric patients with acquired HO aged 4 to 17 years [*see Clinical Studies (14.1)*].

Adverse reactions with IMCIVREE treatment in pediatric patients aged 4 to 17 years with acquired HO were generally similar to those reported in adults [*see Adverse Reactions (6.1)*]. Perform a full body skin examination prior to initiation and periodically during treatment with

IMCIVREE to monitor pre-existing and new skin pigmented lesions [*see Warnings and Precautions (5.4)*].

The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 4 years of age with acquired HO.

BBS or POMC, PCSK1, or LEPR Deficiency

The safety and effectiveness of IMCIVREE have been established to reduce excess body weight and maintain weight reduction long term in pediatric patients aged 2 years and older with obesity due to:

- BBS [*see Clinical Studies (14.2, 14.4)*]
- POMC, PCSK1, or LEPR deficiency with variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [*see Clinical Studies (14.3, 14.4)*]

Use of IMCIVREE for these indications is supported by evidence from one 66-week trial, which included a 14-week, randomized, double-blind, placebo-controlled period followed by a 52-week open-label period, and included 22 pediatric patients with BBS aged 6 to 17 years (Trial 2); from two 1-year, open-label trials that included 9 pediatric patients with POMC, PCSK1, or LEPR deficiency aged 6 to 17 years (Trial 3 and Trial 4); and one 1-year, open-label trial that included 12 pediatric patients with POMC or LEPR deficiency or BBS aged 2 to less than 6 years (Trial 5) [*see Clinical Studies (14.2, 14.3, 14.4)*].

Adverse reactions with IMCIVREE treatment in pediatric patients aged 2 to less than 6 years with BBS, POMC, PCSK1, or LEPR deficiency were generally similar to those reported in adults and in pediatric patients aged 6 years and older. Pediatric patients with BBS, POMC, PCSK1, or LEPR deficiency treated with IMCIVREE had greater incidences of vomiting, skin hyperpigmentation, and new or darkening nevi compared to adults with BBS, POMC, PCSK1, or LEPR deficiency treated with IMCIVREE [*see Adverse Reactions (6.1)*]. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmented lesions [*see Warnings and Precautions (5.4)*].

The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 2 years of age with BBS, POMC, PCSK1, or LEPR deficiency.

8.5 Geriatric Use

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

8.6 Renal Impairment

Patients with severe renal impairment have a higher exposure of setmelanotide relative to patients with normal kidney function. IMCIVREE is not recommended for use in adults and pediatric patients aged 4 years and older with acquired HO and severe renal impairment.

For patients with BBS or POMC, PCSK1, or LEPR deficiency, reduce the recommended starting and maintenance dosage of IMCIVREE in adults and pediatric patients 2 years of age and older

with severe renal impairment (eGFR 15-29 mL/min/1.73 m²). The use of IMCIVREE in pediatric patients aged 2 to less than 6 years with weight less than 20 kg and severe renal impairment is not recommended [see *Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

The recommended dosage in patients with mild (eGFR of 60-89 mL/min/1.73 m²) or moderate renal impairment (eGFR of 30-59 mL/min/1.73 m²) is the same as those with normal kidney function [see *Clinical Pharmacology (12.3)*].

IMCIVREE is not recommended for use in patients with end stage renal disease (eGFR less than 15 mL/min/1.73 m²).

10 OVERDOSAGE

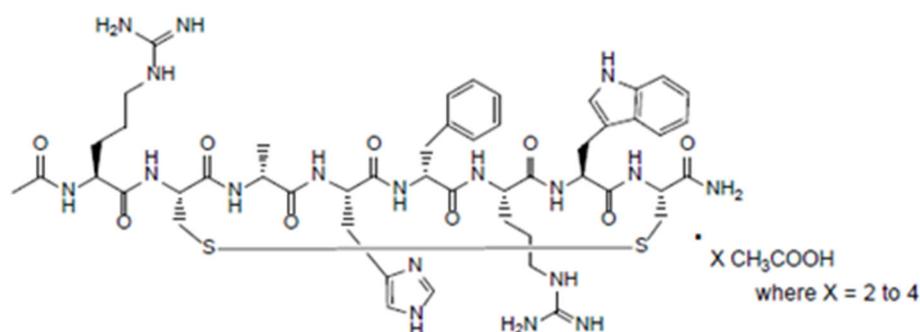
In the event of an overdose of IMCIVREE, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations and initiate appropriate supportive treatment according to the patient's clinical signs and symptoms.

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 C₄₉H₆₈N₁₈O₉S₂ (anhydrous, free-base), and molecular mass is 1117.3 Daltons (anhydrous, free-base).

The chemical structure of setmelanotide acetate is:



IMCIVREE (setmelanotide) injection is a sterile clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous use. Each 1 mL vial 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: 10 mg benzyl alcohol, 8 mg carboxymethylcellulose sodium (average MWt 90,500), 1 mg edetate disodium dihydrate, 100 mg N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-

phosphoethanolamine sodium salt, 11 mg mannitol, 5 mg phenol, hydrochloric acid, sodium hydroxide 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. Based on nonclinical evidence, setmelanotide may re-establish MC4 receptor pathway activity to reduce food intake and promote weight loss through decreased caloric intake and increased energy expenditure in patients with obesity due to acquired HO, BBS, or POMC, PCSK1, or LEPR deficiency associated with insufficient activation of the MC4 receptor. 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 (5.4) and Adverse Reactions (6.1)*].

12.2 Pharmacodynamics

At a dose 2.3 times the maximum recommended dose, IMCIVREE does not prolong the QT interval to any clinically relevant extent.

Energy Expenditure

Short-term administration of IMCIVREE in 12 otherwise healthy patients with obesity increased resting energy expenditure and shifted substrate oxidation to fat. The safety and effectiveness of IMCIVREE have not been established in such patients and IMCIVREE is not approved to treat such patients [*see Indications and Usage (1)*].

