PATIENT PACKAGE INSERT IN ACCORDANCE WITH
THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
This medicine is dispensed with a physician's prescription only

Name of the medicine, its form and strength:

Macrilen®

Granules for Oral Suspension

Each sachet contains:

Macimorelin (as acetate) 60 mg

After reconstitution: each 1 mL of reconstituted suspension contains 500 micrograms of macimorelin

Inactive and allergenic ingredients:

Each sachet contains 1,691.8 mg of lactose monohydrate.

See section 6 "Additional information" and section 2 "Important information about some of the medicine's ingredients".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, consult your physician or pharmacist.

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

1. What is this medicine intended for?

Macrilen is intended for the diagnosis of growth hormone deficiency (GHD) in adults.

Therapeutic group: Macrilen belongs to a group of medicines used to diagnose and test pituitary gland activity.

The medicine contains an active ingredient called macimorelin, which acts like a natural hormone and causes the pituitary gland to release growth hormone into the bloodstream.

Macrilen is used in adults to test the body´s ability to produce growth hormone. **Macrilen** is used when your physician thinks that you may not have enough growth hormone (adult growth hormone deficiency). **Macrilen** is not intended for the treatment of patients who do not have enough growth hormone. **Macrilen** is a test that helps your physician to diagnose this condition.

2. Before using the medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient, macimorelin, or to any of the additional ingredients contained in the medicine.
  For a list of inactive ingredients, see section 6 "Additional information".

Special warnings regarding use of the medicine

- To ensure that the test results are reliable, follow the instructions below:
  - Fasting – Do not eat for at least 8 hours before the test, nor during the test.
  - Physical exercise – Avoid strenuous physical activity for the 24 hours before the test.
  - Drinking – You may drink up to 100 mL of non-carbonated water during the hour before you drink the prepared suspension, and during the hour after you drink the prepared suspension.
- **Before using Macrilen, tell your physician if:**
  - You have recently been treated with growth hormone (somatotropin) or with other medicines that affect secretion of growth hormone from the pituitary gland. This type of treatment must be stopped at least one month before the test.
  - You have recently been treated for Cushing's disease (high cortisol hormone levels), or you are being treated with a high dose of hydrocortisone, which may lead to false positive results in the test.
  - Your body lacks any other hormone, such as cortisol, thyroid hormones, sex hormones, or vasopressin (in diabetes insipidus). Such a deficiency should be adequately corrected before testing for growth hormone deficiency. Other hormone deficiencies, if untreated, could lead to inaccurate results in the growth hormone stimulation test.
  - You have heart disease or heart rhythm problems (including congenital or acquired long QT syndrome or a history of a type of ventricular tachycardia called torsades de pointes). **Macrilen** can cause changes in the ECG (electrocardiogram), including prolongation of the QT interval, that are associated with an increased risk for arrhythmia. Such changes, if they occur, will last for a limited time and will not last long.

If any of the above applies to you, or if you are not sure, talk to your physician or nurse before you are given this medicine.

Macrilen is indicated as a single-dose diagnostic test. No information is available on the safety and effects of macimorelin for long-term use.

Re-test potentially needed in early disease

If the adult growth hormone deficiency began only recently and if it is the result of damage to a part of the brain called the hypothalamus, the test result could be negative even though you have the disease. In such a situation, the test may need to be repeated.

Children and adolescents:

Macrilen is not intended for children and adolescents under 18 years of age.

There is no information regarding the safety and efficacy of using this medicine in children and adolescents below 18 years of age.

