PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Imcivree

Solution for injection

The active ingredient and its concentration:
Each vial of Imcivree contains 10 mg of setmelanotide in 1 ml of solution.
Inactive ingredients and allergens in the preparation – see section 6 "**Additional information**". See also "**Important information about some of the ingredients of the medicine**" in section 2.
Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine.
If you have additional questions, refer to the doctor or the pharmacist.
This medicine has been prescribed for treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Imcivree is intended for the treatment of obesity and for the control of hunger sensation associated with the following genetically confirmed conditions: Bardet-Biedl syndrome (BBS), biallelic loss-of-function of the genes pro-opiomelanocortin (POMC) and PCSK1, biallelic loss-of-function of the gene leptin receptor (LEPR), in adults and children 6 years of age and above.
Therapeutic class: not yet assigned

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient (setmelanotide) or to any of the other ingredients this medicine contains (see section 6 "**Additional information**").

Special warnings regarding the use of the medicine
- While using the medicine, dark marks or patches may appear on the skin. Performing an examination before starting treatment will help you identify new marks that appear once you begin using the medicine.
- Spontaneous erections are very common in male patients using this medicine. If the erection lasts more than 4 hours, please refer to a doctor urgently. Prolonged erections (priapism) that are not treated may reduce your ability to get erections in the future.

Children
This medicine is not intended for children under 6 years of age.
No information is available regarding the safety and efficacy of using this medicine in children under the age of 6 years.

Tests and follow-up
- Before starting treatment and during treatment with the medicine, the doctor should examine your skin for dark marks or patches.
- The impact on weight loss, as well as growth and development in children and adolescents, should be monitored.

Drug interactions
If you are taking, have recently taken or might take other medicines, including non-prescription medicines and dietary supplements, tell the doctor or pharmacist.

Use of the medicine and food
The medicine can be used regardless of food.

Pregnancy and breastfeeding
If you are pregnant, breastfeeding, think you might be pregnant or are planning to become pregnant, consult a doctor or pharmacist before using the medicine.

Pregnancy
Using the medicine is not recommended during pregnancy or while attempting to become pregnant, as the medicine has not been tested in pregnant women. Weight loss during pregnancy may harm the fetus.

Breastfeeding
If you are breastfeeding, consult the doctor before using the medicine. The doctor will talk to you about the pros and cons of using the medicine while breastfeeding.

Driving and operating machinery
Imcivree should not have any effect on your ability to drive or operate machinery.

Important information about some of the ingredients of the medicine

Benzyl alcohol
This medicine contains 10 mg benzyl alcohol in each 1 ml of solution, which is equivalent to 1 mg for each mg of your dose. Benzyl alcohol may cause allergic reactions.
Consult a doctor or pharmacist if you are pregnant or breastfeeding. Benzyl alcohol may build up in your body and may cause a side effect called "metabolic acidosis".
Consult a doctor or pharmacist if you suffer from a liver or kidney disease. Benzyl alcohol may build up in your body and may cause a side effect called "metabolic acidosis".

Sodium
Imcivree contains less than 23 mg sodium per dose, and is therefore considered "sodium free".

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the medicine.
The dosage and treatment regimen will be determined only by the doctor.
Imcivree is given as a subcutaneous injection, once a day, at the beginning of the day. The medicine is intended for long-term use.
The generally accepted dosage is:

Biallelic loss-of-function of the genes pro-opiomelanocortin (POMC) and PCSK1, biallelic loss-of-function of the gene leptin receptor (LEPR).

The recommended doses **in adults and adolescents 12 years old and above** are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	1 mg once a day	0.1 ml once a day
Week 3 and onward	2 mg once a day	0.2 ml once a day
If the dose is not enough and the side effects are well-tolerated	2.5 mg once a day	0.25 ml once a day
If the dose is not enough and the side effects are well-tolerated	3 mg once a day	0.3 ml once a day

The recommended doses **in children 6 to less than 12 years old** are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	0.5 mg once a day	0.05 ml once a day
Weeks 3-5	1 mg once a day	0.1 ml once a day
Week 6 and onward	2 mg once a day	0.2 ml once a day
If the dose is not enough and the side effects are well-tolerated	2.5 mg once a day	0.25 ml once a day

In patients with mild to moderate kidney disease, dose adjustments are not necessary.