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 31 ng/mL, 373 h*ng/mL, and 5 ng/mL, respectively simulated using individual PK model parameters from 109 adult patients with normal renal function. 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 to be 75.2 L. Protein binding of setmelanotide is 79.1%.

Elimination

The effective elimination half-life ($t_{1/2}$) 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 to be 7.15 L/h in a typical male patient weighing 120 kg (actual body weight) with normal renal function.

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 or disease. 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 2 to less than 6 years, 6 to less than 12 years, and aged 12 to 17 years. Simulations were performed using population pharmacokinetic analysis for pediatric patients aged 2 to less than 6 years, following the maximum recommended doses in each of the body weight groups - 2 mg, 1.5 mg, 1 mg, and 0.5 mg in patients weighing ≥ 40 kg, 30 to < 40 kg, 20 to < 30 kg, and 15 to < 20 kg, respectively. The analyses suggest that AUC and C_{max} in pediatric patients aged 2 to less than 6 years are 52% and 75% higher in patients weighing ≥ 40 kg, 45% and 63% higher in patients weighing 30 to < 40 kg, 24% and 38% higher in patients weighing 20 to < 30 kg, and 17% and 14% lower in patients weighing 15 to < 20 kg as compared to patients greater than or equal to 18 years (3 mg dose). For patients aged 6 to less than 12 years, the setmelanotide AUC and C_{max} were 88% and 89% higher compared to patients greater than or equal to 18 years. For patients aged 12 to 17 years, the setmelanotide AUC and C_{max} were both 26% higher as compared to patients aged greater than or equal to 18 years [see *Dosage and Administration* (2.2, 2.3)].

Patients with Renal Impairment

Exposure parameters, AUC_{0-t} and AUC_{0-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 [see *Dosage and Administration* (2.4)].

Renal impairment did not appear to affect plasma protein binding. The average fraction unbound (f_u) was approximately 0.2 and was independent of renal function.

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.

12.6 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 trials described below with the incidence of ADA in other trials, including those of IMCIVREE or of other setmelanotide products.

Across 5 clinical trials with an exposure time of at least 52 weeks, 4 of 245 subjects (1.6%) were positive for antibodies against setmelanotide. Anti-setmelanotide antibodies prevalence by indication: BBS 3/50 (6.0%), AS 1/8 (12.5%), POMC deficiency (0/16), PCSK1 deficiency (0/2), LEPR deficiency (0/21), and acquired HO (0/142). Reported titers among ADA-positive subjects were generally low.

In 5 clinical trials with an exposure time of at least 52 weeks anti- α -MSH antibodies were measured in 17 of 245 subjects (6.9%). Anti- α -MSH antibodies by genetic deficiency: BBS 5/50 (10.0%), AS 1/8 (12.5%), POMC 1/16 (6.3%), LEPR 6/21 (28.6%), PCSK1 0/2 (0%), and acquired HO 4/142 (2.8%). The reported titer of ADA against α -MSH was generally low.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Setmelanotide was not carcinogenic in Tg.rasH2 mice at doses up to 10 mg/kg/day when given subcutaneously for 26 weeks.

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

14.1 Acquired HO (Adults and Pediatric Patients Aged 4 Years and Older)

Clinical Trial Overview

The efficacy of IMCIVREE for weight reduction in adults and pediatric patients aged 4 years and older with acquired HO was assessed in a randomized, double-blinded, placebo-controlled 56- to 60-week clinical trial [Trial 1 (NCT05774756)]. The trial enrolled patients 4 years and older with acquired HO due to hypothalamic injury or dysfunction. Adult patients had a BMI of ≥ 30 kg/m² and pediatric patients had a BMI $\geq 95^{\text{th}}$ percentile for age and sex.

In Trial 1, eligible patients were randomized to either setmelanotide or placebo and entered an up to 8-week dose titration period followed by a 52-week treatment period. Efficacy analyses were conducted for 142 patients.

A total of 142 patients with acquired HO were randomized and analyzed; 47% were adults, 31% were aged 12 to less than 18 years, and 23% were 4 to less than 12 years; 40% were male; 75% were White, 11% were Asian, 5% were Black or African American, and 9% had an unknown or not reported race; 11% were Hispanic or Latino ethnicity and less than 1% had an unknown or not reported ethnicity; and the mean BMI was 36 kg/m² (range: 21-70 kg/m²).

Effect of IMCIVREE on BMI in Patients with Obesity and a Clinical Diagnosis of Acquired HO

The proportion of patients who discontinued trial drug in Trial 1 were 10.6% of the IMCIVREE-treated group and 12.5% of the placebo-treated group.

The primary efficacy parameter was mean percent change in BMI from baseline after 52 weeks on a therapeutic regimen of setmelanotide compared to placebo. After 52 weeks of treatment at the therapeutic dose, the mean percent change in BMI compared to placebo was -18.40% (Table 9), and greater proportions of patients treated with IMCIVREE achieved at least 5%, 10%, and 15% BMI reduction compared to placebo (Table 9 and Figure 1).

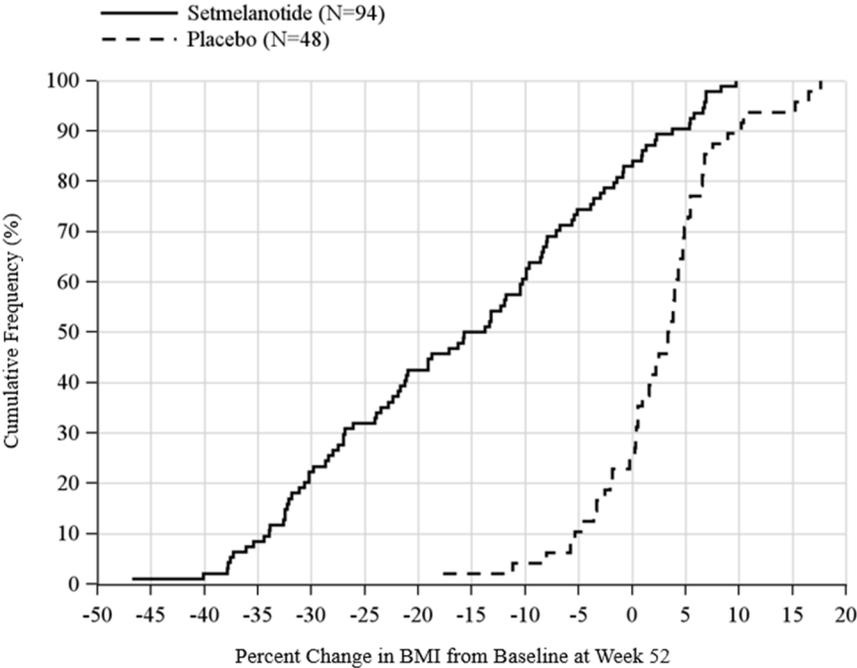
Table 9: Percent Change from Baseline in BMI after 52 Weeks on Therapeutic Regimen in Patients Aged ≥ 4 Years with Acquired HO (Trial 1)

