Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Increlex

Solution for injection

Active ingredient and its quantity:
Each ml contains: mecasermin 10 mg

For the list of inactive ingredients and allergens in the medicine – see section 6 **"Additional information"**. See also **"Important information about some of this medicine's ingredients"** in section 2.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat your or your child's illness. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar to yours.

The medicine is intended for children and adolescents aged 2 to 18 years.
The medicine is not intended for premature babies or neonates.

1. What is this medicine intended for?

Increlex is intended for long-term treatment of children and adolescents aged 2 to 18 years suffering from growth failure due to confirmed severe primary insulin-like growth factor-1 deficiency (Primary IGFD).

Therapeutic group: somatropin and somatropin agonists

2. Before using this medicine

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredient mecasermin or to any of the other ingredients in this medicine (see section 6 **"Additional information"**).
- you currently have or suspected to have any cancerous or non-cancerous tumor.
- you have had cancer in the past.
- you have or have had any conditions which may increase the risk of cancer.
- Stop the treatment in case of tumor development.
- Do not use in premature babies or neonates since the medicine contains benzyl alcohol.

Special warnings about using this medicine

There is an increased risk of tumors (both cancerous and non-cancerous) in children and adolescents treated with Increlex. If any new tumor, skin lesion or any other unexpected symptom occurs during treatment or after treatment, contact your doctor immediately since mecasermin may play a role in the development and progression of benign and malignant tumors.

Before treatment with Increlex, tell your doctor or pharmacist if:

- you have a curved spine (scoliosis). See section **"Tests and follow up"**.
- you develop a limp or hip or knee pain.
- you have enlarged tonsils. See section **"Tests and follow up"**.
- you have symptoms of increased pressure in the brain (intracranial hypertension), such as visual changes, headache, nausea and/or vomiting.
- you have a localized reaction at the injection site or a systemic allergic reaction due to Increlex. Contact the doctor immediately if you develop a localized rash. Call medical help immediately if you have a systemic allergic reaction (hives, trouble breathing, faintness or collapse and feeling generally unwell).
- the growth stage has been finished (the bone growth plates are closed). In this case Increlex cannot help you grow and should not be used.

Children and adolescents:
The use of this medicine has not been studied in children under 2 years of age and is therefore not intended for this age group.

Tests and follow up:

- If you have scoliosis, you should be monitored for progression of scoliosis.
- If you have enlarged tonsils, you should have examinations periodically.
- Your doctor may perform an echocardiogram before, during and after mecasermin treatment.

Drug interactions:
If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Particularly if you are using insulin or other anti-diabetes medicines. A dose adjustment may be needed for these medicines.

Using this medicine and food:
Inject the medicine shortly before or after a meal or snack because it may cause insulin-like effects, and may therefore decrease blood sugar levels (see hypoglycemia in section 4).

Pregnancy, breastfeeding and fertility:
If you are pregnant or breastfeeding, think you are pregnant or are planning to become pregnant, ask your doctor for advice before using this medicine.

A negative pregnancy test is recommended for all women of childbearing potential prior to beginning treatment with mecasermin. It is also recommended that all women of childbearing potential use effective contraception methods during the treatment.

Mecasermin treatment should be discontinued if you become pregnant.
Mecasermin should not be administered to breastfeeding women.

Driving and using machines:
Do not drive or operate dangerous machines while using this medicine since mecasermin may cause hypoglycemia (a very common side effect, see section 4), therefore your ability to concentrate or react may be reduced.

Do not drive or operate dangerous machines or ride a bicycle within 2-3 hours after the injection, particularly at the start of Increlex treatment, until a dose of Increlex is found, which does not cause side effects making these activities risky.

Important information about some of this medicine's ingredients:
Increlex contains benzyl alcohol as a preservative, which may cause toxic reactions and allergic reactions in children up to 3 years old.

The vial contains less than 23 mg sodium, i.e. the medicine is essentially "sodium-free".

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually 0.04 to 0.12 mg/kg body weight administered twice a day. See the **"Instructions for use"** at the end of the leaflet.

Inject the medicine just under the skin shortly before or after a meal or snack because it may cause insulin-like effects, and may therefore decrease blood sugar levels (see hypoglycemia in section 4). Do not inject your dose of Increlex if you cannot eat for any reason. Do not compensate for a forgotten dose by injecting two doses at the next time. The next dose should be injected as scheduled, with a meal or snack.

