



IMCIVREE[®]

(setmelanotide) injection

Beginning Treatment

An overview for people living with obesity due to POMC, PCSK1, or LEPR deficiency

WHAT IS IMCIVREE?

IMCIVREE is a prescription medicine used in adults and children 2 years of age and older with obesity due to the genetic conditions pro-opiomelanocortin (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 POMC, PCSK1, or LEPR deficiency, or other FDA-approved uses of IMCIVREE, 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.

IMPORTANT SAFETY INFORMATION

Do not use IMCIVREE if you have had a serious allergic reaction to it or any of its ingredients. Serious allergic reactions, including anaphylaxis, can happen.

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

Learn more about IMCIVREE

Whether you're starting treatment with IMCIVREE or caring for someone who is, this brochure provides helpful information about what to expect.

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This brochure is intended to provide useful information about IMCIVREE but doesn't replace important conversations with your healthcare provider. If you have any questions, always ask your healthcare provider.

Important Safety Information (cont'd)

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

- Have or have had areas of darkened skin, including skin discoloration (hyperpigmentation)
- Have or have had depression, or suicidal thoughts or behavior
- Have kidney problems
- Are pregnant or planning to become pregnant. Losing weight while pregnant may harm your unborn baby. Your healthcare provider may stop your treatment with IMCIVREE if you become pregnant. Tell your healthcare provider if you become pregnant or think you might be pregnant during treatment with IMCIVREE
- Are breastfeeding or plan to breastfeed. It is not known if IMCIVREE passes into your breast milk. You should not breastfeed during treatment with IMCIVREE

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

A treatment for long-term weight management

IMCIVREE is a prescription medicine for adults and children 2 years and older who have certain types of obesity caused by genetic changes that affect some parts of the brain. These changes are called genetic variants.

IMCIVREE is approved to treat obesity due to:

POMC deficiency

POMC stands for proopiomelanocortin

PCSK1 deficiency

PCSK1 stands for proprotein convertase subtilisin/kexin type 1

LEPR deficiency

LEPR stands for leptin receptor



These conditions occur when both copies of the relevant gene (one inherited from the mother and one from the father) have a specific change. Genetic testing is required to confirm this change prior to starting IMCIVREE.

Important Safety Information (cont'd)

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

See the detailed Instructions for Use that come with your IMCIVREE to learn how to prepare and inject IMCIVREE, and how to properly throw away (dispose of) used syringes and needles.

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

About POMC, PCSK1, and LEPR deficiencies

In people with obesity due to POMC, PCSK1, or LEPR deficiency, these genetic changes affect how the brain controls feelings of hunger, which leads to weight gain.

A change in the
POMC gene

POMC deficiency

A change in the
PCSK1 gene

PCSK1 deficiency

A change in the
LEPR gene

LEPR deficiency

SYMPTOMS



Early-onset
obesity



Constant,
hard-to-control
hunger

IMCIVREE is a prescription medicine used in adults and children 2 years of age and older with obesity due to the genetic conditions pro-opiomelanocortin (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 POMC, PCSK1, or LEPR deficiency, or other FDA-approved uses of IMCIVREE, 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.

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IMCIVREE clinical studies

IMCIVREE was evaluated across three, first-ever Phase 3 clinical trials dedicated to obesity and hunger reduction in people with POMC, PCSK1, or LEPR deficiency.

STUDY 1	STUDY 2	STUDY 3
<p>Children & adults 6 years and older with obesity due to</p> <p>POMC or PCSK1 deficiency</p> <p> 10 participants Results after 1 year</p>	<p>Children & adults 6 years and older with obesity due to</p> <p>LEPR deficiency</p> <p> 11 participants Results after 1 year</p>	<p>Young children ages 2 to less than 6 years old with obesity due to</p> <p>POMC, PCSK1, or LEPR deficiency*</p> <p> 7 participants Results after 1 year</p>

In the clinical studies

Adults had a body mass index (BMI) of 30 kg/m² or more. Children ages 6 to less than 18 years old had BMI in the 95th percentile or higher using growth chart assessments. Young children ages 2 to less than 6 years old had BMI in the 97th percentile or higher.

*Patients with PCSK1 deficiency were eligible but none enrolled in the trial.

