

**Patient Leaflet in Accordance with the Pharmacists' Regulations**  
**(Preparations) - 1986**

This medicine is to be supplied by a physician's prescription only

**Humulin R - Regular**

Solution  
10 ml vial

**Active ingredient and its quantity:**

Each vial contains:  
Human insulin (rDNA origin)  
100 U/ml

**Humulin N - NPH**

Suspension  
10 ml vial

**Active ingredient and its quantity:**

Each vial contains:  
Isophane human insulin (rDNA origin)  
100 U/ml

**Humulin 70/30**

Suspension  
10 ml vial

**Active ingredient and its quantity:**

Each vial contains:  
70% Isophane human insulin and 30% human insulin (rDNA origin)  
100 U/ml

**Humulin R - Regular**

Solution  
5 X 3 ml cartridge

**Active ingredient and its quantity:**

Each cartridge contains:  
Human insulin (rDNA origin)  
100 U/ml

**Humulin N - NPH**

Suspension  
5 X 3 ml cartridge

**Active ingredient and its quantity:**

Each cartridge contains:  
Isophane human insulin (rDNA origin)  
100 U/ml

**Humulin 70/30**

Suspension  
5 X 3 ml cartridge

**Active ingredient and its quantity:**

Each cartridge contains:  
70% Isophane human insulin and 30% human insulin (rDNA origin)  
100 U/ml

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

All preparations are manufactured by means of genetic engineering technology using *E. COLI*.

**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, 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?**

To treat patients who suffer from diabetes and need insulin in order to maintain balanced blood sugar levels.

**Therapeutic group:** Insulins and insulin analogs from a human source.

Insulin is a hormone secreted by the pancreas, a gland situated near the stomach. This hormone is needed by the body for utilization of glucose from a food source. Diabetes occurs when the pancreas does not provide enough insulin to meet the body's needs. To balance the diabetes, the doctor has prescribed insulin injections for you.

Refer to your doctor so he/she can explain to you the operating mechanism of the different types of insulin and their range of action.

## **2. BEFORE USING THIS MEDICINE:**

**Do not use this medicine if:**

- You have a known sensitivity to one of its ingredients (please see section 6 "*Additional information*").
- Do not use in case of hypoglycemia (low blood sugar levels).

**Special warnings regarding the use of this medicine:**

Do not inject insulin directly into the vein!

- A change in the type of insulin usually requires dosage adjustment. Therefore, any change should be made under the supervision of the attending doctor.
- If your blood sugar levels are well controlled by your current insulin therapy, you may not identify the warning symptoms when your blood sugar levels are too low. Warning signs are listed further on in this leaflet. You must carefully plan when you should eat your meals and at what frequency and intensity to exercise. You must meticulously test your blood sugar levels.
- Several patients have reported that after switching to use of human insulin, the early warning symptoms for hypoglycemia were less obvious or different than

with insulin of animal origin. If you often experience episodes of hypoglycemia or have difficulty recognizing the symptoms, please discuss this with your doctor.

**Prior to treatment with Humulin, tell the doctor if:**

- You have been ill recently?
- You currently have or had in the past problems with your kidneys or liver?
- You exercise more than usual?
- You drink alcohol since the amount of insulin you need may change.
- You are planning to go abroad. The time difference between countries may mean that you have to have your injections and meals at different times from when you are used to.
- You suffer or have suffered in the past from impaired function of the thyroid gland.
- You are experiencing/have experienced signs that indicate heart failure such as: unusual shortness of breath, rapid weight gain or localised swelling (oedema). 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 were treated with insulin in combination with preparations containing pioglitazone (an oral medicine for treating diabetes).

**Drug Interactions:**

**If you are taking or have recently taken other medicines, including nonprescription medications and nutritional supplements, inform your doctor or pharmacist.**

The body's insulin requirement may change upon concomitant administration of medicines such as:

- Steroids
- Thyroid hormone
- Oral medicines for treatment of diabetes
- Salicylates (for example: acetyl salicylic acid - aspirin)
- Growth hormone
- Octreotide, lanreotide
- Beta<sub>2</sub> stimulants (for example: ritodrine, salbutamol, terbutaline)
- Beta blockers (for blood pressure or the heart)

- Thiazides (diuretics) and certain antidepressants (MAOIs – monoamine oxidase inhibitors)
- Danazol
- ACE inhibitors (administered for treatment of hypertension and the heart), for example: captopril and enalapril
- Angiotensin II receptor blockers

**Use of this medicine and food:**

Consult your doctor.