Inject Increlex just under the skin in your upper arm, thigh, abdomen area, or buttocks. Never inject the medicine into a vein or muscle. Change the injection site for each injection.

Use Increlex only if the fluid is clear and colorless.

Treatment with mecasermin is a long-term therapy. For further information ask the doctor.

Do not exceed the recommended dose.

If you have accidentally injected or have been administered a higher Increlex dosage than you should
Mecasermin, like insulin, may lower blood sugar levels (see hypoglycemia in section 4). If you have injected an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

Acute overdose could lead to hypoglycemia (low blood sugar levels).

Treatment of acute overdose of mecasermin should be directed at reversing hypoglycemia. Sugar-containing fluids or foods should be consumed. If the patient is not awake or alert enough to drink sugar-containing fluids, an injection of glucagon into the muscle may be necessary to reverse hypoglycemia. Your doctor or nurse will instruct you how to give the injection of glucagon.

Long-term overdose may result in enlargement of certain body parts (e.g., hands, feet, parts of the face) or excessive growth of the entire body. If you suspect long-term overdose, contact your doctor immediately.

If you miss Increlex injection
Do not inject a double dose to compensate for the forgotten dose.
If you missed a dose, the next dose should not be made larger to compensate. The next dose should be injected at the usual time, with a meal or snack.

Adhere to the treatment as recommended by your doctor. Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine
Early discontinuation or disruption of treatment with mecasermin may impair the success of the treatment. Ask the doctor for advice before stopping the treatment.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take a medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

Like with all medicines, using Increlex may cause side effects in some users. Do not be alarmed by this list of side effects. You may not suffer from any of them.

The most common side effects of mecasermin are: low blood sugar levels (hypoglycemia), vomiting, injection site reactions, headache and middle ear infections. Serious side effects have also been reported with Increlex. If you develop any of the following conditions, please follow the recommendations detailed below.

Very common side effects (may affect more than 1 in 10 people):

- <u>Low blood sugar levels (hypoglycemia)</u>
  Mecasermin may lower blood sugar levels. Signs of low blood sugar levels are: dizziness, tiredness, restlessness, hunger, irritability, trouble concentrating, sweating, nausea and fast or irregular heartbeats.

  Severe hypoglycemia may cause unconsciousness, seizures or death. Stop treatment immediately and contact a doctor if you develop seizures or become unconscious.

  If you use Increlex, you should avoid participating in high risk activities (such as vigorous physical activity) within 2 to 3 hours after Increlex injection, especially at the beginning of treatment.

  Before beginning treatment with Increlex, the doctor or nurse will explain to you how to treat hypoglycemia. You should always have a source of sugar such as orange juice, glucose gel, sweets, or milk available in case symptoms of hypoglycemia occur. For severe hypoglycemia, if you or your child are not responsive and cannot drink sugar-containing fluids, you should receive or give your child an injection of glucagon. The doctor or nurse will instruct you how to give the injection. Glucagon raises the blood sugar when it is injected.

It is very important that you have a well-balanced diet including protein and fat, such as meat and cheese, in addition to sugar-containing foods.

- Injection site hypertrophy (tissue thickening at the injection site) and bruising
  These can be avoided by changing the injection site at each injection.

- Digestive system
  Vomiting and pain in the upper abdomen have occurred with mecasermin treatment.

- Infections
  Infections of the middle ear have been observed in children with mecasermin treatment.

- Musculoskeletal system
  Joint pain and pain in the limbs have occurred with mecasermin treatment.

- Nervous system
  Headache has occurred with mecasermin treatment.

Common side effects (may affect up to 1 in 10 people):

- Seizures
  Seizures have been observed with mecasermin treatment. Dizziness and tremor have also been reported with mecasermin treatment.

- Heart abnormalities
  A fast heart rate and abnormal heart sounds have been reported with mecasermin treatment.

- Increased blood sugar levels (hyperglycemia)
  Increased blood sugar has also been observed with mecasermin treatment.

- Enlarged tonsils
  Mecasermin may enlarge the tonsils/adenoids. Some signs of enlarged tonsils/adenoids include: snoring, difficulty breathing or swallowing, sleep apnea (a condition where breathing stops briefly during sleep), or fluid in the middle ear, as well as infections of the ear. Sleep apnea can cause excessive daytime sleepiness. Contact the doctor if you suffer from these symptoms. The doctor should regularly examine your tonsils/adenoids.