Important Safety Information (cont'd)

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

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

IMCIVREE was evaluated in 3 clinical studies

The information in this brochure includes data from 28 individuals (10 from Study 1, 11 from Study 2, and 7 from Study 3) who completed at least 1 year of treatment.

There were 6 additional participants who had not yet completed 1 year of treatment when this information was collected. Their results were not included in efficacy information, but are included in safety information.

STUDY 1

Both Studies 1 and 2 included a period of time taking IMCIVREE, followed by a withdrawal period lasting 8 weeks, which included 4 weeks of IMCIVREE followed by 4 weeks of no treatment. Neither the investigators nor the participants were aware of when the 4-week non-treatment time period was occurring.

After the withdrawal period, participants went on to receive up to 32 additional weeks of treatment with IMCIVREE.

STUDY 2

STUDY 3

In Study 3, all participants received IMCIVREE and were observed over a 52-week period.

Obesity due to POMC or PCSK1 deficiency

In clinical studies, IMCIVREE reduced weight and hunger for people with obesity due to POMC or PCSK1 deficiency.



*Participants who experienced weight loss of 5 kg/11 lbs (or 5% if their starting weight was less than 100 kg/220 lbs) during the first 10 weeks

Important Safety Information (cont'd)

What are the possible side effects of IMCIVREE? (cont'd)

IMCIVREE may cause serious side effects, including:

- **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

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

Obesity due to POMC or PCSK1 deficiency



Hunger



After 1 year, participants (n=8) experienced a **decrease from 7.9 to 5.5** in the median[†] daily hunger score.

Changes in hunger were evaluated using a questionnaire that was completed each day for 1 year by participants who were 12 years of age or older. The questionnaire measured hunger using a score ranging from 0 (not hungry at all) to 10 (hungriest possible).

Impact of stopping treatment

Treatment was stopped for a period of time to see how it impacted weight and hunger. Over this withdrawal period:



Weight increased; when the withdrawal period ended and treatment was restarted, weight loss continued

