

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 units/ml

Humulin N - NPH

Suspension
10 ml vial

Active ingredient and its quantity:

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

Humulin R - Regular

Solution
5 X 3 ml cartridge

Active ingredient and its quantity:

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

Humulin N - NPH

Suspension
5 X 3 ml cartridge

Active ingredient and its quantity:

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

Inactive ingredients and allergens: see section 2 "important information about some of the ingredients of this medicine" and section 6 "Additional information".

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 analogue for injection.

Humulin preparations contain insulin of human origin, which is used to treat diabetes. You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood.

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

Do not change your insulin unless your doctor tells you to. Be very careful if you do change your insulin.

Each type of insulin has a different color on the pack and the label so that you can easily tell the difference.

2. BEFORE USING THIS MEDICINE:

Do not use this medicine if:

- you are allergic to the active ingredient or any of the other ingredients this medicine contains (please see section 6 "Additional information").
- **you think hypoglycemia (low blood sugar) is starting.** Further in this leaflet it tells you how to deal with mild hypoglycemia (see section 4 "Side effects").

Special warnings regarding the use of this medicine:

Talk to your doctor, pharmacist or nurse before using this medicine.

- If your blood sugar levels are well controlled by your current insulin therapy, you may not feel the warning symptoms when your blood sugar is falling too low. Warning signs are listed later in this leaflet. You must think carefully about when to have your meals, how often to exercise and how much to do. You must also keep a close watch on your blood sugar levels by testing your blood glucose often.
- A few people who have had hypoglycaemia (low blood sugar) after switching from animal insulin to human insulin have reported that the early warning symptoms were less obvious or different. If you often have hypoglycemia or have difficulty recognizing the symptoms, please discuss this with your doctor.

Prior to treatment with Humulin, tell the doctor if:

- you have recently become ill?
- you have trouble with your kidneys or liver?
- you are exercising more than usual?
- The amount of insulin you need may also change if you drink alcohol.
- 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 to when you are at home.
- Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible, if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (edema).

Skin changes at the injection site

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work well if you inject into a lumpy area (See section "How to use this medicine"). Contact your doctor if you are currently injecting into a lumpy area before you start injecting into a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Interactions/drug Interactions:

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

Your insulin needs may change if you are taking any of the following:

- steroids
- thyroid hormone replacement therapy
- oral hypoglycemics (antidiabetic medication)
- acetylsalicylic acid (aspirin)

- growth hormone
- octreotide, lanreotide
- beta₂ stimulants (for example: ritodrine, salbutamol or terbutaline)
- beta blockers
- thiazides (diuretics) or some antidepressants (MAOIs – monoamine oxidase inhibitors)
- danazol
- some angiotensin converting (ACE) inhibitors (for example captopril, enalapril) or 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, breastfeeding and fertility:

The amount of insulin you need usually falls during the first trimester and increases during the second and third trimesters.

If you are breastfeeding, you may need to alter your insulin intake or diet. Consult your doctor.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to get pregnant, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines:

Your ability to concentrate and react may be impaired if you have hypoglycemia (low blood sugar). Please remember this in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your diabetes specialist nurse or doctor about the advisability of driving if you have:

- frequent episodes of hypoglycemia
- reduced or absent warning signs of hypoglycemia

Important information about some of the ingredients of this medicine:

This medicine contains less than 1 mmol sodium (23 mg) per dose unit, that is to say essentially 'sodium-free'

3. HOW TO USE THIS MEDICINE?

Always check the pack and the vial label for the name and type of the insulin when you get it from your pharmacy. Make sure you get the Humulin that your doctor has prescribed to you.

- Always use this medicine according to the doctor's instructions. You should check with your doctor or pharmacist if you are not sure about the dosage and manner of treatment with this medicine. In order to prevent transmission of diseases, the cartridge must be used exclusively by you, even if you have replaced the needle in the reusable pen.

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work well if you inject into a lumpy area (See section "Side effects")

Dosage

- Your doctor has told you which insulin to use, how much, when and how often to inject. These instructions are only for you. Follow them exactly and visit your diabetes clinic regularly.

- If you change your insulin type (for example from animal to human), you may have to take more or less than before. This might just be 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.**

Preparing cartridges or vials of Humulin R:

Humulin R is already dissolved in water, so you do not need to mix it. You must use it **only** if it looks like water. It must be clear, have no color and no solid particles in it. Check each time before you inject yourself.

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

Before the injection, the vial or cartridge should be rotated in the palms of the hands a few times and inverted 180° about 10 times until it appears uniformly cloudy or milky. Repeat the above procedure until contents are mixed. The cartridges contain a small glass bead to assist mixing. **Do not** shake vigorously as this may cause frothing which may interfere with the correct measurement of the dose. The vial or cartridges should be examined frequently and should not be used 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:

- First wash your hands. Disinfect the rubber membrane of the cartridge.
- **You must only use Humulin cartridges in Lilly insulin pens to ensure you get the correct dose.** Follow the instructions that appear in the leaflet of the pen. Put the cartridge into the pen.
- You will set the dose to 1 or 2 units. Then hold the pen with the needle pointing up and tap the side of the pen so that any bubbles float to the top. With the pen still pointing up, press the injection mechanism. Do this until a drop of Humulin comes out of the needle. There may still be some small air bubbles left in the pen. These bubbles are harmless, but if the air bubble is too big, it may make the dose of your injection less accurate.
- Before you make an injection, clean your skin as you have been instructed.
- Inject under the skin, as you were taught. **Do not** inject directly into a vein. After your injection, leave the needle in the skin for 5 seconds to make sure you have taken the whole dose. Do not rub the area you have just injected. Make sure you inject at least 1 cm from where you last injected. You should 'rotate' the places you inject, as you have been taught.
- Do not inject Humulin R into a vein. Inject Humulin R as your diabetes specialist nurse or doctor has taught you. Only your doctor can inject Humulin R into a vein. He or she will only do this under special circumstances such as surgery or if you are ill and your glucose levels are too high.