Parameter	IMCIVREE (N=94)	Placebo (N=48)
Baseline BMI (Mean [SD]) (kg/m ²)	36.04 (9.18)	36.35 (8.77)
Percent Change from Baseline to 52 Weeks (LSM [95% CI])	-15.84 (1.52)	2.55 (0.98)
Placebo-Adjusted Difference (LSM [95% CI])*	-18.40 (-21.94, -14.85)	
Patients Achieving at Least 5% BMI Loss at 52 Weeks (Proportion, %)	75.79%	9.73%
Placebo-Adjusted Difference (RD [95% CI])*	66.23% (53.81, 78.65)	
Patients Achieving at Least 10% BMI Loss at 52 Weeks (Proportion, %)**	60.99%	4.69%
Placebo-Adjusted Difference (RD [95% CI])	56.59 (44.85, 68.32)	
Patients Achieving at Least 15% BMI Loss at 52 Weeks (Proportion, %)**	50.12%	2.15%
Placebo-Adjusted Difference (RD [95% CI])	47.75 (36.66, 58.85)	

Parameter	IMCIVREE (N=94)	Placebo (N=48)
Abbreviations: BMI = body mass index; CI = confidence interval; LSM = least squared mean; N = number of patients in the treatment group; n = number of patients with non-missing values; QD = once daily; RD=Risk Difference; SD = Standard Deviation; SE = Standard error; ANCOVA = Analysis of covariance; CMH = Cochran-Mantel-Haenszel.		
Note: The modified intention to treat population includes all randomized and treated patients. BMI after Week 52 was missing for 13% and 6% of patients randomly assigned to IMCIVREE and placebo, respectively. Missing data after Week 52 were imputed using placebo-washout MI method.		
BMI is calculated as weight (kg) / height (m) ² . ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the stratification factors of age group (≥18 years, ≥12 and <18 years, and <12 years) and subpopulation (Japanese and non-Japanese).		
RD is calculated using CMH risk difference test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese) based on the imputed BMI datasets.		
* p<0.0001 (2-sided) for superiority, controlled for multiplicity.		
** Not controlled for type I error rate.		

The cumulative frequency distributions of change in BMI are shown in Figure 1 for Trial 1. One way to interpret this figure is to select a change in BMI of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of BMI reduction. For example, a vertical line arising from -10% change in BMI in Trial 1 intersects the IMCIVREE and placebo curves at approximately 61%, and 5%, respectively, which correspond to the values shown in Table 1.

Figure 1: Cumulative Distribution of Percent Change from Baseline in BMI after 52 Weeks on Therapeutic Regimen in Patients Aged ≥4 Years with Acquired HO (Trial 1)



Note: Based on observed percent change of BMI from baseline after 52 weeks treatment, and patient-level average of 100 multiply imputed datasets (washout MI method) for patients with missing values

A reduction of BMI Z-score and BMI 95th percentile for pediatric patients less than 18 years of age was observed.

In Trial 1, patients 12 years and older who were able to self-report their hunger (n=110), recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 (“not hungry at all”) to 10 (“hungeriest possible”). After 52 weeks of treatment at the therapeutic dose, IMCIVREE resulted in a statistically significant reduction in hunger compared to placebo (Table 10).

Table 10: Daily Hunger Scores – Change from Baseline After 52 Weeks on Therapeutic Regimen in Patients Aged ≥12 Years with Acquired HO (Trial 1)

Statistic	IMCIVREE (N=74)	Placebo (N=36)
Baseline Most Hunger Score (Mean [SD])	6.70 (2.20)	7.05 (2.03)
Change from Baseline to 52 Weeks (LSM [SE])	-2.27 (0.25)	-1.44 (0.33)
Placebo-Adjusted Difference (LSM [95% CI])*	-0.82 (-1.62, -0.02)	
Abbreviations: CI = confidence interval; LSM = least squared mean; max = maximum; min = minimum; MI= multiple imputation; N = number of Randomized Patients; QD = once daily; SD = standard deviation; SE = standard error; ANCOVA = Analysis of Covariance Note: Weekly average of daily hunger scores is equal to the average of the daily scores over the 7 days immediately preceding the visit. The hunger scores on the day of the visit were not considered as prior to visit scores. Only if all 7 days prior to randomization (baseline) are missing, then consider the day of visit (Day 1) scores as prior. The modified intention to treat population includes all randomized and treated patients aged ≥ 12 years. Baseline score data were missing for 11% and 11% of patients randomly assigned to IMCIVREE and placebo, respectively. Missing data at baseline were imputed using all observed scores at baseline. Score data after Week 52 were missing for 27% and 25% of patients randomly assigned to IMCIVREE and placebo, respectively. Missing score data after Week 52 were imputed using placebo-washout MI method. The mean and SD of Baseline Most Hunger Score is calculated by the observed scores. ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the baseline weekly average hunger score, stratification factors of age group (≥18 years, and ≥12 and <18 years) and subpopulation (Japanese and non-Japanese). * p=0.04 (2-sided) for superiority, controlled for multiplicity.		