The recommended doses **in adolescents 12 to 17 years old** with severe kidney disease are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	0.5 mg once a day	0.05 ml once a day
Week 3 and onward (if the side effects are well-tolerated)	1 mg once a day	0.1 ml once a day
If the dose is not enough and the side effects are well-tolerated	2 mg once a day	0.2 ml once a day
If the dose is not enough and the side effects are well-tolerated	2.5 mg once a day	0.25 ml once a day
If the dose is not enough and the side effects are well-tolerated	3 mg once a day	0.3 ml once a day

If the side effects of the 0.5 mg starting dose are not tolerated, the dose will be reduced to 0.25 mg (0.025 ml) once daily.
If the side effects of the 0.25 mg dose once daily are well-tolerated, the dose will be increased gradually.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table. If the side effects of the reduced dose are well-tolerated, the dose increase will continue according to the table.
If the side effects of the 3 mg dose are not tolerated, the dose will be reduced to 2.5 mg, and you will have to continue with this dose.

The recommended doses **in children 6 to less than 12 years old** with severe kidney disease are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	0.25 mg once a day	0.025 ml once a day
Weeks 3-5 (if the side effects are well-tolerated)	0.5 mg once a day	0.05 ml once a day
Week 6 and onward (if the side effects are well-tolerated)	1 mg once a day	0.1 ml once a day
If the dose is not enough and the side effects are well-tolerated	2 mg once a day	0.2 ml once a day

If the side effects of the 0.25 mg starting dose are not tolerated, the treatment will be discontinued.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table.
If the side effects of the reduced dose are well-tolerated, the gradual dose increase will continue according to the table.
If the side effects of the 2 mg dose are not tolerated, the dose will be reduced to 1 mg, and you will have to continue with this dose.
The doctor may instruct you to stop the treatment with Imcivree if you have not achieved a weight loss of at least 5% of your body weight or 5% of the BMI after 12-16 weeks of treatment.

Bardet-Biedl syndrome

The recommended doses **in adults and adolescents 16 years old and above** are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	2 mg once a day	0.2 ml once a day
Week 3 and onward (if the side effects are well-tolerated)	3 mg once a day	0.3 ml once a day

If the side effects of the 2 mg starting dose are not tolerated, the dose will be reduced to 1 mg (0.1 ml). If the side effects of the 1 mg dose once a day are well-tolerated, the gradual dose increase will continue according to the table.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table.
If the side effects of the reduced dose are well-tolerated, the gradual dose increase will continue according to the table.
If the side effects of the 3 mg dose are not tolerated, the dose will be reduced to 2 mg, and you will have to continue with this dose.

The recommended doses **in children and adolescents 6 to less than 16 years old** are:

Week of treatment	Daily dose in mg	Volume of injection
Week 1	1 mg once a day	0.1 ml once a day
Week 2 (if the side effects are well-tolerated)	2 mg once a day	0.2 ml once a day
Week 3 and onward (if the side effects are well-tolerated)	3 mg once a day	0.3 ml once a day

If the side effects of the 1 mg starting dose are not tolerated, the dose will be reduced to 0.5 mg (0.05 ml). If the side effects of the 0.5 mg dose are well-tolerated, the gradual dose increase will continue according to the table.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table.
If the side effects of the reduced dose are well-tolerated, the gradual dose increase will continue according to the table.
If the side effects of the 3 mg dose are not tolerated, the dose will be reduced to 2 mg, and you will have to continue with this dose.
In patients with mild to moderate kidney disease, dose adjustments are not necessary.