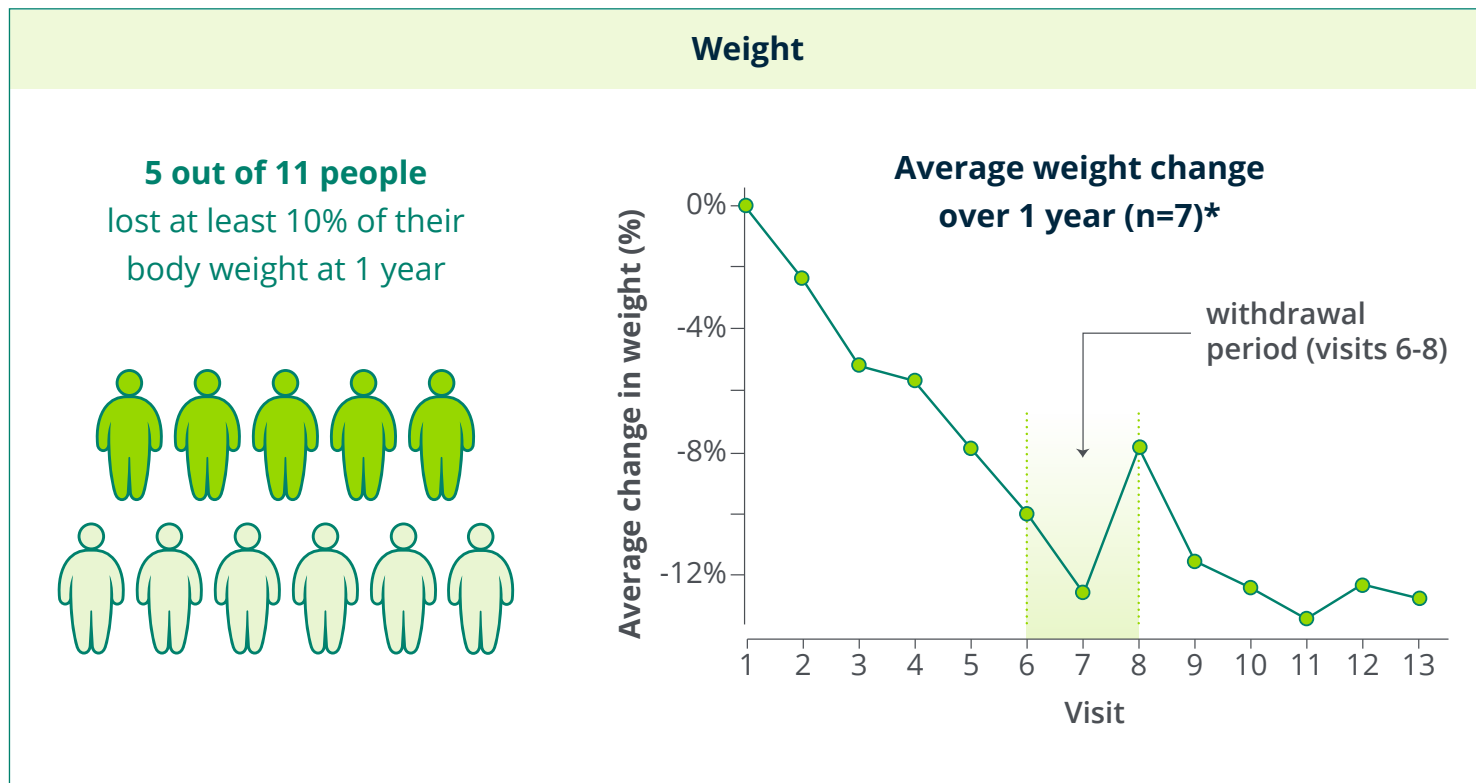


Hunger scores generally worsened; hunger scores improved once treatment was restarted

[†]A median is the middle value of a set of data that have been put into numerical order. The median is the value that divides the data into two halves.

Obesity due to LEPR deficiency

In clinical studies, IMCIVREE reduced weight and hunger for people with obesity due to LEPR deficiency.



*Participants who experienced weight loss of 5 kg/11 lbs (or 5% if their starting weight was less than 100 kg/220 lbs) during the first 10 weeks

Important Safety Information (cont'd)

What are the possible side effects of IMCIVREE? (cont'd)

IMCIVREE may cause serious side effects, including:

- 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

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

Obesity due to LEPR deficiency



Hunger



After 1 year, participants (n=8) experienced a **decrease from 7.0 to 4.4** in the median[†] daily hunger score.

Changes in hunger were evaluated using a questionnaire that was completed each day for 1 year by participants who were 12 years of age or older. The questionnaire measured hunger using a score ranging from 0 (not hungry at all) to 10 (hungriest possible).

Impact of stopping treatment

Treatment was stopped for a period of time to see how it impacted weight and hunger. Over this withdrawal period:



Weight increased; when the withdrawal period ended and treatment was restarted, weight loss continued