IMCIVREE resulted in a reduction in waist circumference and general numeric improvements in blood pressure, lipids, and glycemic parameters compared with placebo.

14.2 Bardet-Biedl Syndrome (Adults and Pediatric Patients Aged 6 Years and Older)

Clinical Trial Overview

The efficacy of IMCIVREE for weight reduction in adults 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 trial, which included a 14-week randomized, double-blind, placebo-controlled period and a 52-week open-label period (Trial 2 [NCT03746522]). The trial enrolled patients aged 6 years and above with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of ≥30 kg/m² and pediatric patients had weight ≥97th percentile using growth chart assessments.

In Trial 2, 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.

Efficacy analyses were conducted in 44 patients at the end of Period 1 (Week 14, placebo-controlled data) and in 31 patients during the 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. Analyses of the active-treatment period include patients who had either completed 52 weeks from the start of IMCIVREE treatment or discontinued the trial early at the time of the prespecified data cutoff.

A total of 44 patients with obesity and a clinical diagnosis of BBS were enrolled; 50% were adults, 32% were aged 12 to <18 years, and 18% were aged 6 to <12 years; 46% were male; 77% were White, 5% were Black or African American, 2% were Asian, and 16% had an unknown or not reported race; 2% were Hispanic or Latino ethnicity and 14% had an unknown or not reported ethnicity; and the mean BMI was 41.5 kg/m² (range: 24.4-66.1 kg/m²) at baseline.

Effect of IMCIVREE on BMI in Patients with Obesity and a Clinical Diagnosis of BBS

In patients aged ≥6 years with obesity and a clinical diagnosis of BBS in Trial 2, the mean percent change in BMI after 52 weeks of IMCIVREE treatment was -7.9% (Table 11), 61.3% of patients achieved a ≥5% BMI decrease from baseline, and 38.7% had a ≥10% decrease in BMI (Table 12).

Table 11: Percent Change from Baseline in BMI after 52 Weeks from the Start of IMCIVREE Treatment in Patients Aged ≥6 Years with Obesity and a Clinical Diagnosis of BBS (Trial 2) *

Parameter Statistic	Result
Baseline BMI (kg/m²)	
Mean (SD)	41.8 (9.0)
Median	41.5
Min, Max	24.4, 61.3
BMI after 52 Weeks (kg/m²)	
Mean (SD)	38.6 (9.2)
Median	39.1
Min, Max	20.4, 60.9
95% CI	35.2, 41.9
Percent Change from Baseline to 52 Weeks (%)	
Mean (SD)	-7.9 (6.7)
Median	-8.8
Min, Max	-25.4, 5.3
95% CI	-10.4, -5.5
Abbreviations: CI = confidence interval; SD = standard deviation	
*BBS patients (N=31) who completed 52 weeks from the start of IMCIVREE treatment or discontinued the trial early. Five patients who discontinued trial early were defined as 0 percent change.	

Table 12: Proportion of IMCIVREE-Treated Patients Aged ≥6 Years with Obesity and a Clinical Diagnosis of BBS Who Achieved at Least 5% and 10% BMI Decrease from Baseline After 52 Weeks from the Start of IMCIVREE Treatment (Trial 2)

Parameter	Statistic	Result
Patients* Achieving at Least 5% BMI Loss at 52 Weeks	%	61.3
	95% CI	42.2, 78.2
Patients* Achieving at Least 10% BMI Loss at 52 Weeks	%	38.7
	95% CI	21.8, 57.8
Abbreviations: CI = confidence interval; SD = standard deviation		
*BBS patients (N=31) who completed 52 weeks from the start of IMCIVREE treatment or discontinued the trial early. Five patients who discontinued trial early were defined as not achieving 5% or 10% reduction.		

During the 14-week double-blind, placebo-controlled portion of Trial 2 (Period 1), there was a statistically significant difference in BMI reduction between the IMCIVREE-treated group and the placebo-treated group (Table 13).

Table 13: Percent Change from Baseline in BMI after 14 Weeks of Treatment in Patients Aged ≥6 Years with Obesity and a Clinical Diagnosis of BBS (Trial 2)*

Parameter	IMCIVREE (N = 22)	Placebo (N = 22)
Baseline BMI (SD)	41.4 (10.0)	41.6 (10.1)
BMI at 14 Weeks (SD)	39.5 (9.9)	41.6 (9.9)
Percent Change from Baseline to 14 Weeks (SD)	-4.6 (4.1)	-0.1 (2.3)
Placebo-Adjusted Difference	-4.5	
95% CI	-6.5, -2.5	
Abbreviations: CI = confidence interval; SD = standard deviation		
*BBS subjects who completed the 14-week double-blind, placebo-controlled period (N=44).		

Effect of IMCIVREE on Hunger in Patients with Obesity and a Clinical Diagnosis of BBS

In Trial 2, patients 12 years and older who were able to self-report their hunger (n=14), recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 (“not hungry at all”) to 10 (“hungriest possible”). Weekly means of daily maximal hunger scores after 52 weeks from the start of IMCIVREE treatment are summarized in Table 14.

Hunger scores decreased in IMCIVREE-treated patients during the 14-week placebo-controlled period and during the open-label treatment period.

Table 14: Daily Hunger Scores – Change from Baseline in IMCIVREE-Treated Patients Aged ≥12 Years with Obesity and a Clinical Diagnosis of BBS After 52 Weeks From the Start of IMCIVREE Treatment (Trial 2)

Timepoint	Statistic	Result
Baseline	N	14
	Mean (SD)	6.99 (1.893)
	Median	7.29
	Min, Max	4.0, 10.0
Week 52	N	14
	Mean (SD)	4.87 (2.499)
	Median	4.43
	Min, Max	2.0, 10.0
Change at Week 52	N	14
	Mean (SD)	-2.12 (2.051)
	Median	-1.69
	Min, Max	-6.7, 0.0
Abbreviations: BBS = Bardet-Biedl syndrome; CI=confidence interval; Max=maximum; Min=minimum; NC=Not calculated; SD=Standard Deviation.		
Note: Baseline is the last assessment prior to initiation of setmelanotide in both trials.		
Note: The Daily Hunger Questionnaire is not administered to patients <12 years or to patients with cognitive impairment as assessed by the Investigator.		

