IMCIVREE®
(setmelanotide) injection

Beginning treatment

An overview

Please see accompanying full Prescribing Information and Patient Information.

Establishing a new routine

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

Inside, you'll learn:

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

What is IMCIVREE?

IMCIVREE is a prescription medicine used in adults and children 6 years of age and older with obesity due to the genetic conditions 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 an FDA-approved 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 6 years of age.

Please see accompanying full Prescribing Information and Patient Information.

IMCIVREE® (setmelanotide) injection

A treatment for long-term weight management

IMCIVREE is a prescription medicine for adults and children 6 years and older who have certain types of obesity caused by genetic changes in the brain. These changes are called genetic variants.

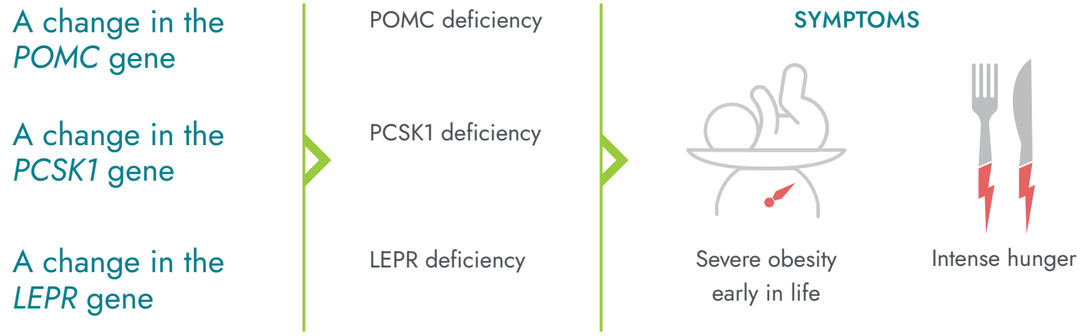
IMCIVREE is approved to treat obesity due to:

POMC deficiency / POMC stands for proopiomelanocortin

PCSK1 deficiency / PCSK1 stands for proprotein convertase subtilisin/kexin type 1

LEPR deficiency / LEPR stands for leptin receptor

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.



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

IMCIVREE is approved for use in people with certain genetic changes. The FDA-approved test must show that the changes, or variants, are considered pathogenic, likely pathogenic, or uncertain.

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 FDA-approved testing (benign or likely benign result).
- Other types of obesity not related to POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic conditions and general obesity.

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

Important Safety Information (continued)

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 accompanying full Prescribing Information and Patient Information.

IMCIVREE® (setmelanotide) injection

IMCIVREE clinical studies

IMCIVREE was evaluated in 2 clinical studies of people 6 years and older with POMC, PCSK1 or LEPR deficiency.

STUDY 1

people with obesity due to

POMC or PCSK1 deficiency

10 participants
Results after 1 year

STUDY 2

people with obesity due to

LEPR deficiency

11 participants
Results after 1 year

IN BOTH STUDIES

Adults had a body mass index (BMI) of 30 kg/m² or more, and children had weight in the 95th percentile or higher using growth chart assessments.

The information in this brochure includes data from 21 individuals (10 from Study 1 and 11 from Study 2) 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.

Both studies 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.

LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Important Safety Information (continued)

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 accompanying full Prescribing Information and Patient Information.

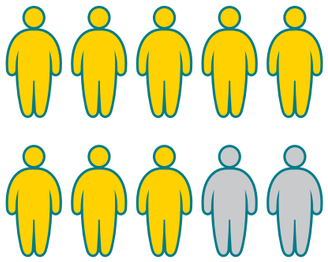
IMCIVREE® (setmelanotide) injection

Clinical study results: POMC or PCSK1 deficiency

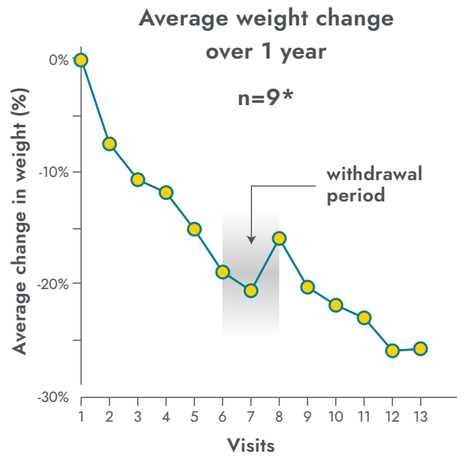
In clinical studies, IMCIVREE reduced weight and hunger for people with obesity due to POMC or PCSK1 deficiency.

Weight

STUDY 1
People with obesity due to POMC or PCSK1 deficiency



8 out of 10 people lost at least 10% of their body weight at 1 year



*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.

PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Important Safety Information (continued)

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

Hunger

STUDY 1
People with obesity due to POMC or PCSK1 deficiency

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.

Please see accompanying full Prescribing Information and Patient Information.

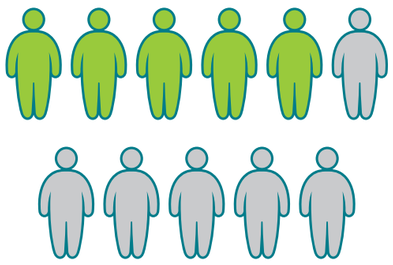
IMCIVREE® (setmelanotide) injection

Clinical study results: LEPR deficiency

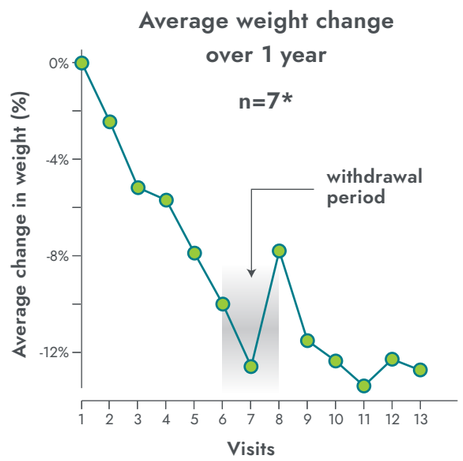
In clinical studies, IMCIVREE reduced weight and hunger for people with obesity due to LEPR deficiency.

Weight

STUDY 2
People with obesity due to LEPR deficiency



5 out of 11 people lost at least 10% of their body weight at 1 year



*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.

LEPR, leptin receptor.

Hunger

STUDY 2
People with obesity due to LEPR deficiency

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.

Important Safety Information (continued)

What are the possible side effects of IMCIVREE? (continued)

- **Increased skin pigmentation and darkening of skin lesions (moles or nevi) you already have.** These changes happen because of how IMCIVREE works in the body and will go away when you stop using IMCIVREE. You should have a full body skin exam before starting and during treatment with IMCIVREE to check for skin changes
- **Benzyl alcohol toxicity.** Benzyl alcohol is a preservative in IMCIVREE. Benzyl alcohol can cause serious side effects, including death, in premature and low-birth weight infants who have received medicines that contain benzyl alcohol. IMCIVREE should not be used in premature and low-birth weight infants

Please see accompanying full Prescribing Information and Patient Information.

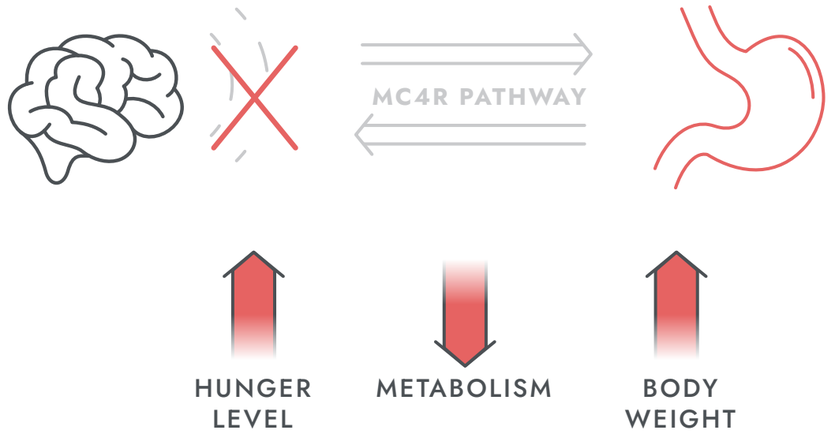
IMCIVREE® (setmelanotide) injection

How it works

In the brain, important "roads," called pathways, are responsible for carrying messages between the brain and the body.

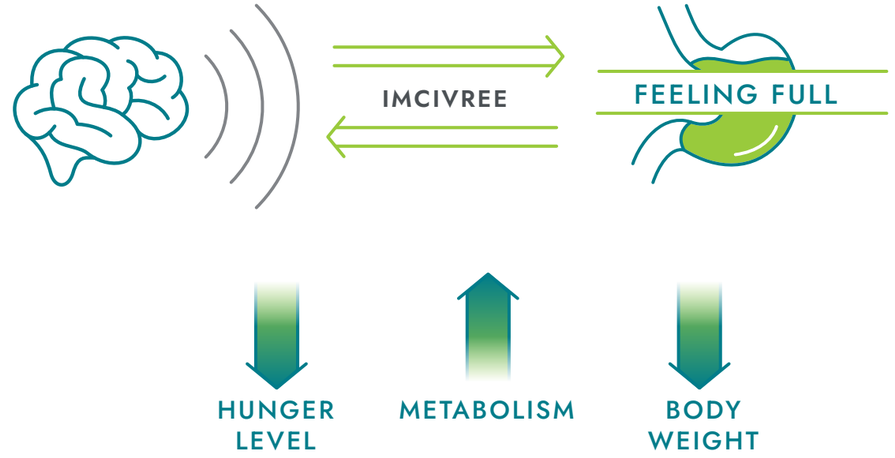
One of these roads, called the MC4R pathway, signals to the body when to eat and when to stop eating, and helps regulate metabolism.

