

The first and only FDA-approved treatment to target the impaired MC4R pathway, a root cause of obesity and hunger, in people living with BBS MC4R=melanocortin-4 receptor.

WHAT IS IMCIVREE?

IMCIVREE is a prescription medicine used in adults and children 2 years of age and older with obesity due to Bardet-Biedl syndrome (BBS) to help them lose weight and keep the weight off.

IMCIVREE is not for use in people with the following conditions because it may not work:

 Other types of obesity not related to BBS 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.



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)

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What is BBS?

Bardet-Biedl syndrome (pronounced BAR-day BEED-el), or BBS, is a rare genetic disease that can cause obesity

BBS has a wide range of symptoms

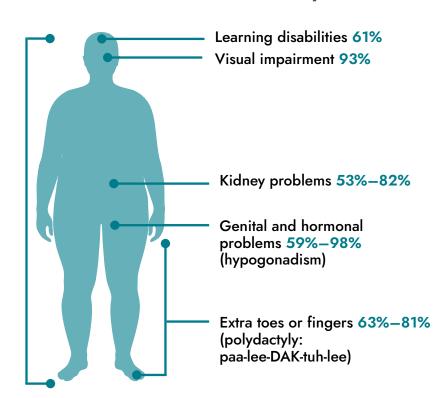
Early-onset obesity 72%-92%

Many people with BBS have earlyonset obesity. This may mean that weight gain starts at a young age, even as young as 2 years.

Hyperphagia

(hi-per-FAY-juh)

Hyperphagia is insatiable hunger, also described as a constant, hard-to-control hunger.



The symptoms of BBS may affect multiple parts of the body, vary in severity, and may change with age. While the symptoms above are some of the most common, not all people with BBS will experience every symptom listed here.

BBS is inherited. It can be passed from parent to child if both parents have variants, or changes, in a BBS gene.

People living with BBS may experience constant, hard-to-control hunger. This feeling is not their fault. Changes in BBS genes can stop a key area of the brain that controls hunger from working properly

IMPORTANT SAFETY INFORMATION (cont'd)

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

Have or have had depression, or suicidal thoughts or behavior

Hunger and obesity due to BBS come from the brain

The key area of the brain that controls hunger or fullness is known as the hypothalamus (pronounced hy-puh-THAL-uh-mus)

Think of the hypothalamus as a neighborhood within the brain.





In this neighborhood, there are roads that allow trucks to travel to and from the brain. One road is called the melanocortin-4 receptor, or MC4R, pathway.



The trucks on this road deliver messages between the body and the brain. These messages control hunger.

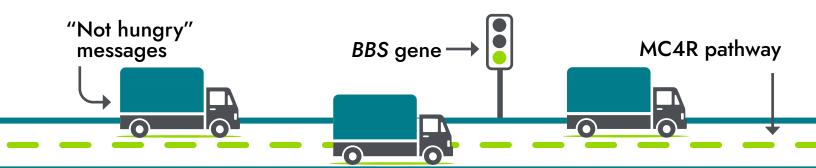


On this road, there is a traffic light, or a *BBS* gene, that helps guide the trucks to deliver their messages.



What causes hunger and obesity in BBS?

In people living with BBS, the signals that turn hunger "off" don't work correctly in the brain



When the BBS 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.

IMPORTANT SAFETY INFORMATION (cont'd)

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

- 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

In people living with BBS, the traffic light is broken due to the change in the BBS gene



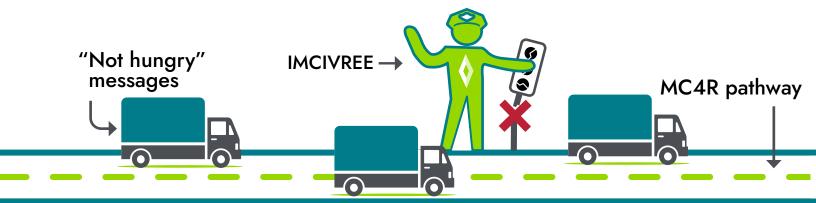
When the BBS gene has a variant (or change), the traffic light is broken, which causes a traffic jam. The trucks can no longer travel along the road (MC4R pathway) to properly deliver messages to the brain that the body is satisfied and doesn't need more food. Instead, the body believes that it's still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

IMCIVREE is the first and only treatment to target impairment of the MC4R pathway, a root cause of obesity and hunger in people living with BBS



How does IMCIVREE work?