Supportive of IMCIVREE’s effect on weight loss, there were general numeric improvements in blood pressure, lipids, 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.

14.3 POMC, PCSK1, and LEPR Deficiency (Adults and Pediatric Patients Aged 6 Years and Older)

Overview of Clinical Trials

The efficacy of IMCIVREE for weight reduction in adults 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 trials, each with an 8-week, double-blind withdrawal period.

- Trial 3 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency.
- Trial 4 (NCT03287960) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency.

The trials enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for either the *POMC* or *PCSK1* genes (Trial 3) or the *LEPR* gene (Trial 4). In both trials, 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 trials, adult patients had a body mass index (BMI) of ≥30 kg/m². 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.

Efficacy analyses were conducted in 21 patients (10 in Trial 3 and 11 in Trial 4) who had completed at least 1 year of treatment at the time of a prespecified data cutoff. Six additional patients enrolled in the trials (4 in Trial 3 and 2 in Trial 4) who had not yet completed 1 year of treatment at the time of the cutoff were not included in the efficacy analyses.

Of the 21 patients included in the efficacy analysis in Trials 3 and 4, 62% were adults and 38% were pediatric patients aged 16 years or younger.

- In Trial 3, 50% of patients were female, 70% were White, and the median BMI was 40 kg/m² (range: 26.6-53.3) at baseline.
- In Trial 4, 73% of patients were female, 91% were White, and the median BMI was 46.6 kg/m² (range: 35.8-64.6) at baseline.

Effect of IMCIVREE on Body Weight in Patients with Obesity due to POMC, PCSK1, or LEPR Deficiency

In Trial 3, 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 Trial 4, 46% of patients with obesity due to LEPR deficiency achieved a ≥10% weight loss after 1 year of treatment with IMCIVREE (Table 15).

Table 15: Body Weight (kg) – Proportion of IMCIVREE-Treated Patients Aged ≥6 Years with Obesity due to POMC, PCSK1, or LEPR Deficiency Who Achieved at Least 10% Weight Loss from Baseline at 1 Year in Trials 3 and 4

Parameter	Statistic	Trial 3 (POMC or PCSK1) (N=10)	Trial 4 (LEPR) (N=11)
Patients Achieving at Least 10% Weight Loss at Year 1	n (%)	8 (80%)	5 (46%)
	95% CI ¹	(44.4%, 97.5%)	(16.8%, 76.6%)
	P-value ²	<0.0001	0.0002
Abbreviations: CI = confidence interval			
Note: The analysis set includes patients who received at least 1 dose of trial drug and had at least 1 baseline assessment.			
1 From the Clopper-Pearson (exact) method			
2 Testing the null hypothesis: Proportion =5%			

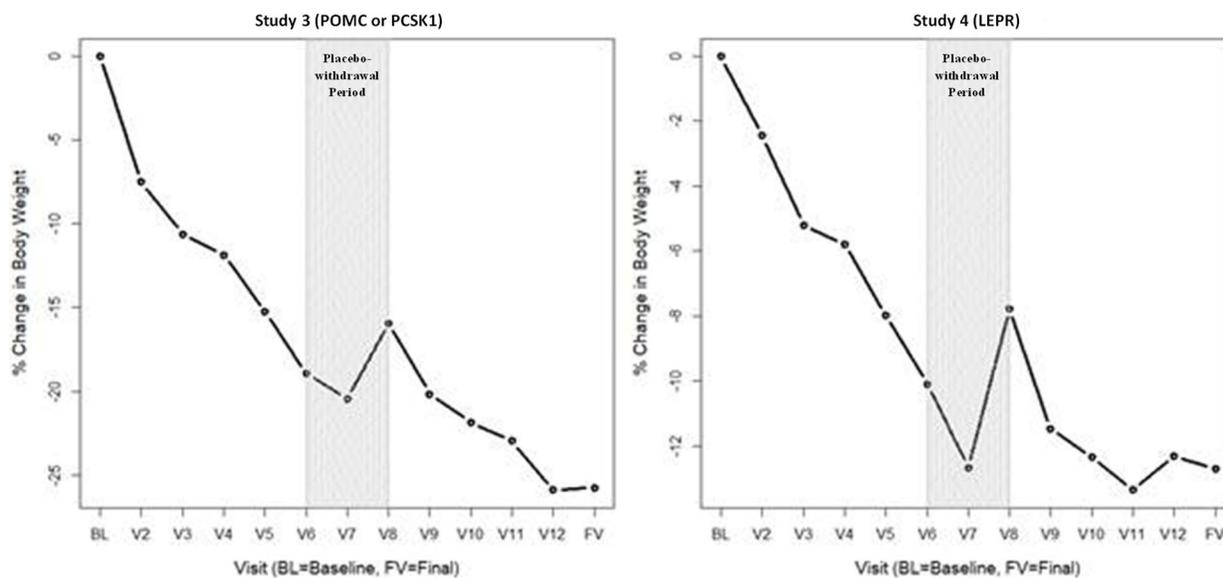
When treatment with IMCIVREE was withdrawn in the 16 patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was <100 kg) during the 10-week open-label period in Trials 3 and 4, these patients gained an average of 5.5 kg in Trial 3 and 5.0 kg in Trial 4 over 4 weeks. Re-initiation of treatment with IMCIVREE resulted in subsequent weight loss (see Figure 2).

Table 16: Percent Change from Baseline in Weight in IMCIVREE-Treated Patients Aged ≥ 6 Years with Obesity due to POMC, PCSK1, or LEPR Deficiency at 1 Year in Trials 3 and 4 (Full Analysis Set)

Parameter	Statistic	Trial 3 (POMC or PCSK1) (N=10)	Trial 4 (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

Abbreviations: CI = confidence interval; SD = standard deviation
 Note: This analysis includes patients who received at least 1 dose of trial 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 2: Mean Percent Change in Body Weight from Baseline in Patients Aged ≥ 6 Years with Obesity due to POMC, PCSK1, or LEPR Deficiency by Visit (Trial 3 [N=9] and Trial 4 [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 in Patients with Obesity due to POMC, PCSK1, or LEPR Deficiency

In Trials 3 and 4, 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 numeric rating 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 17.