The recommended doses **in adolescents 16 to 17 years old** with severe kidney disease are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	0.5 mg once a day	0.05 ml once a day
Week 3 and onward (if the side effects are well-tolerated)	1 mg once a day	0.1 ml once a day
If the dose is not enough and the side effects are well-tolerated	2 mg once a day	0.2 ml once a day
If the dose is not enough and the side effects are well-tolerated	2.5 mg once a day	0.25 ml once a day
If the dose is not enough and the side effects are well-tolerated	3 mg once a day	0.3 ml once a day

If the side effects of the 0.5 mg starting dose are not tolerated, the dose will be reduced to 0.25 mg (0.025 ml). If the side effects of the 0.25 mg dose once a day are well-tolerated, the gradual dose increase will continue according to the table.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table.
If the side effects of the reduced dose are well-tolerated, the gradual dose increase will continue according to the table.
If the side effects of the 3 mg dose are not tolerated, the dose will be reduced to 2.5 mg, and you will have to continue with this dose.

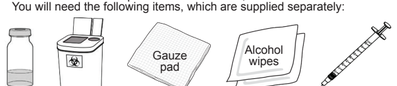
The recommended doses **in children and adolescents 6 to 16 years old** with severe kidney disease are:

Week of treatment	Daily dose in mg	Volume of injection
Weeks 1-2	0.25 mg once a day	0.025 ml once a day
Weeks 3-5 (if the side effects are well-tolerated)	0.5 mg once a day	0.05 ml once a day
Week 6 and onward (if the side effects are well-tolerated)	1 mg once a day	0.1 ml once a day
If the dose is not enough and the side effects are well-tolerated	2 mg once a day	0.2 ml once a day

If the side effects of the 0.25 mg starting dose are not tolerated, the treatment will be discontinued.
After receiving the starting dose, if the side effects of the subsequent dose are not tolerated, the dose will be reduced to the previous dose in the table.
If the side effects of the reduced dose are well-tolerated, the gradual dose increase will continue according to the table.
If the side effects of the 2 mg dose are not tolerated, the dose will be reduced to 1 mg, and you will have to continue with this dose.
The doctor will regularly check the efficacy of the medicine. The doctor may adjust your dose if necessary.
The medicine is intended for long-term use. Discontinuation or irregular use may lead to the recurrence or worsening of the symptoms. Use the medicine according to the treatment plan that was prescribed by the doctor or pharmacist.
Do not exceed the recommended dose.

How to inject Imcivree
Imcivree is injected into the fat tissue under the skin, in the abdomen. The doctor, pharmacist or nurse will instruct you on how to do so. Once you feel comfortable injecting yourself or your child, you can do it at home.
Inject Imcivree at the beginning of the day to maximize the reduction of hunger sensation while awake.
Imcivree may be used regardless of meal times.
Before injecting Imcivree, please read the following instructions carefully:

Step 1 – Prepare for the injection
- Get the items out and place them on a clean, flat surface.
  You will need the following items, which are supplied separately:



- Wash your hands with soap and warm water.
- Open the 2 alcohol wipes and the gauze pad.

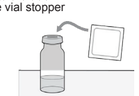
Step 2 – Examine the vial
- Check the expiry date on the vial label, which is shown after "EXP.".

- The liquid should look clear to yellowish.
- Do not use the medicine if:
  - The expiry date has passed
  - The liquid is cloudy
  - There are particles floating in the vial
  - The plastic cap on the new vial is broken or missing
  - The vial has been stored at a temperature greater than 30°C

Step 3 – Prepare the vial
- Before use, let the vial reach room temperature. This can be done by removing the vial from the refrigerator 15 minutes before injection or by rolling the vial gently between the palms of your hands for 60 seconds.
  - Do not use warm water, a microwave or other appliance in order to heat the vial
  - Do not shake the vial

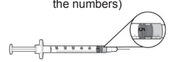
- If you are using a new vial, remove the plastic cap and throw it away into the trash.

- Clean the top part of the gray stopper with an alcohol wipe. Throw away the used alcohol wipe into the trash.
  - Do not remove the vial stopper



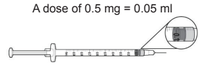
Step 4 – Prepare the syringe
- For a dose of 0.25 mg (0.025 ml or 2.5 units), use a 0.3 ml syringe with 0.5 (half) unit intervals and a 29 to 31 gauge needle with a needle length of 6 to 13 mm, suitable for subcutaneous injection.

