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

The medicine is dispensed with a doctor's prescription only

Olatuton 10 mg

Powder and solvent for preparation of prolonged-release suspension for injection

Composition:

Each vial with powder contains:

Octreotide (as octreotide acetate) 10 mg

Olatuton 20 mg

Powder and solvent for preparation of prolonged-release suspension for injection

Composition:

Each vial with powder contains:

Octreotide (as octreotide acetate) 20 mg

Olatuton 30 mg

Powder and solvent for preparation of prolonged-release suspension for injection

Composition:

Each vial with powder contains:

Octreotide (as octreotide acetate) 30 mg

For information regarding inactive ingredients and allergens in the preparation see section 2 – "Important information about some of the ingredients of the medicine" and section 6 – "Additional information".

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 you. 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?

Olatuton is intended for:

- Treatment of people with acromegaly:
  - Whose illness is sufficiently controlled through treatment with standard doses of subcutaneous octreotide.
  - When surgery or radiotherapy are unsuitable or ineffective.
  - To cover the interim period until radiotherapy becomes fully effective.
- Treatment of gastro-entero-pancreatic (GEP) endocrine tumors, carcinoid tumors.

Therapeutic class:

Somatostatin analogues.

Olatuton is a synthetic compound derived from somatostatin. Somatostatin is normally found in the human body, where it inhibits the release of certain hormones such as growth hormone. Olatuton has advantages over somatostatin, it is stronger and its effects last longer.

Acromegaly is a condition in which the body produces too much growth hormone. Growth hormone normally regulates the growth of tissues, organs and bones. Too much growth hormone leads to an increase in the size of bones and tissues, particularly in the hands and feet. Olatuton markedly reduces the symptoms of acromegaly, which include headache, excessive sweating, numbness of the hands and feet, tiredness and joint pain.

Increased production of specific hormones and other substances may be caused by some rare conditions of the stomach, intestines or pancreas. This condition upsets the body's natural hormonal balance and results in a variety of symptoms, such as: flushing, diarrhea, low blood pressure, rash and weight loss. Treatment with Olatuton helps to control these symptoms.

2. Before using the medicine

Follow all the instructions given to you by your doctor carefully. They may differ from the information provided in this leaflet.

Read the following explanations before using Olatuton.

Do not use this medicine if:

You are sensitive (allergic) to octreotide or to any of the other ingredients this medicine contains (see section 6 – "Additional information").

Special warnings regarding the use of the medicine:

Before treatment with Olatuton, inform the doctor if:

- You know you currently have gallstones, or you have had them in the past, or if you experience complications such as fever, chills, abdominal pain or yellowing of the skin or eyes; since prolonged use of Olatuton may cause the formation of gallstones. Your doctor may wish to check your gallbladder periodically.
- You know you have diabetes; since Olatuton may affect blood sugar levels. If you are diabetic, your blood sugar levels should be checked regularly.
- You have a history of vitamin B12 deficiency; your doctor may wish to check your vitamin B12 levels periodically.

Children and adolescents:

There is little experience with the use of Olatuton in children.

Tests and follow-up:

If you are being treated with Olatuton for a long period of time, your doctor may wish to check your thyroid function periodically. Your doctor will check your liver function.

Your doctor may want to check how your pancreatic enzymes function.

Drug interactions:

If you are taking or have recently taken other medicines including non-prescription medicines and nutritional supplements, tell the doctor or the pharmacist.

In general, you may continue taking other medicines while taking Olatuton. However, certain medicines, such as: cimetidine, cyclosporin, bromocriptine, quinidine and terfenadine have been reported to be affected by Olatuton.

If you are taking any medicine to regulate your blood pressure (e.g., a beta blocker or a calcium channel blocker), or if you are taking any preparation to regulate your fluid and electrolyte balance, your doctor may need to adjust your dosage.

If you are diabetic, your doctor may need to adjust your insulin dosage.

If you are about to receive lutetium (^{177}Lu) oxodotreotide, a radiobiological treatment, your doctor may stop and/or adjust your Olatuton treatment for a short period of time.

Pregnancy, breastfeeding and fertility:

If you are pregnant or breastfeeding, think you might be pregnant or are planning to become pregnant, consult your doctor before taking this medicine.

Olatuton should only be used during pregnancy if clearly needed.

Women of childbearing age should use effective contraceptives during this treatment.

Do not breastfeed during treatment with Olatuton. It is unknown whether Olatuton passes into breastmilk.