Drug interactions:

If you are taking or have recently taken any other medicines, including non-prescription medicines or nutritional supplements, tell your physician or pharmacist. Especially if you are taking:

- Medicines that can alter your heart rhythm, such as:
  - medicines to treat psychosis (such as chlorpromazine, haloperidol)
  - medicines to treat infections (antibiotics such as erythromycin, clarithromycin, moxifloxacin)
  - medicines to correct heart rhythm (antiarrhythmic medicines such as amiodarone, procainamide, quinidine or sotalol)
  - any other medicine that can prolong the QT interval or cause torsades de pointes
- Medicines that may increase breakdown of macimorelin, such as specific medicines intended for the treatment of:
  - seizures/epilepsy (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone)
  - sleep disorder (modafinil, pitolisant)
  - mild to moderate depressive episodes (extract of the herbal medicine hypericum [St. John's wort])
  - cystic fibrosis (lumacaftor)
  - infections (antibiotics such as rifabutin, rifampicin)
  - HIV (efavirenz, nevirapine)
  - Type 2 diabetes (pioglitazone)
  - cancer (dabrafenib, enzalutamide)
- Medicines that may affect the accuracy of the diagnostic test. Avoid concomitant use with medicines:
  - that could have a direct influence on growth hormone secretion from the pituitary gland, such as somatostatin, insulin, glucocorticoids, acetylsalicylic acid, indometacin
  - that could increase growth hormone levels, such as clonidine, levodopa, insulin
  - that may reduce the growth hormone response to macimorelin, such as atropine, propylthiouracil, growth hormone drugs

Pregnancy, breastfeeding and fertility:

If you are pregnant or breastfeeding, think that you may be pregnant or are planning to have a baby, ask your physician or nurse for advice before using the medicine.

Macrilen is not recommended for use during pregnancy. If you are a woman of reproductive age, you must use effective contraceptive methods to ensure you are not pregnant at the time of the test. If you are breastfeeding or intend to breastfeed, risk to the suckling child cannot be ruled out. Ask your physician whether to stop breastfeeding or to avoid from the macimorelin test.

Driving and using machines:

Dizziness can appear with **Macrilen**. If this occurs, do not drive or use machines.

Important information about some of the medicine's ingredients:

Macrilen contains lactose

If you have been told by your physician that you have an intolerance to some sugars, consult your physician before taking this medicine.

Macrilen contains sodium

This medicine contains less than **1 mmol** sodium (23 mg) per sachet. It is therefore considered to be a "sodium-free" medicine.

3. How should you use the medicine?

A healthcare professional must supervise the preparation and use of **Macrilen**. Instructions for preparing the test appear at the end of this leaflet.

Always use **Macrilen** according to your physician's instructions.

You must check with your physician or pharmacist if you are unsure about the dosage or treatment regimen of this medicine.

The description in this leaflet is meant to provide information about the testing procedure.

You must be fasting for at least 8 hours before being given **Macrilen**. Refrain from strenuous physical exercise for 24 hours before the test. You may drink up to 100 mL of non-carbonated water during the hour before as well as during the hour after you drink the prepared suspension.

Dose for adults:

The recommended dose for adults is 0.5 mg of **Macrilen** (1 mL of the prepared suspension) per kg of body weight.

Drink the complete test dose within 30 seconds.

Three blood samples will be taken to measure growth hormone levels, one at each of the following time intervals: 45, 60 and 90 minutes after drinking the prepared suspension.

Do not exceed the recommended dose.

Patients with liver and/or kidney failure

The safety and efficacy of **Macrilen** in patients with liver and/or kidney failure has not been proven. If **Macrilen** is given to patients with liver and/or kidney failure, the possibility of an elevated blood concentration of macimorelin cannot be ruled out. It is not known whether this could cause arrhythmia. The physician may therefore wish to monitor your ECG before administering **Macrilen**, and again 1, 2, 4 and 6 hours after administering **Macrilen**.

Elderly

Secretion of growth hormone generally decreases with age. The efficacy of **Macrilen** in patients over the age of 65 has not been proven.

Pediatric population

There is no information regarding the safety and efficacy of the use of this medicine in children and adolescents under 18 years of age.

If you have accidentally taken a higher dose of Macrilen, tell your physician or nurse. Possible side effects in case of overdose may include headache, nausea, vomiting and diarrhea. In case of arrhythmia, an ECG monitoring should be performed.