Table 17: Daily Hunger Scores – Change from Baseline at 1 Year in IMCIVREE-Treated Patients Aged ≥12 Years with Obesity due to POMC, PCSK1, or LEPR Deficiency in Trials 3 and 4 with Available Hunger Data

Parameter	Statistic	Hunger in 24 Hours	
		Trial 3 (POMC or PCSK1) (N=8)	Trial 4 (LEPR) (N=8)
Baseline Hunger Score	Median	7.9	7.0
	Min, Max	7.0, 9.1	5.0, 8.4
1-Year Hunger Score	Median	5.5	4.4
	Min, Max	2.5, 8.0	2.1, 8.0
Change from Baseline to 1 Year	Median	-2.0	-3.4
	Min, Max	-6.5, -0.1	-4.7, 1.0

Note: This analysis includes patients aged 12 years and older who received at least 1 dose of trial drug and had available data. Three patients in Trial 3 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 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.

14.4 POMC, PCSK1, and LEPR Deficiency and BBS (Pediatric Patients Aged 2 to Less Than 6 Years)

Clinical Trial Overview

The efficacy of IMCIVREE for weight reduction in pediatric patients aged 2 to less than 6 years with obesity due to POMC, PCSK1, or LEPR deficiency or BBS were assessed in a 52-week clinical trial [Trial 5 (NCT04966741)]. Patients with PCSK1 deficiency were eligible but none enrolled. POMC and LEPR deficiency were confirmed by genetic testing demonstrating biallelic variants interpreted as pathogenic, likely pathogenic, or of undetermined significance; BBS was diagnosed clinically with genetic confirmation. Obesity was defined as baseline BMI ≥97th percentile for age and sex and body weight ≥20 kg.

In Trial 5, IMCIVREE dose titration occurred over an 8-week period, followed by a 44-week open-label treatment period with IMCIVREE.

Twelve (12) patients were enrolled (3 patients with POMC deficiency, 4 patients with LEPR deficiency, and 5 patients with BBS); 58% were male; 58% were White, 8% were Asian, and 33% had an unknown or not reported race; 8% were Hispanic or Latino ethnicity and 17% had an unknown or not reported ethnicity; and the mean BMI was 29.9 kg/m² (range: 19-43 kg/m²) at baseline.

Efficacy analyses were conducted in all 12 patients at the end of treatment.

Effect of IMCIVREE on BMI in Patients Aged 2 to Less Than 6 Years with POMC or LEPR Deficiency or BBS

In Trial 5, 8% of patients discontinued trial drug.

The mean percent change in BMI after 52 weeks of IMCIVREE treatment was -33.8%, -13.1%, and -9.7% in patients with POMC deficiency, LEPR deficiency, and BBS, respectively (Table 18).

Table 18: Percent Change from Baseline in BMI after 52 Weeks of IMCIVREE Treatment in Patients Aged 2 to Less Than 6 Years with Obesity due to POMC Deficiency, LEPR Deficiency, or BBS (Trial 5)

Statistic	POMC (N=3)	LEPR (N=4)	BBS (N=5)
Baseline BMI (kg/m²)			
N	3	4	5
Mean (SD)	27.8 (1.6)	39.3 (4.8)	23.7 (3.5)
Median	28.4	41.2	23.0
Min, Max	26.0, 28.9	32.2, 42.5	19.3, 29.0
BMI at Week 52 (kg/m²)			
N	3	4	5
Mean (SD)	18.3 (1.2)	34.0 (5.0) ²	21.4 (3.3)
Median	18.0	32.7	22.2
Min, Max	17.3, 19.7	29.5, 41.1	17.9, 25.2
Percent Change from Baseline to 52 Weeks (%)			
Mean (SE)	-33.8 (4.7)	-13.1 (5.4) ³	-9.7 (4.0)
Median	-37.6	-15.1	-9.0
Min, Max	-39.3, -24.3	-22.1, 0	-21.6, 2.5
95% CI ¹	-54.1, -13.4	-30.4, 4.2	-20.7, 1.3
Abbreviations: CI = confidence interval; SD = standard deviation			
¹ Two-sided 95% CI is calculated with Student's t-distribution.			
² Using last observation carried forward (LOCF), the mean BMI (SD), median, min, and max at Week 52 are 34.9 (6.8), 32.7, 29.5, and 44.9, respectively. Using observed data only, the mean BMI (SD), median, min, and max at Week 52 are 31.6 (1.9), 32.2, 29.5, and 33.1, respectively.			
³ Week 52 results are based off baseline observation carried forward (BOCF) for 1 patient lost to follow up after Week 8. Results using last observation carried forward are -10.8 (-34.4, 12.8) and using observed data excluding 1 patient lost to follow up are -17.4 (-37.2, 2.4).			

Supportive of IMCIVREE's effect on weight loss, general numeric improvements in waist circumference were observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

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: NDC 72829-010-01

Store unopened IMCIVREE vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. 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 19 for a summary of storage conditions for IMCIVREE. Store vials in the original carton.

Table 19: 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 and caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Disturbance in Sexual Arousal

Inform patients and caregivers that sexual adverse reactions, including spontaneous erection, may occur in patients treated with IMCIVREE. Advise patients to seek emergency medical treatment if an erection lasts longer than 4 hours [see *Warnings and Precautions (5.1)*].

Depression and Suicidal Ideation

Inform patients and caregivers that IMCIVREE may cause depression or suicidal ideation. Advise patients and caregivers to report any new or worsening symptoms of depression, suicidal thoughts or behaviors, or unusual changes in mood or behavior [see *Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Inform patients and caregivers that serious hypersensitivity reactions have been reported with use of IMCIVREE. Advise patients and caregivers on the symptoms of hypersensitivity reactions and instruct them to stop taking IMCIVREE and seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.3)*].

Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi

Inform patients and caregivers that skin darkening occurs in the majority of patients treated with IMCIVREE because of its mechanism of action. This change is reversible upon discontinuation of IMCIVREE. Inform patients and caregivers that the development of new melanocytic nevi may occur. Inform patients and 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 (5.4)*].

Acute Adrenal Insufficiency in Patients with Acquired HO

Inform patients with adrenal insufficiency and their caregivers to contact their healthcare provider for any significant changes in fatigue or lethargy, mental status, dizziness, fever, or signs of infection which may require an increase in steroid dosing occur during treatment with IMCIVREE [see *Warnings and Precautions (5.5)*].

Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus

Inform patients with diabetes insipidus and their caregivers to contact their healthcare provider if changes in fluid intake or urine output or other signs of dehydration, mental status changes (e.g., confusion, lethargy), or significant nausea and vomiting occur which may require adjustments in concomitant therapies during treatment with IMCIVREE [see *Warnings and Precautions (5.6)*].

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 [see *Dosage and Administration (2.5)*].

Manufactured for:

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

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

What is IMCIVREE?

- IMCIVREE is a prescription medicine used in adults and children:
 - 4 years of age and older with acquired hypothalamic obesity (HO) to help them lose weight and keep the weight off.
 - 2 years of age and older with obesity due to Bardet-Biedl syndrome (BBS) to help them lose weight and keep the weight off.
 - 2 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 or with benign or likely benign genetic testing results.
 - Other types of obesity not related to acquired HO, BBS, or 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 2 years of age.

Do not use IMCIVREE if you have had a serious allergic reaction to setmelanotide or any of the ingredients in IMCIVREE. Serious allergic reactions, including a severe allergic reaction called anaphylaxis, can happen when you use IMCIVREE. See the end of this Patient Information leaflet for a complete list of ingredients in IMCIVREE.

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 had a prior allergic reaction to setmelanotide or any of the ingredients in IMCIVREE.
- have kidney problems.
- have adrenal insufficiency.
- have diabetes insipidus.
- 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.
- 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, suicidal thoughts or behaviors, or any unusual changes in mood or behavior.
- **Serious allergic reactions.** Stop taking IMCIVREE and get medical help right away if you have any symptoms of a serious allergic reaction including:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - rapid heartbeat
- **Increased skin pigmentation, darkening of skin lesions (moles or nevi) you already have, and development of new skin lesions.** 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.

- **Adrenal insufficiency.** If you have acquired HO and adrenal insufficiency, your healthcare provider should evaluate your adrenal function before starting IMCIVREE. You or your caregiver should call your healthcare provider if you have changes in feeling tired or exhausted (fatigue), lack of energy (lethargy), mental status, or dizziness, or fever, or signs of infection during treatment with IMCIVREE. Your healthcare provider should monitor and adjust any medicines that may be affected during treatment.
- **Low sodium levels in the blood.** If you have acquired HO and diabetes insipidus, you or your caregiver should watch for signs of dehydration. You or your caregiver should contact your healthcare provider if you have changes in fluid intake or urine output, confusion, lethargy, or nausea and vomiting during treatment with IMCIVREE. Your healthcare provider should closely monitor sodium levels in your blood and adjust your other medicines if needed.

The most common side effects of IMCIVREE include:

- darkening of the skin
- injection site reactions
- nausea
- headache
- diarrhea
- stomach pain
- vomiting
- depression
- 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.

You may also report side effects to 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: benzyl alcohol, carboxymethylcellulose sodium, edetate disodium dihydrate, N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl- glycero-3-phosphoethanolamine sodium salt, mannitol, phenol, hydrochloric acid, sodium hydroxide, 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.
- The IMCIVREE vial may be used to give more than 1 dose of medicine (multiple-dose vial) but is for single patient use only and should not be shared with other patients.
- 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.

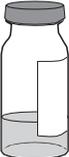
Important note:

- 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.

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

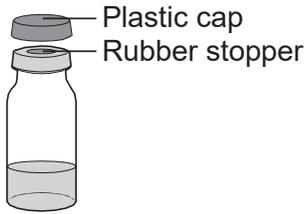
Preparing to Inject IMCIVREE

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

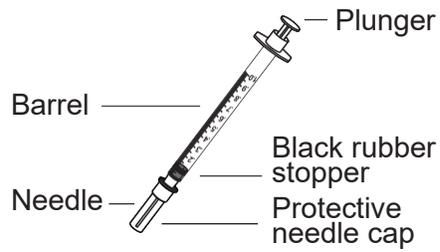
You will need the following supplies:



Vial



2 Alcohol
wipes



1 mL syringe with 28- or
29-gauge (28-29G) needle



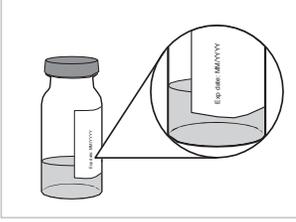
Sharps
container



Gauze
pad

Step 2 Check your IMCIVREE vial.

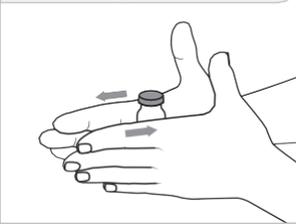
Figure C



- 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.

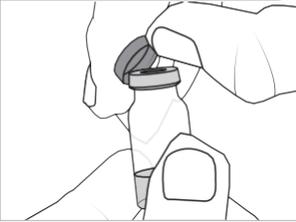
Step 3 Prepare your IMCIVREE vial.

