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

This medicine is dispensed by a physician's prescription only

Humalog Mix 50
Suspension

Active ingredient and its concentration:
Each cartridge contains:
Insulin Lispro 100 U/ml
50% Insulin Lispro (free fast-acting) and 50% Insulin Lispro Protamine in suspension (long-acting)

For the list of inactive ingredients, please see section 6.

Read this patient leaflet carefully in its entirety before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, please contact your doctor 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?

For the treatment of diabetes in patients who require insulin to maintain balanced blood sugar levels.

Therapeutic group:
Insulins and insulin analogs.

Insulin is a hormone secreted by the pancreas, a gland located near the stomach. This hormone is essential to the body in utilizing glucose obtained from the food. Diabetes occurs when the pancreas does not provide the sufficient amount of insulin to meet the body's needs. To balance the diabetes, the doctor has prescribed insulin injections for you.
Humalog Mix 50 is a faster acting insulin than the regular insulin mixture, therefore it can be injected close to mealtime, before or shortly after.

2. BEFORE USING THIS MEDICINE:

Do not use the preparation if:
• You are sensitive (allergic) to one of the medicine's ingredients. • Do not use in a state of hypoglycemia (low blood sugar).

Special warnings regarding the use of this medicine:
Do not inject **Humalog Mix 50** directly into the vein!

Before starting treatment with Humalog Mix 50 tell your doctor if:
- You suffer from fever and vomiting or an emotional disturbance.
- You suffer or have suffered in the past from impaired function of: the liver, kidney/urinary system, thyroid gland.

A change in the type of insulin usually requires a dosage adjustment; therefore, every change should be made under the supervision of the attending doctor. In certain cases, the usual dose may cause hypoglycemia, which is a result of administering a dose of insulin that is too high, skipping a meal, more than usual physical activity or following an illness (vomiting, diarrhea, fever). Initial symptoms of hypoglycemia can manifest as cold sweat, tachycardia, headache, vomiting, fever, nervousness, tremor, confusion or apathy. These symptoms can pass with the consumption of sugar or food that contains sugar (it is therefore desirable to always carry around with you sugar cubes or sucking candies).

Your relatives and colleagues must know that you are diabetic and how they can help you in a state of hypoglycemia. They must know that an unconscious person should not be given food or drink for fear of choking. They should roll the patient over on his side and call for immediate medical help. Unconsciousness can be treated with an injection of glucagon, performed by a person who has been trained in dealing with these situations. Upon regaining consciousness, the patient should be instructed to take sugar orally. Consult your doctor if you have experienced repetitive reactions to insulin or another event that was accompanied by unconsciousness, since in these cases changing the dose of insulin is necessary. If a significant drop in blood sugar level is left untreated, it could cause loss of consciousness, temporary or permanent brain damage and even death.

Diabetic ketosis, ketoacidosis or loss of consciousness can result from very high sugar levels in the blood - hyperglycemia. This condition can occur if there is an increased demand for insulin during an illness, infection, mental stress, failure to maintain a proper diet or injecting a smaller amount of insulin than what has been prescribed by the attending physician. Ketoacidosis symptoms can be diagnosed through a urine test that shows high levels of sugar and acetone. The following symptoms can gradually develop within hours or days: thirst, excessive urine volumes, loss of appetite, fatigue, dry skin, rapid and deep breathing, flushing, acetone odor from the breath. If you feel any of these symptoms and/or breathe heavily and have a rapid pulse, consult your doctor immediately. If these symptoms are left untreated, they can cause diabetic coma and death.

You should tell your doctor, pharmacist or diabetes nurse whether you plan to go abroad. Due to the time difference between countries, you may have to change the times of your meals and injections.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including non-prescription medications and nutritional supplements.

The insulin requirement of the body may change upon concomitant administration with medicines such as:

- Contraceptive pills
- Steroids
- Thyroid hormones
- Oral antidiabetic medicines
- Salicylates (for example: acetylsalicylic acid - aspirin)
- Sulfa antibiotics
- Octreotide (for the treatment of pulmonary hypertension)
- Beta-2 agonists (for example: salbutamol, terbutaline)
- Beta-blockers (for blood pressure or the heart)

- Certain antidepressant drugs (MAOIs or SSRIs)
- Danazol
- Certain ACE inhibitors (given for blood pressure and the heart), for example: captopril and enalapril
- Angiotensin II receptor blockers

Cases of heart failure were reported in type 2 diabetes patients who also suffer from a heart disease or have experienced a stroke in the past, who have been treated with insulin in combination with preparations containing pioglitazone (an oral medicine for the treatment of diabetes). Therefore, inform your doctor as soon as possible if you experience symptoms such as: unusual shortness of breath, rapid weight gain or localized swelling (oedema).

Use of this medicine and food:
Consult the doctor.