IMCIVREE is designed to re-establish 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. This allows the "Not hungry" messages to reach the brain so that the body feels full and doesn't want more food.

This is how IMCIVREE helps the pathway work properly.

IMCIVREE helps to re-establish MC4R pathway activity and supports long-term reductions in weight when used continuously

IMPORTANT SAFETY INFORMATION (cont'd)

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

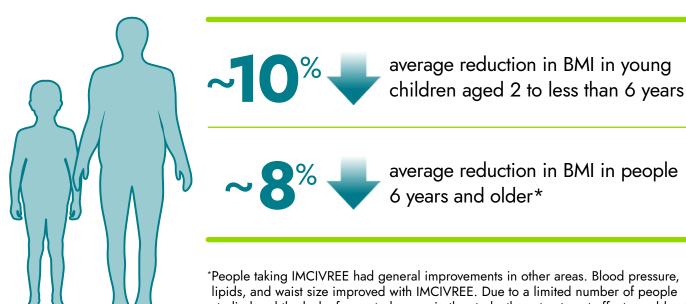
 Are breastfeeding or plan to breastfeed. It is not known if IMCIVREE passes into your breast milk. You should not breastfeed during treatment with IMCIVREE

What are the IMCIVREE study results?

IMCIVREE was studied in two, first-ever year-long clinical trials dedicated to obesity and hunger reduction in people with BBS

- The people studied in the trials included:
 - 5 young children aged 2 to less than 6 years old with obesity due to BBS
 - 31 children & adults who were 6 years and older with obesity due to BBS
- People included in the clinical trials had to have a certain weight or body mass index (BMI). BMI is a measure of body fat based on height and weight
 - Both young children aged 2 to less than 6 and children aged 6 to less than 18, had to have a weight in the 97th percentile or higher
 - Adults aged 18 years and older had to have a BMI of 30 or more

IMCIVREE reduced BMI over the course of both clinical trials



*People taking IMCIVREE had general improvements in other areas. Blood pressure, lipids, and waist size improved with IMCIVREE. Due to a limited number of people studied and the lack of a control group in the study, these treatment effects could not be accurately measured.



How did IMCIVREE help reduce measures of weight in young children and children in the clinical trials?

A Body Mass Index, or BMI, Z-score was used to measure reductions in weight in both young children aged 2 to less than 6 and children aged 6 to less than 18.

BMI Z-scores are reliable measures of weight in growing children because the score takes into account height, age, and gender.

He is no longer digging through the fridge or garbage, so we do not lock them anymore. He isn't asking for food constantly between meals and snacks, and I sometimes find myself realizing it's been a few hours and asking him if he's ready for a snack.

- Rachel, caregiver of a child living with BBS

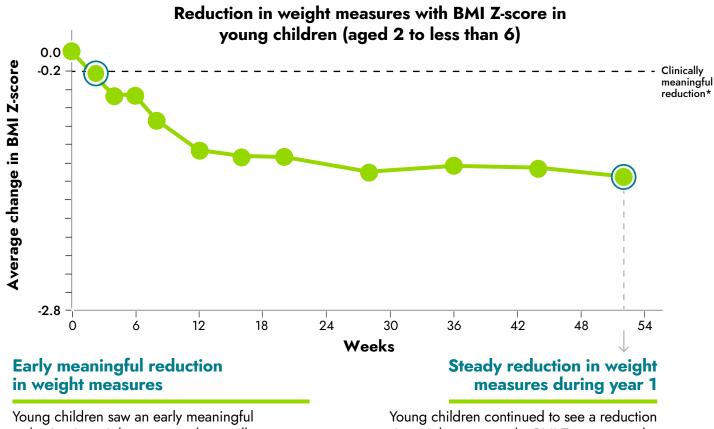
Individual results may vary

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.