Driving and operating machinery:

Olatuton has no effects, or has negligible effects, on the ability to drive and operate machinery. However, some side effects you may experience while using Olatuton, such as headaches and tiredness, may impair your ability to safely drive and operate machinery.

Children should be cautioned against riding a bicycle or playing near a road etc.

Important information about some of the ingredients of the medicine:

Olatuton contains less than 1 mmol of sodium (23 mg) per vial, and is thus considered to be 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 preparation.

The dosage and treatment regimen will be determined only by the doctor.

Do not exceed the recommended dose.

Olatuton must always be administered as an injection into the muscle of the buttocks. With repeated administration, the left and right buttocks should be used alternately.

The medicine should only be administered by trained medical personnel.

If you accidentally took a higher dosage

No life-threatening effects have been reported following an overdose of octreotide when administered as a prolonged-release injection.

Overdose symptoms are: hot flashes, frequent urination, tiredness, depression, anxiety and lack of concentration.

If you think you may have received an overdose and are experiencing such symptoms, inform your doctor immediately.

If this medicine has been injected to a child by mistake, immediately go to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine

If you forgot to receive the injection at the required time, it is recommended to receive it as soon as you remember, and then continue as usual.

No damage would result from a few days delay in administration, but some symptoms may temporarily recur until you return to the regular treatment plan.

Follow the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

If you stop taking the medicine

If you stop your treatment with Olatuton, your symptoms may recur. Therefore, do not stop using Olatuton unless your doctor tells you to.

Do not take medicines in the dark! Check the label and the dose <u>every time</u> you take the medicine. Wear glasses if you need them.

If you have any other questions regarding the use of this medicine, consult your doctor, pharmacist or nurse.

4. Side effects

As with any medicine, using Olatuton 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.

Some side effects may be serious. If you experience any of the following effects, inform your doctor immediately:

Very common side effects – side effects that occur in more than one out of ten users:

- Gallstones, may cause sudden back pain
- Too much sugar in the blood

Common side effects – side effects that occur in 1-10 out of 100 users:

- Underactive thyroid (hypothyroidism) which causes changes in heart rate, appetite or weight, as well as tiredness, cold sensation or swelling at the front of the neck
- Changes in thyroid function tests
- Gallbladder inflammation (cholecystitis): the symptoms may include pain in the upper right abdomen, fever, nausea, yellowing of the skin and the eyes (jaundice)
- Too little sugar in the blood
- Impaired glucose tolerance
- Slow heartbeat

Uncommon side effects – side effects that occur in 1-10 out of 1,000 users:

- Thirst, reduced urine output, dark urine, dry and flushed skin
- Rapid heartbeat

Other severe side effects:

- Hypersensitivity reactions (allergy), including skin rash
- A type of allergic reaction (anaphylaxis), which can cause swallowing or breathing difficulty, swelling and tingling, possibly with a decrease in blood pressure with dizziness or with loss of consciousness
- Inflammation of the pancreas (pancreatitis): the symptoms may include sudden pain in the upper abdomen, nausea, vomiting, diarrhea
- Inflammation of the liver (hepatitis): the symptoms may include yellowing of the skin and the eyes (jaundice), nausea, vomiting, loss of appetite, general malaise, itching, light-colored urine
- Irregular heart rhythm
- Low blood platelet count: may cause increased bleeding or bruises

Tell your doctor immediately if you observe any of the side effects mentioned above.

Other side effects:

Inform your doctor, pharmacist or nurse if you observe any of the following side effects. These are usually moderate and tend to go away as the treatment progresses.

Very common side effects – side effects that occur in more than one out of ten users:

- Diarrhea
- Abdominal pain
- Nausea
- Constipation
- Accumulation of gas in the digestive system
- Headache
- Local pain at the site of injection

Common side effects – side effects that occur in 1-10 out of 100 users:

- Abdominal discomfort after a meal (dyspepsia)
- Vomiting
- Feeling of fullness in the stomach
- Fatty stools
- Loose stools
- Discoloration of stools
- Dizziness
- Loss of appetite
- Change in liver function tests
- Hair loss
- Shortness of breath
- Weakness

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 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. The expiry date refers to the last day of that month.

Storage conditions:

Store in the refrigerator (2°-8°C).

Do not freeze.

Store in the original package to protect from light.

On the day of administration Olatuton may be stored below 25°C.

Use immediately after reconstitution.