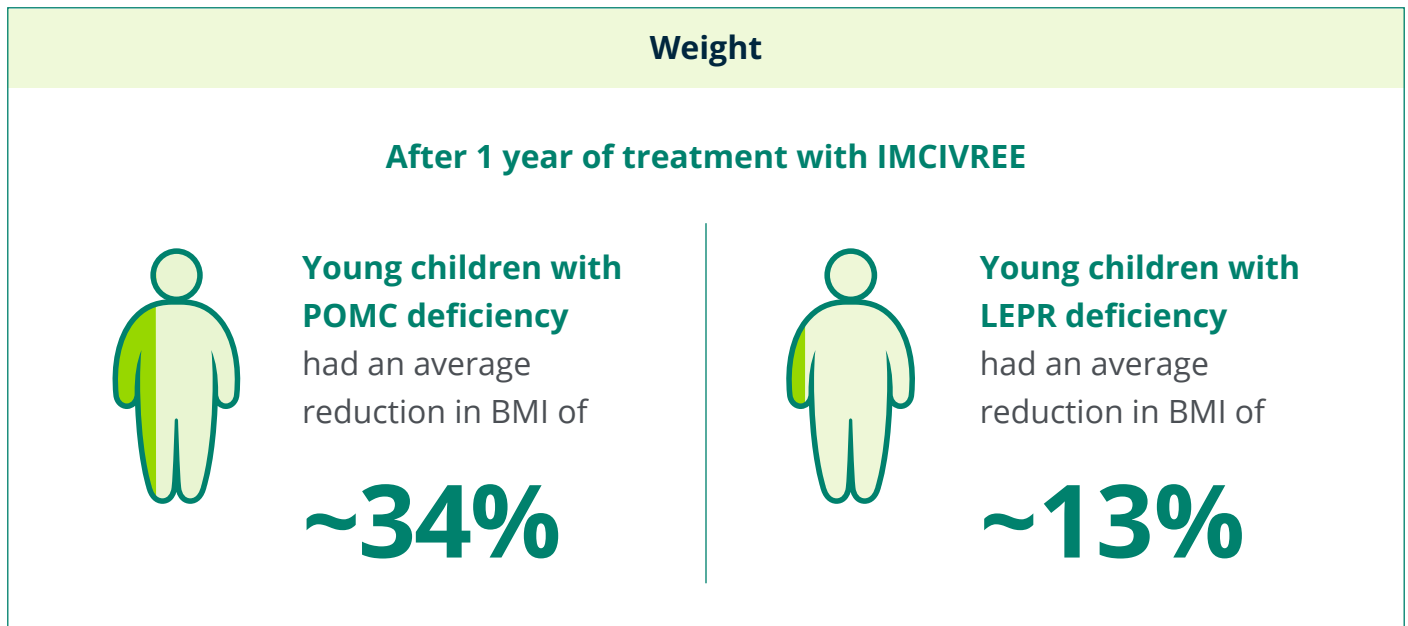


Hunger scores generally worsened; hunger scores improved once treatment was restarted

[†]A median is the middle value of a set of data that have been put into numerical order. The median is the value that divides the data into two halves.

Obesity due to POMC, PCSK1, or LEPR deficiency*

In a clinical study, IMCIVREE reduced weight in young children ages 2 to less than 6 years old with obesity due to POMC or LEPR deficiency.



*Patients with PCSK1 deficiency were eligible but none enrolled in the trial.

Important Safety Information (cont'd)

The most common side effects of IMCIVREE include darkening of the skin, injection site reactions, nausea, headache, diarrhea, stomach pain, vomiting, depression, and an 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 are encouraged to report negative side effects of prescription drugs to FDA. Visit www.fda.gov/medwatch or call FDA at 1-800-FDA-1088.

Please see Important Safety Information throughout, and full Prescribing Information and Patient Information.

Obesity due to POMC, PCSK1, or LEPR deficiency*

Weight



100%

of young children
(3 out of 3) with
POMC deficiency

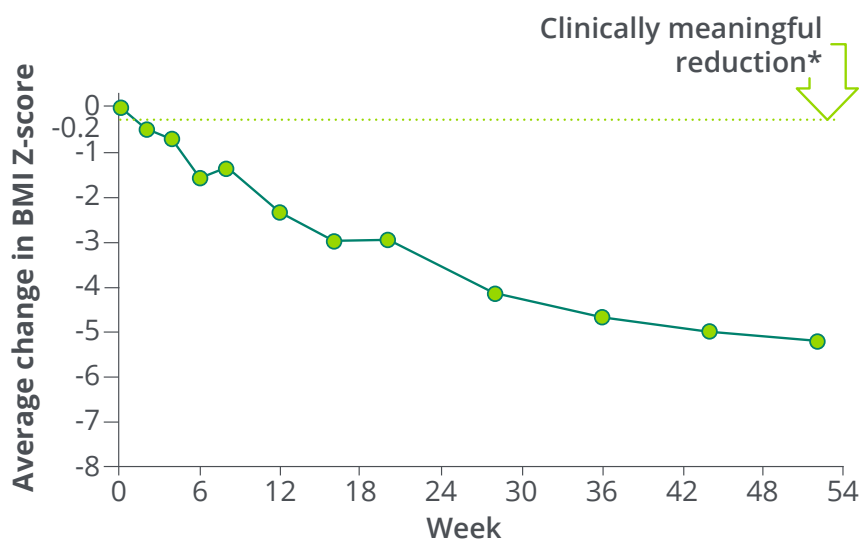


75%

of young children
(3 out of 4) with
LEPR deficiency

had a meaningful reduction in BMI Z-score over 1 year

Average change in BMI Z-score over 1 year



A clinically meaningful
5.19 mean reduction
in BMI Z-score at week 52

*A clinically meaningful reduction is generally considered a ≥ 0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.

POMC, PCSK1, or LEPR deficiency can affect weight and hunger

In POMC, PCSK1, or LEPR deficiency, constant, hard-to-control hunger and obesity are caused by a genetic change that makes it difficult for the brain's hunger signaling pathway to help you feel full.