**Use of this medicine and alcohol consumption:**

Insulin requirement may change during concomitant use of alcohol. Dosage adjustment may be needed.

**Pregnancy and breastfeeding:**

Consult your doctor or pharmacist prior to using the medicine.

Insulin requirements usually decrease during the first trimester 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:**

Your ability to concentrate and react may be impaired as a result of hypoglycemia (low blood sugar levels). Please remember this in situations where you or others may be in danger (for example when driving a car or operating machinery). Consult a nurse or doctor who specializes in diabetes treatment about your capability to drive in the following cases:

- Frequent episodes of hypoglycemia
- Reduced or absence of warning signs of hypoglycemia

**3. HOW TO USE THIS MEDICINE?**

- **Always check the name of the medicine and the insulin type indicated on the package and label of the product dispensed to you at the pharmacy. Ensure that you received the Humulin that your doctor has prescribed to you.**

- Always use according to the doctor's instructions. The doctor has told you which type of insulin you must use, at what amount, when and how often to inject. In order to prevent the possibility of transmission of diseases, the injector pen and needle must be used exclusively by you, even if you have changed the needle in the reusable pen.
- These instructions are intended only for you. Follow them exactly and visit your diabetes clinic regularly.
- You may be required to take a larger or smaller amount of insulin if you change the type of insulin (for example from animal insulin to human). The change in dosage may be only for the first injection or it may be a gradual change over several weeks or months.
- **Inject Humulin under the skin. It is absolutely prohibited to inject Humulin into a vein.**

The amount of insulin for injection is measured in units. It is important to recognize the unit marks on the syringe, since the volume of insulin that is injected depends on the strength and is actually the number of units per ml. Use only with an appropriate syringe; using an inappropriate syringe may cause an error in dosage.

#### **Preparing cartridges or vials of Humulin R:**

Humulin R is already dissolved in water and so does not need to be mixed. You must use it **only** if it looks like water. It must be clear, colorless and free of solid particles. Check every time before you inject yourself.

#### **Preparing cartridges or vials of Humulin N and Humulin 70/30:**

Before injection, roll the vial or cartridge in your hands a few times and invert it 180° about 10 times until milky or uniformly cloudy insulin is obtained. Repeat the above procedure until the content is mixed. **Do not** shake vigorously as it may cause frothing which may interfere with the correct measurement of the dose. Examine the vial or cartridge frequently. Do not use them if clumps of material are present or if solid white particles stick to the bottom or sides of the cartridge, giving it a frosted appearance. Check each time before you inject yourself.

#### **Use of cartridges:**

- Wash your hands. Disinfect the rubber stopper of the cartridge.

- You must only use Humulin cartridges in Lilly company pens. Please make sure that Humulin or Lilly cartridges are mentioned in the leaflet accompanying your pen. The 3 ml cartridges only fit the 3 ml pens.
- Follow the instructions that appear in the leaflet of the pen. Insert the cartridge into the pen.
- Set the dose to 1 or 2 units. Then, hold the pen with the needle pointing up and tap the sides of the pen so that any bubbles float to the top part of the pen. Press the injection mechanism, while the pen is still pointing up. Repeat this action until a drop of Humulin appears at the tip of the needle. A few small air bubbles may remain in the pen. These bubbles are harmless, but if the air bubble is too big, the injection dose may be less accurate.
- Before the injection, clean your skin according to the instructions you received.
- Inject under the skin, as you were taught. **Do not** inject directly into a vein. After the injection, leave the needle in the skin for 5 seconds to make sure that the whole dose has been received. Do not rub the area you have just injected. Make sure you inject at least 1 cm away from the previous injection area. You should inject in different areas by rotating, as you have been taught.

#### After injecting with a pen:

- Right after completing the injection, unscrew the needle from the pen using the outer needle cap. This action will keep the insulin sterile, prevent leakage, entering of air back into the pen and needle clogging. **Do not share use of the needle or pen.** Put the cap of the pen back on.

#### Using the pen for additional injections

- Leave the cartridge in the pen. Before every injection, dial 1 or 2 units and press the injection mechanism while the pen is pointing up and a drop of Humulin appears at the tip of the needle. You can see how much Humulin remains by looking at the gauge on the side of the cartridge. The distance between each mark on the gauge is about 20 units. If there is not enough insulin for your dose, change the cartridge.