Do not use this medicine if you observe particles or discoloration.

Do not dispose of medicines via wastewater or household waste. Consult with the pharmacist on where 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:

Powder (vial):

D,L-Lactide/Glycolide copolymer, mannitol.

Solvent (syringe):

Carboxymethylcellulose sodium, mannitol, poloxamer, water for injection.

What does the medicine look like and what are the contents of the package:

The powder in the vial is white to off-white and is free of foreign particles.

The solvent in the prefilled syringe is clear, colorless and particle-free.

Each pack contains:

- One glass vial containing powder. The vial is sealed with a rubber stopper with a colored aluminum cap (Olatuton 10 mg: dark blue cap, Olatuton 20 mg: orange cap, Olatuton 30 mg: dark red cap).
- One glass prefilled syringe containing 2 ml of solvent.
- The vial and the syringe are packed together in a plastic blister with one safety injection needle and one vial adapter.

Marketing authorization holder and manufacturer and the address:

Teva Israel Ltd., 124 Dvora HaNevi'a St., Tel Aviv.

The leaflet was revised in April 2022 in accordance with the Ministry of Health guidelines.

Registration numbers of the medicine in the national drug registry of the Ministry of Health:

Olatuton 10 mg: 169-38-36088

Olatuton 20 mg: 169-39-36089

Olatuton 30 mg: 169-40-36090

<u>המידע הבא מיועד לאנשי הצוות הרפואי בלבד:</u>

<u>المعلومات التالية مخصصة لأفراد الطاقم الطبي فقط:</u>

<u>The following information is intended for healthcare professionals only:</u>

How much Olatuton to use

Acromegaly

For patients who are adequately controlled with s.c. octreotide, it is recommended to start treatment with the administration of 20 mg Olatuton at 4-week intervals for 3 months. Treatment with Olatuton can be started the day after the last dose of s.c. octreotide. Subsequent dosage adjustment should be based on serum growth hormone (GH) and insulin-like growth factor-1/somatomedin C (IGF-1) concentrations and on clinical symptoms.

For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF-1) are not fully controlled (GH concentrations still above 2.5 microgram/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF-1 serum concentrations have normalised, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg Olatuton may be administered every 4 weeks. However, particularly in this group of patients, it is recommended to closely monitor adequate control of serum GH and IGF-1 concentrations and clinical signs/symptoms at this low dose of Olatuton.

For patients on a stable dose of Olatuton, assessment of GH and IGF-1 should be made every 6 months.

For patients in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective, a short test dosing period of s.c. administration of octreotide is recommended, to assess the response and systemic tolerability of octreotide prior to initiating treatment with Olatuton as described above.

Gastro-entero-pancreatic endocrine tumours

For patients in whom symptoms are adequately controlled with s.c. octreotide, it is recommended to start treatment with the administration of 20 mg Olatuton at 4-week intervals. The treatment with s.c. octreotide should be continued at the previously effective dosage for 2 weeks after the first injection of Olatuton.

For patients who have not been previously treated with s.c. octreotide, it is recommended to start with the administration of s.c. octreotide at a dosage of 0.1 mg 3 times daily for a short period (approximately 2 weeks), to assess the response and systemic tolerability of octreotide before initiating the treatment with Olatuton as described above. For patients in whom symptoms and biological markers are well controlled after 3 months of treatment, the dose may be reduced to 10 mg Olatuton every 4 weeks.

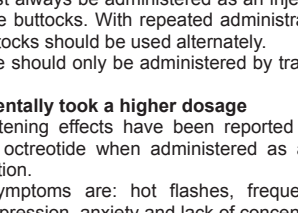
For patients in whom symptoms are only partially controlled after 3 months of treatment, the dose may be increased to 30 mg Olatuton every 4 weeks.

On days when symptoms associated with gastro-entero-pancreatic tumours may increase during treatment with Olatuton, additional administration of s.c. octreotide is recommended at the dose used prior to the Olatuton treatment. This may occur mainly in the first 2 months of treatment until therapeutic concentrations of octreotide are reached.

INSTRUCTIONS FOR PREPARATION AND INTRAMUSCULALR INJECTION FOR OLATUTON

FOR DEEP INTRAMUSCULAR INJECTION ONLY

Included in the injection kit:



a. One vial containing Olatuton powder
b. One prefilled syringe containing the vehicle solution for reconstitution
c. One vial adapter for drug product reconstitution
d. One safety injection needle

Follow the instructions below carefully to ensure proper reconstitution of Olatuton before deep intramuscular injection.