Figure D



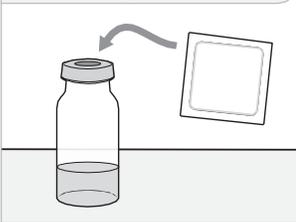
- Allow the vial to reach room temperature.
 - Remove the vial from the refrigerator 15 minutes before injection.
 - You can also warm the vial by rolling it gently between the palms of your hands for 60 seconds (**Figure D**).
- **Do not** try to warm the vial by using a heat source such as hot water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

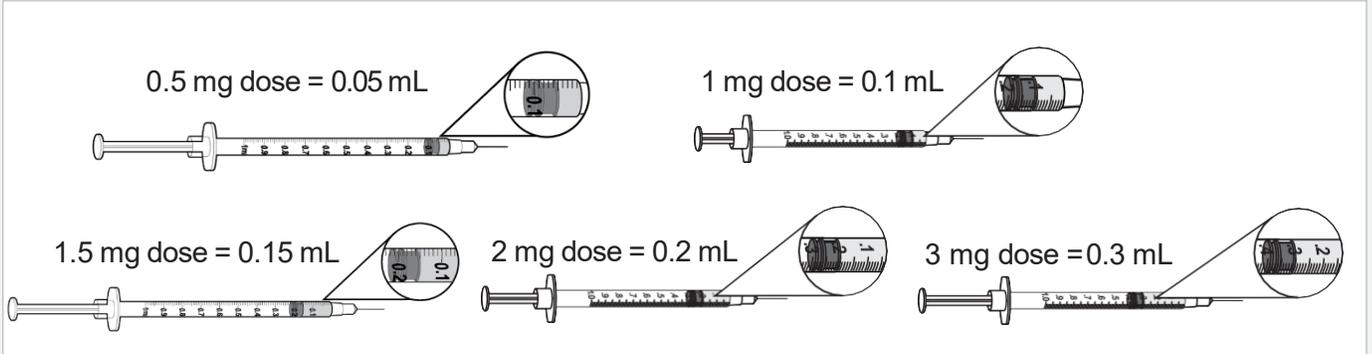


Figure H



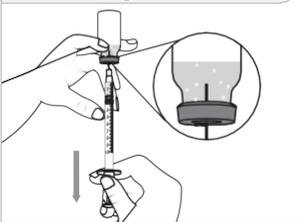
- Fill the syringe with air.
 - Keep the protective needle cap on the syringe.
 - Pull back on the plunger until the end of the black rubber stopper stops at your dose. Fill the syringe with air equal to the amount of the medicine to be given (**Figure H**).
- Remove the protective needle cap from the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

Figure I



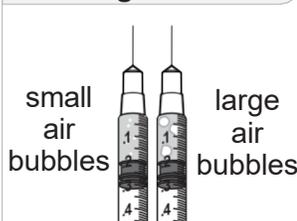
- Insert the needle.
 - Place the vial on the clean, flat work surface.
 - With the vial in the upright position, place the syringe directly over the vial and insert the needle straight down into the center of the vial rubber stopper (**Figure I**).
 - Push the air from the syringe into the vial.

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



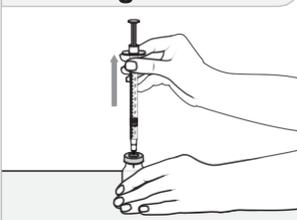
- Check for large air bubbles (**Figure K**).
 - Keep the needle in the vial and check the syringe for large air bubbles.

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.

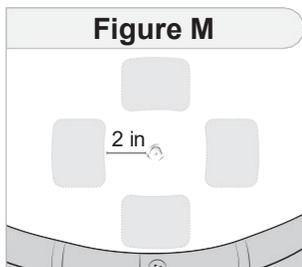
Figure L



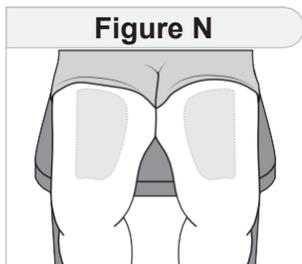
- Withdraw the needle
 - Return the vial to an upright position and place it on the clean, flat work surface.
 - While holding the vial with 1 hand and the barrel of the syringe between the fingertips of your other hand, pull the needle straight out of the vial (**Figure L**).
 - Set the syringe down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

Injecting IMCIVREE

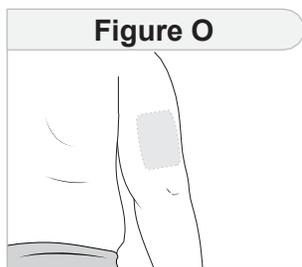
Step 5 Prepare your injection site.



- 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

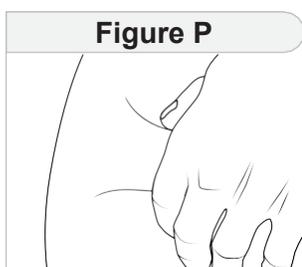


- Clean the injection site with the second alcohol wipe using a circular motion.
- **Do not** touch, fan, or blow on the cleaned area.
- Allow the skin to dry for about 10 seconds.

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.

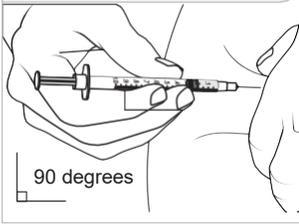
Step 6 Place your hands for the injection.



- 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).

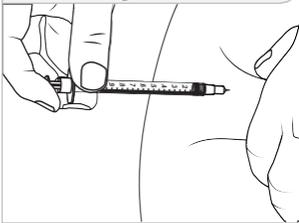
Step 7 Inject and release.

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:

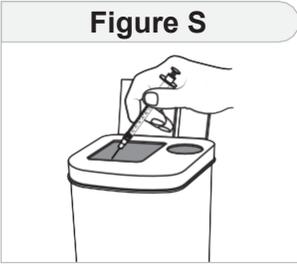
- squeeze something soft like a ball or stuffed animal.
- slowly breathe in and out.
- sing a song, count, or name favorite colors or animals.

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, opened 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)). Vials may be returned to the refrigerator. 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. 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. Throw away IMCIVREE that has been stored above 86°F (30°C).
- Write the date on the carton when you first open the vial.
- **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:

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Boston, MA 02116

Made in France

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