- Enlarged thymus
  An enlarged thymus (an organ of the immune system) has been observed with mecasermin treatment.

- Papilloedema
  A swelling at the back of the eye (due to increased pressure within the brain) may be observed by a doctor or optician during mecasermin treatment.

- Hearing loss (hypoacusis)
  Hearing loss (hypoacusis), ear pain and fluid in the middle ear have been observed with mecasermin treatment. Tell the doctor if you develop hearing problems.

- Worsening of scoliosis (caused by rapid growth)
  If you have scoliosis, you will need to be checked often for scoliosis worsening.
  Pain in muscles has also been observed with mecasermin treatment.

- Reproductive system
  Breast enlargement has been observed with mecasermin treatment.

- Digestive system
  Abdominal pain has been observed with mecasermin treatment.

- Skin and hair changes
  Skin thickening, moles and abnormal hair texture have been observed with mecasermin treatment.

- Injection site reactions
  Reactions including pain, irritation, bleeding, bruising, redness and hardening have been reported with Increlex treatment. Injection site reactions can be avoided by changing the injection site at each injection.

Uncommon side effects (may affect up to 1 in 100 people):

- Increased pressure in the brain (intracranial hypertension)
  Increlex can sometimes cause a temporary increase in pressure within the brain. The symptoms of intracranial hypertension can include visual changes, headache, nausea and/or vomiting. Tell the doctor immediately if you have any of these symptoms. Your doctor can check whether intracranial hypertension is present. If it is present, your doctor may decide to temporarily reduce or discontinue mecasermin therapy. Mecasermin treatment may be started again after the episode is over.

- Heart abnormalities
  In some patients treated with mecasermin, an ultrasound examination of the heart (echocardiogram) showed an increased size of the heart muscle and abnormal heart valve function. See section "Tests and follow up".

- Injection site reactions
  Reactions including rash, swelling and fatty lumps have been reported with Increlex treatment. Injection site reactions can be avoided by changing the injection site at each injection.

- Weight gain
  Weight gain has been observed with mecasermin treatment.

Additional side effects observed with mecasermin treatment are depression and nervousness.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Reporting side effects following drug treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/

5. How to store the medicine?

Avoid poisoning! This medicine, and any other medicine, should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp. date) that appears on the package and label. The expiry date refers to the last day of that month.

Storage conditions:
Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.
After first opening, the vial should be stored in a refrigerator (2°C - 8°C) for up to 30 days.

Do not throw any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Benzyl alcohol, sodium chloride, sodium acetate trihydrate, polysorbate 20, glacial acetic acid, and water for injection

What the medicine looks like and contents of the pack:
A glass vial containing a clear and colorless solution for injection. The vial is closed with a stopper and protective cap.
The vial contains 4 ml of solution.

The pack contains one vial.

Registration holder's name and address:
Medison Pharma Ltd., 10 Hashiloach St., POB 7090, Petach Tikva.

Manufacturer's name and address:
Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France.

This leaflet was revised in August 2020.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 163-53-35755-00

Instructions for use

The medicine should be injected using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with adequate accuracy.

Preparing the dose for injection:

1. Wash your hands before preparing the dose for injection
2. Use a new disposable needle and syringe every time you inject a dose. Use syringes and needles only once. Throw them away properly in a sharps container (such as a biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). **Never** share needles and syringes.
3. Check the liquid to make sure it is clear and colorless. Do not use after the expiry date (which is stated on the label and refers to the last day of that month) or if the liquid is cloudy or if you notice particles. If a vial freezes, dispose of it appropriately. Ask your pharmacist how to dispose of medicines you no longer use.
4. If you are using a new vial, remove the protective cap. Do not remove the rubber stopper.
5. Wipe the rubber stopper of the vial with an alcohol swab to prevent contamination of the vial by germs that may be introduced by repeated needle insertions (see Figure 1).