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 further questions regarding use of the medicine, consult your physician or pharmacist.

4. Side effects

As with any medicine, the use of **Macrilen** 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.

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

- A bitter or metallic taste (dysgeusia)
- Fatigue
- Headache
- Nausea
- Dizziness
- Diarrhea
- Feeling hot

These side effects are mostly mild, do not last long, and usually go away quickly without treatment.

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

- Abdominal pain
- Feeling cold
- Hunger
- Palpitations
- Heart rate lower than normal (sinus bradycardia)
- Sleepiness
- Thirst
- Tremor
- Spinning sensation (vertigo)

Side effects with unknown frequency (effects for which their frequency has not yet been determined):

Changes in electrocardiogram (ECG)

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 physician.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" on the homepage of the Ministry of Health website (www.health.gov.il), which will direct you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. How should the medicine be stored?

- Avoid poisoning! This medicine, and every 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 your physician.
- Do not use this medicine after the expiry date (exp. date) which appears on the outer package. The expiry date refers to the last day of that month.

Storage conditions:

- Store in a refrigerator, between 2-8ºC.
- Store in the original package to protect the medicine from exposure to light and moisture.
- The prepared suspension must be used within 30 minutes after preparation.

Discard any remaining unused suspension. Do not throw away medicines via wastewater or in household waste. Ask your pharmacist how to discard 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:

Lactose, Crospovidone Type A, Sodium Stearyl Fumarate, Saccharin Sodium Dihydrate and Colloidal Silicon Dioxide

See section 2 "Important information about some of the medicine's ingredients".

- **What the medicine looks like and what the package contains:**

Macrilen is marketed as white to off-white granules for preparation of an oral suspension.

Each sachet contains 1,817 mg of granules. Each cardboard box contains one sachet.

- **Registration holder and address:** Megapharm Ltd., 15 HaTidhar St., Ra'anana, Israel
- **Manufacturer name and address:** Aeterna Zentaris, Frankfurt, Germany
- **Approved by the Ministry of Health in September 2022**
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: **170-69-36962-99**

Detailed Instructions for the Preparation and Use of Macrilen

Preparation and administration of the suspension to the patient must be carried out by a healthcare professional.

Items needed: Sachet of **Macrilen**, tap water in a decanter, a graduated glass or transparent plastic container, a stirring device, a 50 mL graduated syringe without a needle, a drinking glass

o Step 1

Weigh the patient.

o Step 2

Determine the number of **Macrilen** sachets needed based on body weight:

One sachet will be required for a patient weighing up to 120 kg; two sachets will be required if the patient weighs more than 120 kg.

o Step 3

Add the required volume of water into the graduated glass or transparent plastic container.

Dissolve the entire contents of the sachet in the water: one sachet in 120 mL or two sachets in 240 mL.

Stir the suspension gently for 2 minutes (a small quantity of undissolved particles will remain, and the suspension will have a slightly cloudy appearance).

Stir the suspension until it is slightly cloudy, with no particles at the bottom of the container.

Stir the suspension again when some of the particles settle at the bottom of the container for example after the suspension has been left standing for a while.

o Step 4

Determine the volume of suspension required for the recommended macimorelin dose of 0.5 mg/kg. The suspension volume in mL is equal to the patient's body weight in kg. For example, a 70 kg patient will require 70 mL of the macimorelin suspension.

Measure the required volume using a 50 mL graduated syringe without a needle.

Transfer the measured amount to a drinking glass.

o Step 5

Ask the patient to drink the entire contents of the drinking glass within 30 seconds.

The suspension must be used within 30 minutes of preparation. Any suspension that remains should not be stored and must be discarded.

Any unused medicine or waste material should be disposed in accordance with local requirements.

o Step 6

Take venous blood samples for growth hormone determination at the following times: 45, 60 and 90 minutes after administering the medicine.

o Step 7

Prepare samples of plasma or serum and send them to a laboratory for growth hormone determination.