The key area of the brain that communicates being hungry or full is known as the hypothalamus—think of the hypothalamus as a neighborhood within the brain

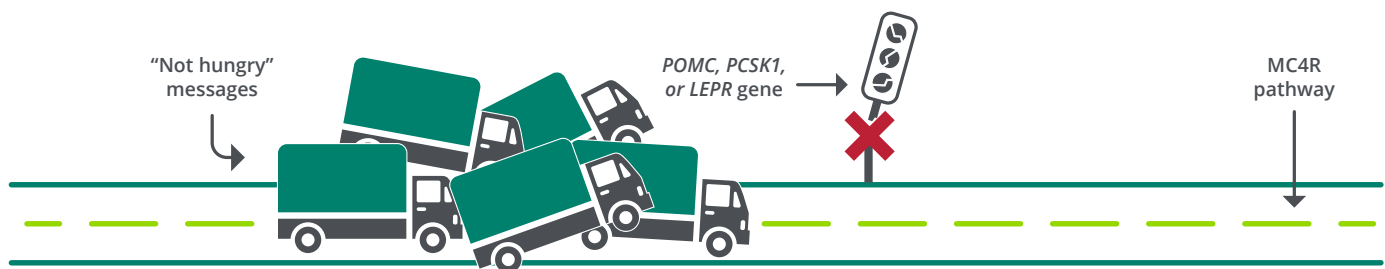


In this neighborhood, there are roads that allow trucks carrying messages about hunger and fullness to travel to and from the brain; one road is called the MC4R pathway



When the POMC, PCSK1, or LEPR gene is normal, without a variant (or change), the traffic light works correctly—the road (MC4R pathway) is open, and the trucks can deliver messages to the brain that the body is satisfied and doesn't need more food

In people living with POMC, PCSK1, or LEPR deficiency, the signals that turn hunger "off" don't work correctly in the brain.

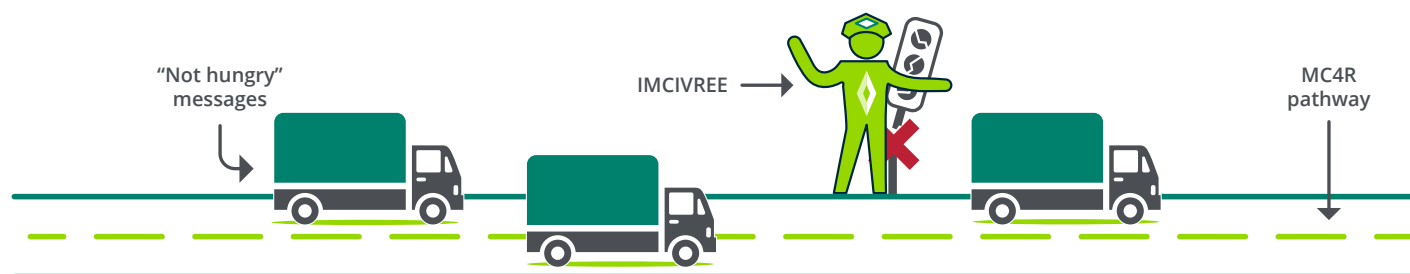


When the POMC, PCSK1, or LEPR gene has a variant (or change), the traffic light is broken, which causes a traffic jam. The trucks can no longer travel along the road (MC4R pathway) to properly deliver messages to the brain that the body is satisfied and doesn't need more food. Instead, the brain believes that the body is still hungry.

IMCIVREE works to target the source

IMCIVREE targets the impaired MC4R pathway in the brain, a root cause of obesity and hunger in people living with POMC, PCSK1, or LEPR deficiency.

IMCIVREE is designed to reestablish function to the road (MC4R pathway) so trucks can deliver messages to the brain that the body is satisfied.



Think of IMCIVREE as a traffic officer. When the traffic light is broken, the traffic officer directs trucks on the road (MC4R pathway), allowing them to deliver messages to the brain that the body is satisfied and doesn't need more food. This is how IMCIVREE works to help the MC4R pathway function properly.

Important Safety Information (cont'd)

Do not use IMCIVREE if you have had a serious allergic reaction to it or any of its ingredients. Serious allergic reactions, including anaphylaxis, can happen.