Certain genetic changes, including those in the *POMC*, *PCSK1*, and *LEPR* genes, can "block" this pathway, stopping these messages from getting through. This leads to severe obesity.



LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

IMCIVREE helps activate the areas in the brain that control appetite, feeling full, and metabolism to help lose weight and keep it off.



Important Safety Information (continued)

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 may report side effects to FDA at 1-800-FDA-1088 or to Rhythm Pharmaceuticals at 1-833-789-6337.

US-SET-2200031 06/2022

Please see accompanying full Prescribing Information and Patient Information.

IMCIVREE® (setmelanotide) injection

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.
- **Increased skin pigmentation and darkening of skin lesions (moles or nevi) you already have.** These changes happen due to how IMCIVREE works in the body and will go away when you stop using IMCIVREE. You should have a full body skin exam before starting and during treatment with IMCIVREE to check for skin changes.
- **Benzyl alcohol toxicity.** Benzyl alcohol is a preservative in IMCIVREE. Benzyl alcohol can cause serious side effects, including death, in premature and low-birth weight infants, who have received medicines that contain benzyl alcohol. IMCIVREE should not be used in premature and low-birth weight infants.

The most common side effects of IMCIVREE include:

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

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IMCIVREE® (setmelanotide) injection

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.

STARTING TREATMENT

When you first start treatment, you will have an initial dose called a starting dose.

For most people 12 years and older, this dose is 2 mg per day. For individuals between the ages of 6 and 12, this is typically 1 mg per day.

FIRST FEW WEEKS

Over the first few weeks of treatment, your doctor will evaluate if your dose needs to change.

Your dose can be either increased or decreased depending on how you tolerate the medicine and respond to treatment. Like many new medicines, side effects can be expected. Your healthcare provider may adjust your dose to help manage initial side effects. This process of adjusting your dose is called titration.

ONGOING TREATMENT

Over time, you and your healthcare provider will continue to evaluate your response to treatment to determine if your dose needs any further adjustment.

Your healthcare provider may tell you to stop using IMCIVREE if you have not lost a certain amount of weight after 12 to 16 weeks of treatment.

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 number of potential doses included in each vial based on different prescribed doses.

10 mg/1 mL multiple-dose vial

Prescribed dose (mg)	Prescribed dose (mL)	Number of doses per vial
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.

Important Safety Information (continued)

What is IMCIVREE?

IMCIVREE is a prescription medicine used in adults and children 6 years of age and older with obesity due to the genetic conditions 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.

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IMCIVREE® (setmelanotide) injection

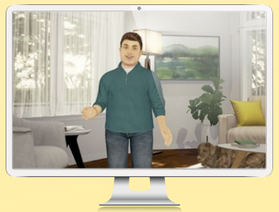
Resources to help you inject

A healthcare provider will show you how to prepare and inject IMCIVREE before you inject on your own.

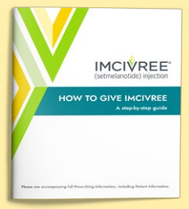
Do not try to inject IMCIVREE unless you have been trained by a healthcare provider.

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

As a reminder of what you learned, you can find:



A training video at **imcivree.com/takingimcivree**.



A brochure explaining the steps to inject your medicine at **IMCIVREE.com/howtoinject**.

Rhythm InTune
Support made personal

A support program designed for caregivers and people living with POMC deficiency, PCSK1 deficiency, or LEPR deficiency.

A Rhythm InTune Patient Education Manager is a single point of contact who can help you:

- **Access educational resources**
- **Connect to a community**
- **Understand your insurance coverage**
- **Get started on a Rhythm treatment**

If you're interested in speaking with a Patient Education Manager about the education and support Rhythm InTune can offer you or the person you care for, you can email or call us at:

patientsupport@rhythmtx.com

1-855-206-0815

Please see accompanying full Prescribing Information and Patient Information.

IMCIVREE®
(setmelanotide) injection

Rhythm®
PHARMACEUTICALS

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US-SET-2000092 08/2022