IMCIVREE helped young children aged 2 to less than 6 years achieve early and clinically meaningful reduction in weight measures



Young children saw an early meaningful reduction in weight measures (generally considered 0.2 reduction)*

Young children continued to see a reduction in weight measures by BMI Z-score over the course of their first year of treatment

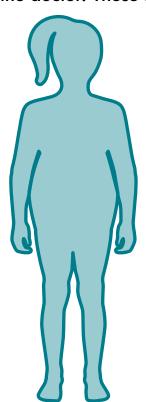
 5 young children between the ages of 2 to less than 6 were evaluated as part of the study

^{*}A clinically meaningful reduction is generally defined as a reduction of greater than or equal to 0.2 in BMI Z-score.



IMCIVREE reduced the severity of obesity in young children living with BBS

You may be familiar with viewing a child's growth as a percentile on a chart from the doctor. These same charts can be used for BMI.



This growth chart is a **hypothetical representation** of what a 4-year-old female with BBS who is taking IMCIVREE may experience in BMI reduction after 1 year, based on results from the clinical study.

After 1 year on IMCIVREE, she would see a 15 percentagepoint reduction of the BMI 95th percentile, dropping into the obesity (class 1) category.

Without IMCIVREE, her BMI may have continued to go up, leading to severe obesity (class 3) by age 7 and remaining in this category as she ages.

Treating children with IMCIVREE early may help reduce the severity of weight gain as they get older

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

Hypothetical growth chart based on clinical study data of IMCIVREE

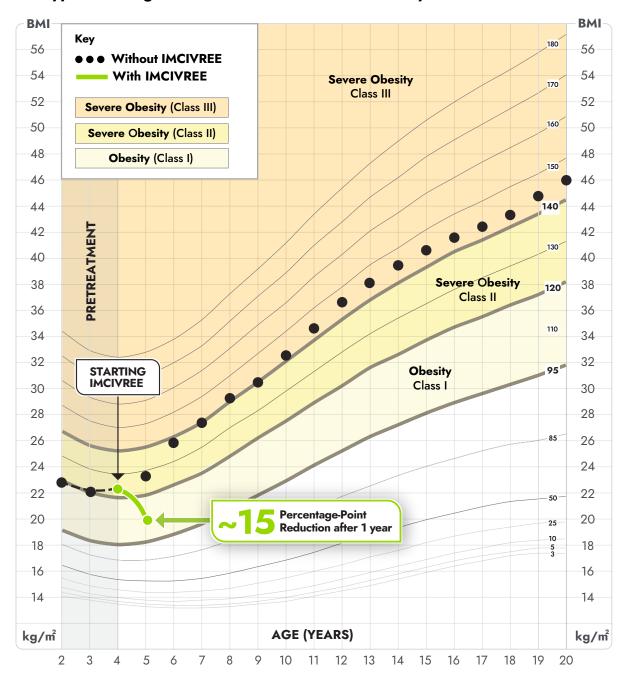
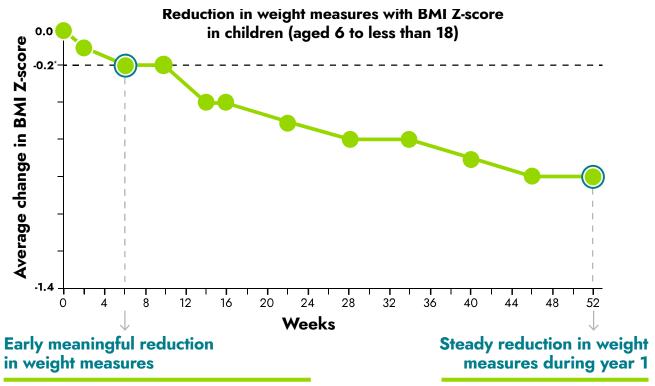


Figure modeled after Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. Pediatrics. 2012 Dec;130(6):1136-40.

Not an actual patient. Growth chart is based on females 2 to 20 years of age and is for illustrative purposes only.



IMCIVREE helped children aged 6 to less than 18 years reach steady and long-lasting reduction in weight measures



Children saw an early meaningful reduction in weight measures (generally considered 0.2 reduction)*

Children continued to see a reduction in weight measures by BMI Z-score over the course of their first year of treatment

◆ 16 children between the ages of 6 to less than 18 years were evaluated as part of the study.

IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of IMCIVREE? IMCIVREE may cause serious side effects, including: (cont'd)

 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

^{*}A clinically meaningful reduction is generally defined as a reduction of greater than or equal to 0.2 in BMI Z-score.

IMCIVREE is the first and only treatment to significantly reduce BMI Z-scores in children with obesity due to BBS



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

Some people chose to continue taking IMCIVREE in a separate long-term clinical trial. After they received 2 years of treatment, their results were analyzed.



of people had a meaningful reduction in BMI Z-score after 2 years*

- There was a 0.72 average reduction in BMI Z-score
- ◆ 12 children between the ages of 6 to less than 18 years were evaluated as part of the 2 year follow-up study

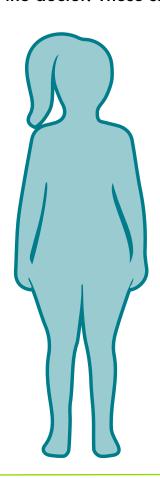
No change in diet or exercise: In the clinical trial, people were not required to change their diet or exercise routine

*A clinically meaningful reduction is generally defined as a reduction of greater than or equal to 0.2 in BMI Z-score.



IMCIVREE reduced the severity of obesity in children living with BBS

You may be familiar with viewing a child's growth as a percentile on a chart from the doctor. These same charts can be used for BMI.



This growth chart is a **hypothetical representation** of what a 12-year-old female with BBS who is taking IMCIVREE may experience in BMI reduction after 1 and 2 years, based on results from the clinical study.

After 1 and 2 years on IMCIVREE, she would see a 17 percentage-point and 30 percentage-point reduction of the BMI 95th percentile, respectively.

With IMCIVREE, her weight-gain trajectory drops down to obesity (class 1). Without IMCIVREE, she would likely remain in the severe obesity (class 3) category as she ages.

Long-term treatment with IMCIVREE helped children achieve and maintain a healthier BMI

IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of IMCIVREE? IMCIVREE may cause serious side effects, including: (cont'd)

 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

Hypothetical growth chart based on clinical study data of IMCIVREE

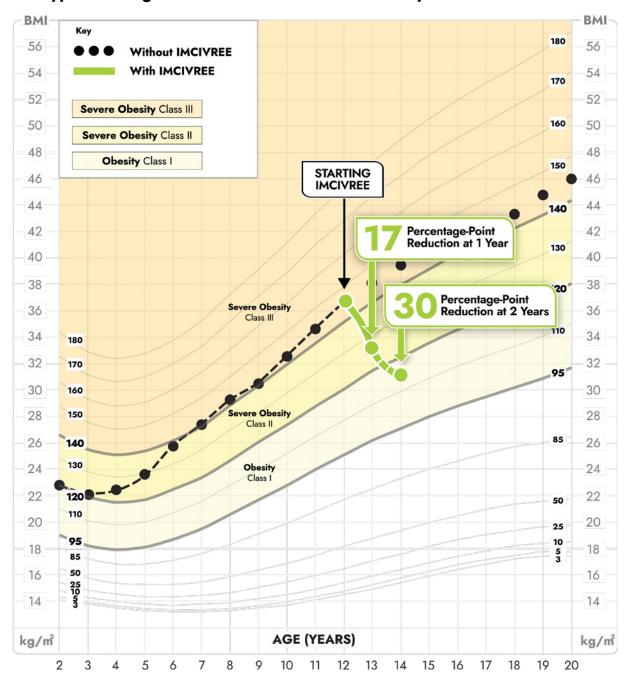
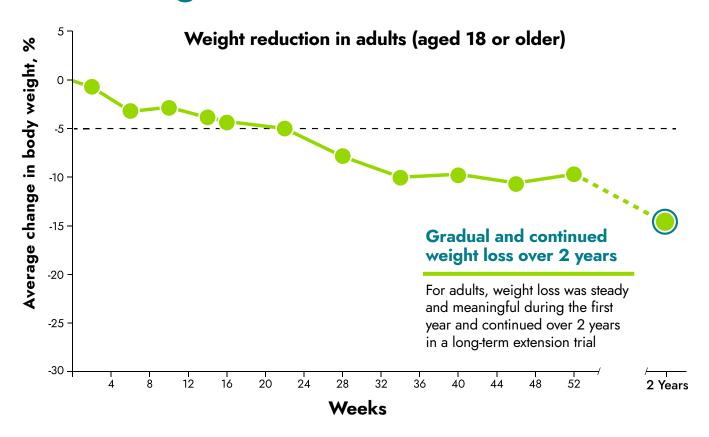


Figure modeled after Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children:a new growth chart. Pediatrics. 2012 Dec;130(6):1136-40.