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

Safety information

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

Please see additional Important Safety Information continued within this brochure, and [full Prescribing Information](#) and [Patient Information](#).

Safety information (cont'd)

IMCIVREE was well studied and most side effects were generally mild and improved over time

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 are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Understanding your dose

Your healthcare provider will determine the dose of IMCIVREE that's right for you.

Your dose will be measured in milligrams (mg) based on your age and response to treatment.

IMCIVREE is given



As an injection under the skin with a short, thin needle



Once daily at home at the beginning of the day



With or without food

Once-daily IMCIVREE may help you reach your weight loss goals

- **Your doctor will monitor you for the first few weeks** while you are on IMCIVREE; during this time, they may increase or decrease your dose until you reach your maintenance dose
- **If any side effects occur**, report them to your doctor immediately. Your doctor may adjust your dose, which is a standard step in deciding which dose works for you
- **You and your healthcare provider will continue to evaluate your response** to treatment as long as you are treated with IMCIVREE to determine if your dose needs any further adjustment
- **If you miss a dose of IMCIVREE**, wait to inject your next dose at the regularly scheduled time the next day

Important Safety Information (cont'd)

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

- Have or have had areas of darkened skin, including skin discoloration (hyperpigmentation)
- Have or have had depression, or suicidal thoughts or behavior
- Have kidney problems

Please see Important Safety Information throughout, and [full Prescribing Information](#) and [Patient Information](#).

Understanding your dose



**10 mg/1 mL
multiple-dose vial**

Each vial of IMCIVREE contains enough medicine for more than one dose. The vial will include both medicine and air. Most of the vial will be filled with air. The number of doses in each vial will depend on your individual dose prescribed by your healthcare provider.

The table below shows the maximum number of doses included in each vial based on different prescribed doses.

Prescribed dose (mg)	Prescribed dose (mL)	Maximum number of doses per vial
0.5 mg	0.05 mL	20
1 mg	0.1 mL	10
2 mg	0.2 mL	5
3 mg	0.3 mL	3

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

Resources to help you inject

Injection training is offered before you start IMCIVREE. Training can be given by your doctor or coordinated through Rhythm InTune.

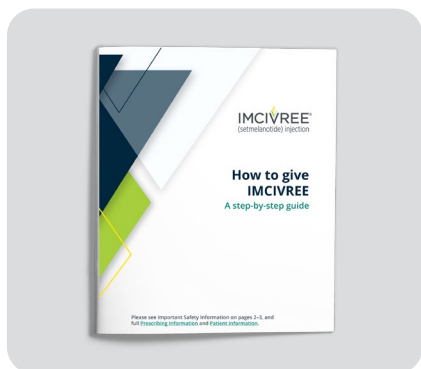


Once trained, you may inject IMCIVREE on your own or with the help of a caregiver.

You can find helpful resources such as the **How to Give IMCIVREE video** and **IMCIVREE Injection Guide** by scanning the QR code here.



How to Give IMCIVREE training video to walk through the injection process.



IMCIVREE Injection Guide explaining the steps to inject your medicine.

Please see Important Safety Information throughout, and **full Prescribing Information** and **Patient Information**.

Personalized support throughout your journey

Rhythm InTune is here to support you



Whether you're learning about POMC, PCSK1, or LEPR deficiency, preparing for a visit, or managing daily routines, a Rhythm InTune Patient Education Manager (PEM)* can provide resources, education, and information.

Patient Education Managers can help you with:



Coverage and Financial Assistance:

Help you understand your insurance coverage and explain financial assistance options for eligible patients



Injection Training:

Provide virtual or live injection training and educational materials



Starting Treatment:

Provide education on what to expect when you start treatment and possible side effects



Accessing Educational Resources:

Provide a library of resources with information about POMC, PCSK1, or LEPR deficiency and treatment with IMCIVREE

Access support at 1-855-206-0815 (M-F, 8 am-6 pm EST), or by emailing patientsupport@rhythmtx.com.

*Patient Education Managers are employees of Rhythm Pharmaceuticals and do not provide medical care or advice. We encourage you to always speak to your healthcare provider regarding your medical care.

Important Safety Information (cont'd)

Before you use IMCIVREE, tell your healthcare provider about all your medical conditions, including if you (cont'd):

- 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

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(setmelanotide) injection

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Rhythm[®]
PHARMACEUTICALS

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