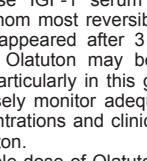
There are 3 critical actions in the reconstitution of Olatuton. **<u>Not following them could result in failure to deliver the drug appropriately.</u>**

- **The injection kit must reach room temperature.** Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the diluent solution, **<u>ensure that the powder is fully saturated</u>** by letting the vial stand for 5 minutes.
- After saturation, **<u>shake the vial moderately</u>** in a horizontal direction for a minimum of 30 seconds **<u>until a uniform suspension is formed</u>**. The Olatuton suspension must only be prepared **immediately** before administration.

Olatuton should only be administered by a trained healthcare professional.

Step 1

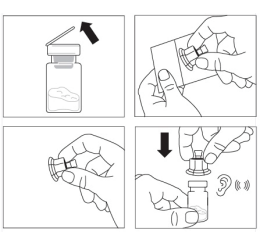
- Remove the Olatuton injection kit from refrigerated storage. **ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.**



Note: The injection kit can be re-refrigerated if needed.

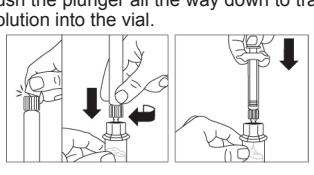
Step 2

- Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.
- Peel the blister film and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. DO NOT touch the tip of the access device at any place.
- Place the vial on a flat surface. Position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible "click".
- Clean the tip of the vial adapter with an alcohol wipe.



Step 3

- Snap off the smooth white cap from the syringe prefilled with diluent solution and screw the syringe onto the vial adapter.
- Slowly push the plunger all the way down to transfer all the diluent solution into the vial.

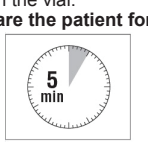


Step 4

ATTENTION: It is essential to let the vial stand for 5 minutes to ensure that the diluent has fully saturated the powder.

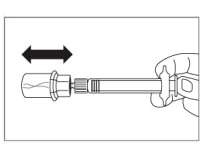
Note: It is normal if the plunger rod moves up as there might be a slight overpressure in the vial.

- **At this stage prepare the patient for injection.**



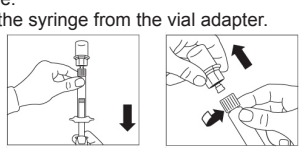
Step 5

- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.
  ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction **for a minimum of 30 seconds** so that the powder is completely suspended (uniform milky suspension). **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**



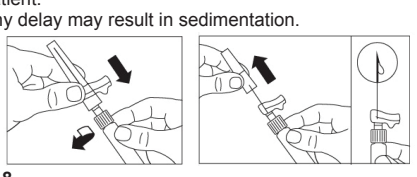
Step 6

- Turn the syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe.
- Unscrew the syringe from the vial adapter.



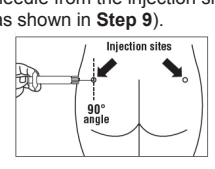
Step 7

- Prepare the injection site with an alcohol wipe.
- Screw the safety injection needle onto the syringe.
- If immediate administration is delayed, gently **re-shake** the syringe to ensure a uniform milky suspension.
- Pull the protective cover straight off the needle.
- Gently tap the syringe to remove any visible bubbles and expel them from the syringe.
- Proceed **immediately** to Step 8 for administration to the patient.
  Any delay may result in sedimentation.



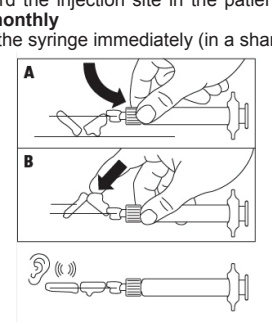
Step 8

- Olatuton must be given only by deep intramuscular injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90° angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- Depress the plunger with **steady pressure** until the syringe is empty.
  Withdraw the needle from the injection site and activate the safety guard (as shown in **Step 9**).



Step 9

- Activate the safety guard over the needle in one of the 2 methods shown:
  - either press the hinged section of the safety guard down onto a hard surface (figure A)
  - or push the hinge forward with your finger (figure B).
- An audible "click" confirms the proper activation.
- Note: Record the injection site in the patient's record and **alternate monthly**
- Dispose of the syringe immediately (in a sharps container).



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