Not an actual patient. Growth chart is based on females 2 to 20 years of age and is for illustrative purposes only.



How did IMCIVREE help adults lose weight in the clinical trial?



- IMCIVREE reduced body weight over the course of the 1-year clinical trial
- 15 adults aged 18 years or older were evaluated as part of the study

IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of IMCIVREE? IMCIVREE may cause serious side effects, including: (cont'd)

• 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

IMCIVREE helped adults 18 years and older reach steady and long-lasting weight reduction



At the end of the clinical trial for IMCIVREE, 19 people continued in a long-term study. 6 of those people were adults. People are being assessed every 3 months until the end of the study (up to 5 years or study withdrawal).

IMCIVREE has mainly helped me lose and control my weight.

I know I couldn't have done it without this medication.

— Adult patient enrolled in the IMCIVREE clinical trial

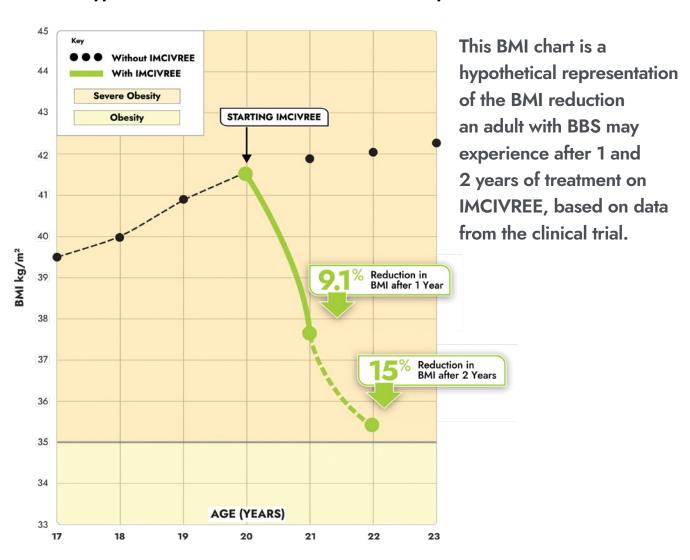
No change in diet or exercise: In the clinical trial, people were not required to change their diet or exercise routine

Individual results may vary



IMCIVREE reduced the severity of obesity in adults living with BBS

Hypothetical BMI chart based on clinical study data of IMCIVREE



IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of IMCIVREE? IMCIVREE may cause serious side effects, including: (cont'd)

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

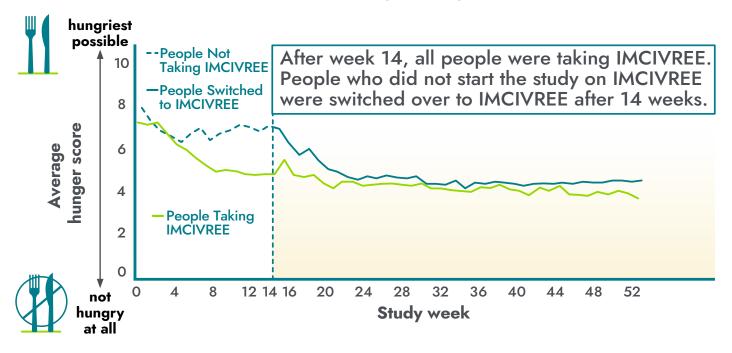
How did IMCIVREE help with hunger reduction in people 12 years and older?

IMCIVREE provided reduction in hunger scores early and continuously throughout treatment in people 12 years and older

The effect of IMCIVREE on reducing hunger was studied in people 12 years and older living with BBS who could self-report their hunger.