#### Use of vials:

- First wash your hands.

- Before the injection, clean your skin according to the instructions you received.
- When using the vial, clean the rubber stopper of the vial, but do not remove the cap.
- Use a clean and sterile syringe and needle in order to penetrate the rubber stopper and draw the amount of Humulin you need. Your doctor or clinic will instruct you how to do so. **Do not share your needle or syringe with others.**
- Inject under the skin, as you were taught. **Do not** inject directly into a vein. After the injection leave the needle in the skin for 5 seconds to make sure that the whole dose has been received. Do not rub the area you have just injected. Make sure you inject at least 1 cm away from the previous injection area. You should inject in different areas by rotating, as you were taught.

If according to the doctor's instructions you need to use long-acting insulin and short-acting insulin concomitantly, they can be mixed in the same syringe. You must always draw the short-acting insulin (Humulin R) and afterwards the long-acting insulin. Inject the liquid right after mixing. You must repeat this action every time. Do not mix insulin from different companies in the same syringe or with insulin of animal origin. You need to inject the insulin as the diabetes specialist nurse or doctor has taught you.

Do not mix insulin in the Humulin R, N and 70/30 cartridges. When the cartridge is empty, do not reuse it.

### **Tests and follow-up:**

Blood and urine tests must be performed during treatment with this medicine.

**If you have accidentally taken a higher dosage of Humulin:** If you take a bigger amount of Humulin than you need, your blood sugar level may become low. You must check your blood sugar levels; see below under section 4a, "hypoglycemia (low blood sugar levels)".

**If you forgot to take Humulin:** If you take a smaller amount of Humulin than necessary, your blood sugar levels may increase. You must check your blood sugar levels.

**If you stop taking Humulin:** If you take less Humulin than you need, your blood sugar levels may become too high. Do not change your insulin unless your doctor instructs you to do so.

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

Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.

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

#### **4. SIDE EFFECTS**

As with any medicine, the use of Humulin may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

**Using human insulin may cause hypoglycemia (low blood sugar level). Additional information on hypoglycemia can be found further in the leaflet under the section "common problems of diabetes".**

##### **Side effects that occur frequently:**

Local sensitivity (allergy) – some people develop redness, swelling or itching around the insulin injection area. This side effect usually clears up within several days or weeks. Notify the doctor if you develop a local allergy.

##### **Side effects that occur rarely:**

- Thickening or pitting of the skin (lipodystrophy): If you notice your skin thickening or pitting at the injection site, change your injection site and report it to a doctor.
- Oedema (swelling in arms, ankles; fluid retention) has been reported, particularly at the beginning of treatment with insulin or during a change in dosage in order to improve control of blood sugar levels.

##### **Side effects that occur very rarely:**

Systemic allergy. Symptoms:

- Drop in blood pressure
- Breathing difficulties
- Fast heartbeat
- Rash all over the body
- Wheezing while breathing
- Sweating

Refer to a medical staff member immediately if you think you have an allergic reaction to insulin during treatment with Humulin.

**Common problems of diabetes:**

a. **Hypoglycemia** (low blood sugar levels) is a condition in which there is not enough sugar in the blood. This condition may be due to the following reasons:

- You injected too much Humulin or other insulin
- You missed a meal or delayed it or due to a change in your diet
- Exercise or strenuous work just before or after a meal
- You have an infection or illness (especially diarrhea or vomiting)
- A change in your need for insulin, or
- Worsening of kidney or liver problems

Drinking alcohol and taking certain medicines may affect your blood sugar levels.

The first symptoms of low blood sugar levels usually appear quickly and include the following signs:

- tiredness
- nervousness or shakiness
- headache
- rapid heartbeat
- nausea
- cold sweat

Avoid driving or performing other activities which may put you and other people at risk until you learn to recognize the symptoms indicating hypoglycemia. **Do not use Humulin if you think that you are at the start of hypoglycemia (low blood sugar levels).**

Your relatives and colleagues should know you have diabetes and how to help you in case of hypoglycemia. They must know that an unconscious person should not be given food or beverage for fear of suffocation.