Use of this medicine and alcohol consumption:
Insulin requirement may decrease during concomitant use of alcohol. Dosage adjustment may be required.

Pregnancy and breastfeeding:
Consult a doctor or pharmacist before using this medicine.
Data on a large number of women who have used insulin lispro during pregnancy did not indicate any adverse effect of insulin lispro on the pregnancy, health of the fetus or newborn. Nevertheless, during pregnancy it is particularly important to maintain balanced blood sugar levels.
Insulin requirements usually decrease during the first trimester of pregnancy and increase during the second and third trimesters.
If you are breastfeeding, there may be a need to change your insulin dosage or diet. Consult your doctor.

Driving and using machines:
The ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia, which can be dangerous when driving a car or operating heavy machinery. If you suffer from frequent episodes of hypoglycemia or unclear symptoms preceding an episode of hypoglycemia, consult your doctor about whether you should drive.

3. HOW TO USE THIS MEDICINE?
Always use according to your doctor's instructions.
The dosage and manner of treatment will be determined only by the doctor.

Humalog Mix 50 is intended for subcutaneous injection. Under no circumstances should you inject intravenously.
Do not mix **Humalog Mix 50** with any other type of insulin.

Below are general instructions for injection. For detailed instructions, please see the user manual enclosed in the package of the pen.
Before using **Humalog Mix 50,** it is very important to read the detailed instructions carefully and follow them strictly. Failure to follow the instructions may result in an inaccurate insulin dose.
The amount of insulin for injection is measured in units. It is important to recognize the unit marks on the injector pen, because the volume of insulin that is injected is calculated based on

the number of units per ml. Use only an appropriate injector pen. Using an inappropriate injector pen may result in an inaccurate insulin dose.
Humalog Mix 50 is presented as a white or milky suspension. The cartridge contains a small bead to assist mixing the suspension. Examine the insulin in use frequently. Do not use if there are clumps or solid particles stuck to the walls or bottom of the cartridge, giving the suspension a frothy appearance.
Discarding of disposable needles after use must be strictly maintained according to the instructions from the medical staff, in order to prevent infections. The pen and needle must be used exclusively by you, even if you have changed the needle, in order to prevent the possibility of transmission of diseases.
Do not store the pen in use with the needle attached.

Preparing an insulin dose when using a cartridge:

1. Wash your hands thoroughly. Disinfect the rubber stopper of the cartridge.
2. Check the appearance of insulin in the cartridge. Do not use the insulin cartridge if you notice a change in appearance.
3. **Humalog Mix 50** cartridges are to be used with Eli Lilly company pens only. Make sure that **Humalog Mix** or Lilly cartridges are mentioned in the leaflet enclosed in the injector pen package. Insert the cartridge into the injector pen.
4. Follow the instructions that appear in the leaflet enclosed in the injector pen package.
5. Prime the injector pen before each use. Set the injector pen to a dose of 1 or 2 units. Hold the injector pen with the needle pointed up and tap on it so that air bubbles will rise to the top. While the injector pen is still pointing up, press the injection button until a drop of **Humalog Mix 50** comes out of the needle. A few small air bubbles may remain in the injector pen. That is harmless, but if the air bubble is too big, the injected insulin dose may be less accurate.
6. Do not mix insulins of different types in the **Humalog Mix 50** cartridge. Do not reuse the empty cartridge. After the injection, leave the cartridge inside the injector pen.
   You can see how much **Humalog Mix 50** remains in the cartridge by looking at the gauge marked on it. The distance between each mark on the gauge is about 20 units. In case there is not enough **Humalog Mix 50** for one dose, replace the cartridge.

General instructions for injection:
Use a new needle for each injection in order to prevent infections.

1. Wash your hands thoroughly.
2. Before injecting, roll the injector pen in your hands about 10 times and invert it 180° about 10 times until the insulin is evenly mixed. This action may be repeated. Do not shake vigorously as this may cause frothing which may interfere with the correct measurement of the dose.
3. Set the injector pen to the desired dose according to the injector pen instructions for use.
4. Clean the injection site with an alcohol-soaked swab.
5. "Pinch" a wide area of skin and lift it.
6. Insert the injector pen needle under the skin.
7. Inject the insulin by pushing the injection button all the way down and wait 5 seconds before retracting the needle from the skin.
8. Pull the injector pen needle out at a straight angle. Do not rub the injection site.
9. Put the external cover of the needle back on and discard the disposable items in accordance with the instructions provided to you by the medical staff.
10. Immediately after injecting, remove the needle from the injector pen in order to ensure sterility, prevent leakage of insulin from the injector pen, entry of air and needle clogging.

Do not reuse the needle. Destroy the needle according to the instructions received from the medical staff. Return the pen cover to its place.

11. Change the injection site each time.
    Consult your doctor or nurse about desirable injection sites.

    Do not mix different insulin types in the **Humalog Mix 50** cartridge. Do not reuse the cartridge if it is empty.