- They completed a questionnaire every day for 1 year to determine changes in their hunger
- People scored their hunger on a daily basis using a scale from 0 to 10

IMCIVREE reduced the most severe feelings of hunger in people 12 years and older



14 people were studied

A majority of people 12 years and older reported a reduction in hunger within weeks of starting IMCIVREE



What are the possible side effects of IMCIVREE?

IMCIVREE was well studied and most side effects were generally mild and improved over time. The safety of IMCIVREE has been evaluated over ~10 years of clinical trials

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.

Most nausea and vomiting events were mild, and none were severe. Nausea and vomiting primarily were reported within the first month of treatment and typically went away after a few days.

Talk to your doctor about how to manage side effects, including nausea and vomiting.

A general darkening of the skin (hyperpigmentation) is common due to the way in which IMCIVREE works

Examples of hyperpigmentation



Baseline



Baseline



Baseline



On treatment



On treatment



On treatment

- Darkening of the skin and/or hair is expected, as IMCIVREE may lead to increased production of melanin (which gives color to your skin)
- The degree of skin darkening can vary from person to person and can sometimes include darkening of existing skin growths (such as moles)
- In the clinical trials, hyperpigmentation increased over the first several weeks of IMCIVREE use and generally leveled off in the initial months of treatment
- Darkening of the skin went away after people stopped using IMCIVREE

If hyperpigmentation is a concern, talk to your doctor, and they will assess your response to treatment and work with you to create a plan to check for skin changes.

You should have a full-body skin exam before starting and during treatment with IMCIVREE to check for skin changes.

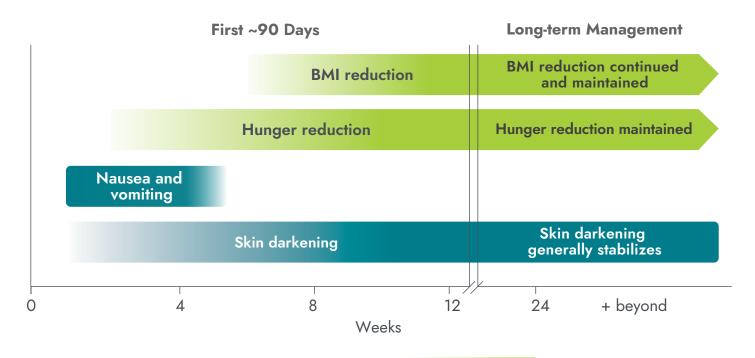
These are not all the possible side effects of IMCIVREE. Please review all the possible side effects of IMCIVREE in the enclosed Patient Information and talk to your doctor about any questions you may have.



What is the timeline for seeing changes with IMCIVREE?

Achieving the benefits of IMCIVREE may take time

In clinical trials, it took some time for weight reductions to occur, while people experienced certain side effects soon after starting treatment. This chart highlights some of the most common side effects, but it does not include all reported side effects.



Staying on IMCIVREE is important to maintain long-term reductions in weight

Talk to your doctor about any side effects you experience while on treatment with IMCIVREE

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.



In clinical trials:

- Meaningful weight reduction began within 6-8 weeks and continued over time
- Hunger reduction began within weeks. Measures of hunger increased quickly upon dose reduction or discontinuation of IMCIVREE
- Nausea and vomiting were primarily reported within the first 4 weeks of treatment and typically went away within a few days; nearly all events were mild and none were serious
- Skin darkening generally appeared within the first month of starting IMCIVREE.
 It usually leveled off within the initial months, then remained stable over long-term treatment

Nausea and vomiting are some of the common side effects of IMCIVREE. There are other side effects reported with IMCIVREE that may occur within the first ~90 days of treatment or later

Tracking your progress and keeping your treatment goals in mind will help you see your results over time

Talk to your doctor about any side effects you experience while on treatment with IMCIVREE



How is IMCIVREE given?

IMCIVREE is a once-daily injection used to help reduce weight in people living with BBS

IMCIVREE is given:



As an injection under the skin



Once daily at the beginning of the day, and can be given at home



With or without food

IMPORTANT SAFETY INFORMATION (cont'd)

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 1-800-FDA-1088.

Because IMCIVREE is injected under the skin, the needle is short and thin

The IMCIVREE needle is half an inch long



Please see the **How to Give IMCIVREE Guide** for illustrated, step-by-step instructions for giving an IMCIVREE injection.