A dose of 0.25 mg = 0.025 ml or 2.5 units (shown as scale marks between the numbers)

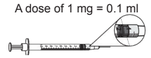


- For a dose of 0.5 mg to 3 mg (0.05 ml to 0.3 ml), use a 1 ml syringe with 0.01 ml dosing intervals and a 28 to 29 gauge needle with a needle length of 6 to 13 mm, suitable for subcutaneous injection.

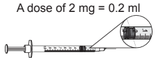
A dose of 0.5 mg = 0.05 ml



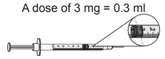
A dose of 1 mg = 0.1 ml



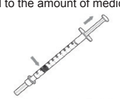
A dose of 2 mg = 0.2 ml



A dose of 3 mg = 0.3 ml

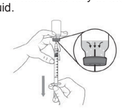


- Keep the protective needle cap in place, and pull back the plunger to fill the syringe with air equal to the amount of medicine needed for injection.

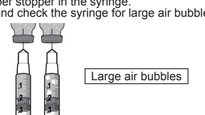


- Remove the needle cap from the syringe. Pull the cap straight off and away from your body.
- Place the vial upright on a flat surface. Hold the syringe and place it directly over the vial.
- Insert the needle straight down into the center of the vial's gray stopper.

- Push the plunger down to inject the air from the syringe into the vial.
- Without removing the needle, gently turn the vial upside down.
  - Make sure the tip of the needle is fully in the medicine liquid and not in the air above the liquid.



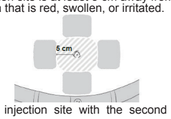
- Slowly pull back the plunger to fill the syringe with the amount of medicine needed for your dose.
  When measuring the dose, be sure to read the units starting from the end closest to the black rubber stopper in the syringe.
- Keep the needle in the vial and check the syringe for large air bubbles.



- If you notice air bubbles, remove them from the syringe in the following way:
  - Gently tap with your finger on the side of the syringe to move the air bubble to the top of the syringe.
  - Empty the syringe content back to the vial.
  - Follow the above steps to fill the syringe again. Pull the plunger more slowly this time and make sure the tip of the needle is fully in the liquid in the vial to reduce the chance of air bubbles.
- Once there are no large air bubbles in the syringe, place the vial upright on a hard surface.
- Hold the vial with one hand and the syringe between the fingertips of the other hand. Pull the needle straight up, out of the vial.

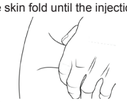
- Place the syringe on the hard surface, make sure the needle does not touch the surface. Do not recap the needle.

Step 5 – Prepare the injection site
- Choose the area on your abdomen for the injection.
- Change the injection site each day.
- Make sure the injection site is at least 5 cm away from the belly button.
- Do not inject an area that is red, swollen, or irritated.



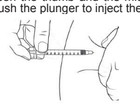
- Clean your chosen injection site with the second alcohol wipe using circular motions.
- Allow the skin to dry for about 10 seconds.
- Do not touch, fan or blow on the clean area.

Step 6 – Injecting Imcivree
- Place the syringe between the thumb and index finger of the hand you write with.
- With the other hand, gently pinch about 5 cm of skin between the thumb and index finger.
  Make sure you hold the skin fold until the injection is complete.



- Hold the middle part of the syringe at a 90° angle to your skin and push the needle straight into the injection site. Make sure the needle goes all the way in.
- Do not hold or push the plunger while inserting the needle.

- Hold the syringe between the thumb and the middle finger and use the index finger to slowly push the plunger to inject the medicine.



- Count to 5 after injecting Imcivree to make sure all the medicine has left the syringe.
- Release the pinched skin and pull the needle out.
- Use a gauze pad to gently apply pressure to the injection site, then throw the gauze pad into the trash.
- Throw the used syringe into the sharps bin. Do not throw into the trash.
- If there is medicine left in the vial, return the vial back to the carton and store either in the refrigerator or in a safe place at a temperature lower than 30°C until receiving the next dose.