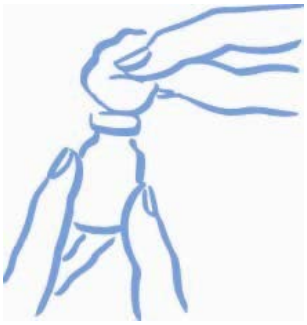


Figure 1: Wipe the rubber stopper with alcohol

6. Before inserting the needle into the vial, pull back the plunger to draw air into the syringe at a quantity equal to the prescribed dose. Insert the needle through the rubber stopper, and push the plunger to inject air into the vial (see Figure 2).

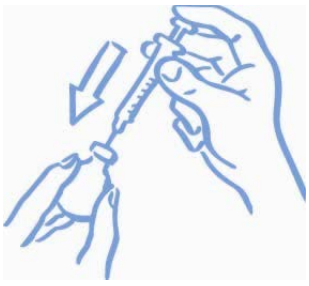


Figure 2: Inject air into vial

7. Leave the syringe in the vial and turn both upside down, so that the rubber stopper is facing down. Hold the syringe and vial firmly (see Figure 3).

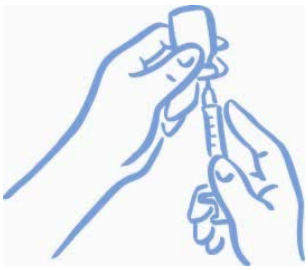


Figure 3: Prepare for extraction

8. Make sure the tip of the needle is in the liquid (see Figure 4). Pull the plunger to withdraw the correct dose into the syringe (see Figure 5).

Figure 5: Extract correct dose

Figure 4: Needle tip in liquid

9. Before you remove the needle from the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the vial and syringe with needle straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw liquid back in until you have the correct dose (see Figure 6).

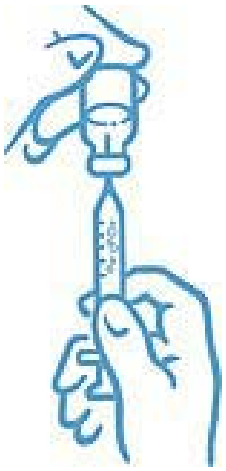


Figure 6: Remove air bubbles and refill syringe with liquid to obtain the correct dose

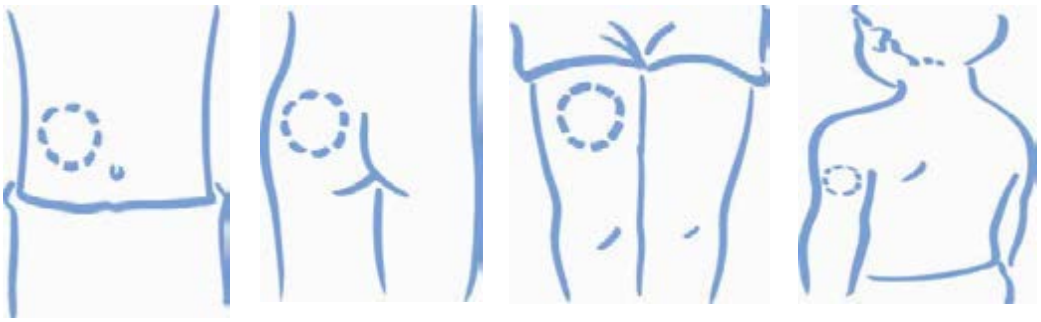
10. Remove the needle from the vial and replace the protective cap. Do not let the needle touch anything around you. You are now ready to inject (see Figure 7).

Figure 7: The syringe is ready for injection

Injecting the dose:

Inject the medicine as instructed by the doctor.
Do not inject the medicine if you are unable to eat shortly before or after the injection.

1. Select an injection site – upper arm, thigh, buttock, or abdomen (see below). The injection site should be changed for each injection.



Abdomen Buttock Thigh Upper arm

2. Use alcohol or soap and water to clean the skin where you are going to inject. The injection site should be dry before you inject.

3. Lightly pinch the skin. Insert the needle as the doctor instructed you. Release the skin (see Figure A).

Figure A: Lightly pinch the skin and inject as instructed

4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the liquid. Pull the needle straight out and gently press on the injection site with gauze or a cotton ball for a few seconds. **Do not rub the area** (see Figure B).

Figure B: Press with gauze or cotton ball

5. Follow the doctor's instructions for disposing of the needle and syringe. Do not recap the needle. Used needle and syringe should be placed in a sharps container (such as a biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). The container should be sealed and disposed of properly as instructed by the doctor.