The first time I gave him the injection, he was scared and thought it was going to hurt. But now it doesn't faze him at all.

Caregiver of child taking IMCIVREE

Individual results may vary



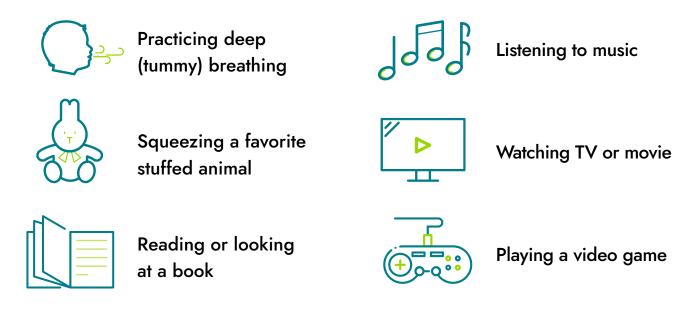
Tips for injecting IMCIVREE

Injection tips for caregivers of young children

Developing a routine and doing it the same way every day can help build your confidence and reassure your child.

Distractions during injections can help

Although you, the caregiver, need to be aware of every step of an injection of IMCIVREE, your child doesn't. Depending on your child and their age, utilizing one or more of these techniques below may ease the injection process.



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.

Develop a strong routine for injection success

Whether you're a caregiver or injecting yourself, make the daily IMCIVREE injection a familiar routine. Doing the injection at the same time every day in the same place in your home can be helpful. Follow these steps:

- 1. Gather your supplies
- 2. Fill your syringe with medicine
- 3. Choose and remember to rotate your injection site
- 4. Inject the medicine
- 5. Dispose of your supplies

What to know about self-injection

A regular routine and familiarity with your supplies are important for regular injections. Make sure there is a designated place in the refrigerator for medication, an assigned spot for supplies, and a time and place in your home where injections happen.

Consult with your Patient Education Manager (PEM) when you are beginning IMCIVREE. PEMs are valuable resources as you start IMCIVREE and adjust to your new routine.

Caregivers of children with BBS should talk to the doctor about the right time for a young person to begin self-injection.



Getting started on IMCIVREE



Deciding on IMCIVREE

You and your doctor decide whether IMCIVREE is an appropriate treatment. If you agree on IMCIVREE, your doctor will submit a start form along with your consent to enroll in **Rhythm InTune**. Rhythm InTune is your dedicated source for personalized support, which includes helping you understand insurance coverage and exploring financial assistance options for eligible patients. For more information about Rhythm InTune, please turn to pages 32 and 33.



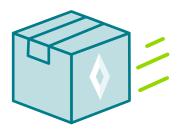
Learning to inject IMCIVREE

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

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)



Starting on IMCIVREE

IMCIVREE is only available through what is known as a specialty pharmacy. Rhythm InTune will coordinate delivery of IMCIVREE. You should start IMCIVREE at your starting dose, as directed by your doctor.



Staying on IMCIVREE

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 the maintenance dose.

Rhythm InTune provides personalized support and educational resources and programs throughout your treatment journey





Your source for personalized support

Rhythm InTune is a support program designed for caregivers and people living with rare genetic diseases that cause obesity, including BBS.

IMPORTANT SAFETY INFORMATION (cont'd)

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

Have or have had depression, or suicidal thoughts or behavior

What can Rhythm InTune do for you?

Rhythm InTune provides resources, education, and information tailored to fit the unique needs of people living with rare genetic diseases that cause obesity, including BBS.

Rhythm InTune can help you:



Access educational resources



Connect to a community



Understand your insurance coverage



Get started on a Rhythm treatment

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.

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





IMCIVREE is the first and only FDA-approved treatment to target the impaired MC4R pathway, a root cause of obesity and hunger in people living with BBS

Want to learn more about BBS or IMCIVREE?

Talk to your doctor. For additional education and support, contact Rhythm InTune at:



patientsupport@rhythmtx.com



1-855-206-0815

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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 full <u>Prescribing Information</u> and <u>Patient Information</u>, as well as Important Safety Information throughout.



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