Do not exceed the recommended dose.

Tests and follow up:

During the course of treatment with this medicine, blood and urine tests should be carried out.

If you have accidentally taken a higher dose, you may experience low blood sugar levels. Check your blood sugar level.
If you are experiencing mild hypoglycemia, eat sugar or drink a sweet beverage. Afterwards, eat a fruit, a biscuit or a sandwich, in accordance with the doctor's instructions. You should rest after a mild hypoglycemic event.
If you have taken an overdose or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or hospital emergency room and bring the package of the medicine with you.

If your condition worsens, breathing becomes shallow and skin turns pale, inform your doctor immediately. In cases of severe hypoglycemia, a glucagon injection can be used. After the injection, you should eat sugar or glucose.
If you do not respond to the glucagon injection, you should be admitted to the hospital.

If you have forgotten to inject Humalog Mix 50, you may experience high blood sugar levels.

If hypoglycemia or hyperglycemia are left untreated, you may experience: headaches, nausea, vomiting, dehydration, loss of consciousness and even death.

If you are ill, you may need to adjust your insulin dosage. Even if you are not eating as usual, you still require insulin! Test your blood and urine and inform the doctor accordingly.

Even if there is an improvement in your health condition, do not stop treatment with this medicine without consulting your doctor.
Do not take medicines in the dark! Check the label and dose each time you take your medicine. Wear glasses if you need them.

If you have further questions regarding the use of this medicine, consult a doctor or pharmacist.

4. SIDE EFFECTS:

As with any medicine, using **Humalog Mix 50** may cause side effects in some users. Do not be alarmed while reading the list of side effects, you may not experience any of them.

Hypoglycemia is the most common side effect that patients treated with insulin may experience. Severe hypoglycemia may lead to loss of consciousness and in extreme cases, even death.

Hypoglycemia may occur as a result of a combination of insulin dosage and other factors such as the patient's nutrition and physical activity.
The first symptoms of low blood sugar levels appear quickly and include: tiredness, nervousness or tremor, headache, rapid heartbeat, nausea and cold sweat.

Oedema - swelling of the arms, ankles, fluid retention, particularly at the beginning of treatment with insulin or during a change in treatment.

Side effects and drug interactions in children and infants:
Parents should report to the doctor about any side effect or additional medicine given to the child!

Common side effects:
Local allergy: redness, swelling, itching at the injection site. This side effect usually clears up within several days or weeks, following the period of adaptation to the medicine.

Uncommon side effects:
Lipodystrophy (thickening of the skin around the injection area) – continue your treatment and refer to a doctor immediately!

Rare side effects:
Systemic allergy: rash over the whole body, shortness of breath, wheezing, drop in blood pressure, fast heartbeat or sweating. Severe cases of a generalised allergy can be life-threatening. Notify the doctor immediately!

If any of these side effects gets worse, or if you suffer from a side effect not mentioned in this leaflet, consult the doctor.

Side effects may be reported to the Ministry of Health by using the on-line form in the following link:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic%40moh.health.gov.il

5. HOW TO STORE THIS MEDICINE?

- Before opening, store refrigerated at a temperature of 2^{O}C-8^{O}C**. Do not freeze**.
- During use, do not store in a refrigerator, but in a place as cool as possible (below 30^{O}C).
- Do not expose to direct sunlight or excessive heat. The insulin can be used for up to 28 days from first opening.
- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.
- In case of any doubt, consult the pharmacist who dispensed this medicine to you.
- Avoid poisoning! This medicine, and all other medicines, must be stored in a closed place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not store different medications in the same package.
- Do not throw the medication into the sewer or household waste bin. Ask your pharmacist how to dispose of medications which you no longer need – this will help protect the environment.

6. ADDITIONAL INFORMATION

In addition to the active ingredients, Humalog Mix 50 also contains:
Dibasic Sodium Phosphate, Glycerol, Liquefied Phenol, Metacresol, Protamine Sulphate, Zinc Oxide, Hydrochloric Acid Solution 10%, Sodium Hydroxide Solution 10%, water for injection.

What the medicine looks like and contents of the package:
Humalog Mix 50 is a white sterile suspension. Each cartridge contains 300 units (3 ml). Every package contains 5 cartridges.

Registration holder: Eli Lilly Israel Ltd., P.O.B. 2160, Herzliya Pituach 46120

Manufacturer: Eli Lilly & Company Ltd., Indianapolis, Indiana, USA

Manufacturing site: Eli Lilly Italia S.p.A, Sesto Fiorentino, Italy
or
Lilly France S.A.S., Fegersheim, France

Drug registration number at the national medicines registry of the Ministry of Health:
Humalog Mix 50: 115-35-29723

This leaflet was reviewed and approved by the Ministry of Health in April 2017.

I HUMICT FS 06