If your blood sugar level is low, eat a glucose tablet, sugar or drink a beverage that contains sugar. Afterwards eat a fruit, biscuit or a sandwich, according to the doctor's recommendation, and have some rest. These actions will usually help you overcome moderate hypoglycemia or a minor insulin overdose. If your condition worsens, your breathing becomes shallow and your skin gets pale, report this to your doctor immediately. A glucagon injection can treat severe cases of hypoglycemia. You must eat sugar after a glucagon injection. If you do not respond to glucagon, you will have to go to the hospital. Ask your doctor to explain to you about glucagon.

#### **b. Hyperglycemia and diabetic ketoacidosis**

Hyperglycemia (high blood sugar levels) is a condition in which there is not enough insulin in your body. This condition may be caused due to the following reasons:

- You did not take your Humulin or other insulin
- You injected less insulin than prescribed by your attending doctor.
- You ate much more than your diet allows or
- Fever, infection or emotional stress

Hyperglycemia can lead to diabetic ketoacidosis. The first signs appear slowly over many hours or days and include the following:

- feeling sleepy
- flushed face
- thirst
- loss of appetite
- fruity smell on the breath
- nausea or vomiting.

Heavy breathing and/or a rapid heartbeat are severe symptoms. **Refer to receive medical attention immediately.**

Hypoglycemia (low blood sugar levels) and hyperglycemia (high blood sugar levels) that are not treated can be very serious and cause headaches, nausea, vomiting, dehydration, unconsciousness, coma or even death.

**Three simple steps** will prevent states of hypoglycemia and hyperglycemia:

- Always keep spare syringes and vials of Humulin
- Always carry with you something to show that you are diabetic
- Always carry sugar with you

**c. Illness:**

The amount of insulin you need may change if you are ill, especially if you suffer from nausea or vomiting. **You still need insulin, even if you are not eating as usual.** Test your urine or blood, follow the guidelines regarding conduct during an illness, and report to your specialist nurse or doctor.

If one of the side effects gets worse, or you suffer from a side effect not mentioned in the leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects due to Drug Treatment" that can be found on the Home Page of the Ministry of Health's website ([www.health.gov.il](http://www.health.gov.il)), which refers to the online form for reporting side effects, or via the following link:  
<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

## **5. HOW TO STORE THIS MEDICINE?**

Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach of children and/or infants to avoid poisoning.

Before opening, store refrigerated at 2°C-8°C. **Do not freeze.** Do not use insulin that has been frozen. Do not expose to sunlight or excessive heat. When in use, do not store the cartridge in the refrigerator.

During use, the product should be kept below 30°C.

May be used for up to 28 days from the first use.

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

Humulin R is a sterile, clear, colorless, aqueous solution. Do not use the medicine if it is not clear or has particles in it. Use it only if it looks like water.

Humulin N and Humulin 70/30 are white sterile suspensions for injection. Do not use them if there are clumps or white particles stuck to the bottom or walls of the vessel, giving a frosted appearance.

Check what the product looks like every time you inject.

During use, do not store the pen with the needle attached.

Store the product in its original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

In case of any doubt, consult the pharmacist who supplied the medicine to you.

Do not store different medicines in the same package.

## **6. ADDITIONAL INFORMATION**

In addition to the active ingredient, Humulin also contains:

**Humulin R:** metacresol, glycerol, water for injection.

**Humulin N, Humulin 70/30:** protamine sulphate, metacresol, phenol, glycerol, dibasic sodium phosphate (heptahydrate), zinc oxide and water for injection.

Sodium hydroxide or hydrochloric acid may have been used during manufacture to adjust the acidity.

### **What the medicine looks like and contents of the pack:**

- Humulin R – Sterile, clear and colorless aqueous solution, in a 10 ml vial or 5 X 3.0 ml cartridges
  - Humulin N – White sterile suspension for injection in a 10 ml vial or 5 X 3.0 ml cartridges
  - Humulin 70/30 - White sterile suspension for injection in a 10 ml vial or 5 X 3.0 ml cartridges
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- **Registration holder:** Eli Lilly Israel Ltd., 4 HaSheizaf St., P.O.Box 4246, Ra'anana 4366411
  - **Manufacturer:**  
Cartridges - Eli Lilly & Company Ltd., Indianapolis, Indiana, USA  
Vials – Lilly S.A., Alcobendas, Madrid, Spain.
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- **This leaflet was reviewed and approved by the Ministry of Health on April 2017.**

**Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:**

Humulin R - 054-43-22714-00/22

Humulin N - 054-12-22715-00/22

Humulin 70/30 - 057-95-26959-00/11

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