If you or your child accidentally used a higher dose or if a child accidentally swallowed the medicine, immediately refer to a doctor or to a hospital emergency room and bring the package of the medicine with you.
If you forgot to inject this medicine at the required time
If you forgot to inject the medicine, skip the dose and inject the next dose at the usual time. Do not use a double dose in order to compensate for a forgotten dose.
If you stop using the medicine
If you stop using this medicine, the hunger sensation may return and the weight loss may stop.
Follow the treatment as recommended by the doctor.
Even if there is an improvement in your health condition, do not stop treatment with the medicine without consulting the doctor, as this may decrease the success of the treatment.
Do not take medicines in the dark! Check the label and the dose every time you take a medicine. Wear glasses if you need them.
If you have any other questions regarding use of the medicine, consult the doctor or the pharmacist.

4. SIDE EFFECTS

As with any medicine, using Imcivree may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
Very common side effects (effects that occur in more than one user out of ten)
- Dark areas or patches on the skin
- Pain, bruising or inflammation (redness and/or swelling) at the site of injection
- General malaise (vomiting)
- Headache
- Spontaneous penile erection

Common side effects (effects that occur in 1-10 users out of 100)
- Dry, red or itchy skin
- Pain
- Increased sweating
- Discolored areas or patches on the skin
- Skin lesions
- Hair loss
- Tiredness
- Weakness
- Dry mouth
- Indigestion
- Diarrhea
- Constipation
- Abdominal pain
- Dizziness
- Increased erections
- Sleeping problems
- Feeling depressed
- Change in sexual arousal
- Increased sex drive
- Skin neoplasm
- Back pain
- Muscle cramps
- Pain in the arms or legs
- Hot flashes
- Vertigo

Uncommon side effects (effects that occur in 1-10 users out of 1,000)
- Brown spots or freckles on the skin
- Skin redness
- Rash
- Lines or streaks on the skin
- Hair discoloration
- Bump on the skin
- Skin inflammation
- Changes in nail color or ridges in the nail
- Chest pain
- Sensitivity to heat or cold
- Itch around the injection site
- Chills
- Sensation of coldness
- Sensation of heat
- Discolored gums
- Abdominal bloating
- An increase in the amount of saliva
- Flatulence
- Heartburn
- Somnolence
- An increase in the sensitivity to sight, sound, touch and smell
- Migraine headache
- Loss of or change in the sense of smell
- Taste disturbances
- Anxiety
- Mood swings
- Ejaculation disturbances
- Female inability to obtain or maintain sexual arousal
- Genital discomfort or sensitivity
- Decreased libido
- Female genital disorder
- Depressed mood
- Sleep disturbance
- Eye neoplasm
- Nightmares
- Flat, colored mole on the skin
- Joint pain
- Yawning
- Cough
- Rhinitis
- Pain in the chest muscles or bones
- Change in the shade of the white part of the eyes
- Yellowing of the eyes

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Reporting of side effects
Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) appearing on the package and the vial. The expiry date refers to the last day of that month.

Storage conditions
Store in a refrigerator (2°C-8°C). Do not freeze. Unopened vials can be stored at room temperature not exceeding 30°C, for a duration of 30 days or until the expiry date, whichever is sooner. Store all the vials (including the opened ones) in the original carton in order to protect them from light.

Shelf life after first opening
Store in a temperature not exceeding 30°C for 28 days or until the expiry date, whichever is sooner.
Do not use the medicine if the vial has been exposed to a temperature higher than 30°C.
Do not use the medicine if the liquid is cloudy or if you observe floating particles.
Always use a new syringe for each injection.
Do not discard medicines in the sink or in the domestic trash. Ask your pharmacist how to dispose of medicines no longer in use. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, the medicine also contains:
mPEG-2000-DSPE, Mannitol, Benzyl alcohol, Carmellose sodium, Phenol, Disodium edetate, Hydrochloric acid, Sodium hydroxide and Water for injections.

What does the medicine look like and what are the contents of the package?
Imcivree is a colorless to yellowish solution. This medicine comes in clear glass vials with a stopper and cap containing 1 ml of solution for injection.

Name and address of the marketing authorization holder
Medison Pharma Ltd., 10 Hashiloach St., Petach Tikva

Name and address of the manufacturer
Rhythm Pharmaceuticals Netherlands B.V.
Radarweg 29, 1043NX Amsterdam, Netherlands
This leaflet was revised in 01/24
Registration number of the medicine in the national drug registry of the Ministry of Health: 171-28-37060-99