After injecting with a pen:

- Immediately after completing the injection, unscrew the needle from the pen using the outer needle cap. This will keep the insulin sterile, prevent leaking, stop air going back into the pen and the needle clogging up. **Do not share your needle or your pen.** Replace the cap on your pen.

Using the pen for further injections

- Leave the cartridge in the pen. Before every injection, dial 1 or 2 units and press the injection mechanism with the pen pointing up until a drop of Humulin comes out of the needle. You can see how much Humulin is left 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 you make an injection, clean your skin as you have been instructed. Clean the rubber stopper on the vial, but do not remove the stopper.
- Use a clean, sterile syringe and needle to pierce the rubber stopper and draw in the amount of Humulin you want. Your doctor or clinic will tell you how to do this. **Do not share your needle and syringe with others.**
- Inject under the skin, as you were taught. **Do not** inject directly into a vein. After your injection, leave the needle in the skin for 5 seconds to make sure you have taken the whole dose. Do not rub the area you have just injected. Make sure you inject at least 1 cm from where you last injected. You should 'rotate' the places you inject, as you have been taught.

If according to the doctor's instructions you need to use long-acting insulin and short-acting insulin concomitantly, they can be mixed together in the same syringe. You must always draw the short-acting insulin (Humulin R) and afterwards the long-acting insulin. Inject the liquid as soon as you have mixed it. Do the same thing every time.

Do not mix insulins produced by other manufacturers or animal insulins in the same syringe. You need to inject the insulin as the diabetes specialist nurse or doctor has taught you.

Do not mix any other insulin in the Humulin R, N and 70/30 cartridges. Once the cartridge is empty, do not use it again.

If you have accidentally taken a higher dosage of Humulin: If you use more Humulin than you should, your blood sugar may become low. Check your blood sugar (see section 4 "Side effects").

If you forgot to take Humulin: If you use less Humulin than you should, your blood sugar levels may increase. Check your blood sugar. Do not inject a double dose to make up for a forgotten dose.

If you stop taking Humulin: If you use less Humulin than you should, your blood sugar levels may become too high. Do not change your insulin unless your doctor tells you to.

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 on the use of this medicine, consult your 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.

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

Possible side effects

Systemic allergy is very rare (affects less than 1 person in 10,000). The symptoms are as follows:

- fall in blood pressure
- difficulty in breathing
- fast heartbeat
- rash over the whole body
- wheezing
- sweating

If you think you are having this sort of insulin allergy with Humulin, tell your doctor at once.

Local allergy is common (affects less than 1 person in 10). Some people get redness, swelling or itching around the area of the insulin injection. This usually clears up in anything from a few days to a few weeks. Tell your doctor if you develop a local allergy.

Skin changes at the injection site:

If you inject insulin too often at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes

Oedema (swelling in arms, ankles; fluid retention) has been reported, particularly at the start of insulin therapy or during a change in dosage in order to improve control of your blood glucose.

Common problems of diabetes:

a. Hypoglycemia

hypoglycemia (low blood sugar) means there is not enough sugar in the blood. This can be caused if you:

- take too much Humulin or other insulin
- miss or delay meals or change your diet
- exercise or work too hard just before or after a meal
- have an infection or illness (especially diarrhea or vomiting)
- have a change in your need for insulin, or
- have trouble with your kidneys or liver which gets worse

Alcohol and some medicines can affect your blood sugar levels.

The first symptoms of low blood sugar usually come on quickly and include the following:

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

Until you become confident in recognizing your warning symptoms, avoid situations such as driving a car, in which you or others would be put at risk by hypoglycemia. **Do not use Humulin if you think hypoglycemia (low blood sugar) is starting.**

If your blood sugar is low, eat glucose tablets, sugar or drink a sugary drink. Then eat fruit, biscuits, or a sandwich, as your doctor has advised you and have some rest. This will often get you over mild hypoglycemia or a minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat quite severe hypoglycemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to go to the hospital. Ask your doctor to tell you about glucagon.

b. Hyperglycemia and diabetic ketoacidosis

Hyperglycemia (too much sugar in the blood) means that your body does not have enough insulin. Hyperglycemia can be brought about by:

- not taking your Humulin or other insulin
- taking less insulin than your doctor tells you to
- eating a lot more than your diet allows or
- fever, infection or emotional stress

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

- feeling sleepy
- flushed face
- thirst
- no appetite
- fruity smell on the breath
- nausea or vomiting.

Severe symptoms are heavy breathing and a rapid pulse. **Get medical help immediately.**

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

Three simple steps to avoid hypoglycemia or hyperglycemia are:

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

c. Illness:

If you are ill, especially if you suffer from nausea or vomiting, the amount of insulin you need may change. **Even when you are not eating normally, you still need insulin.** Test your urine or blood, follow the guidelines regarding conduct during an illness, and tell 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.

Reporting side effects

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), which refers to the online form for reporting side effects, or via the following link: <https://sideeffects.health.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 and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Before opening, store refrigerated at 2°C-8°C. **Do not freeze.** 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 clumps of material are present or if solid white particles stick to the bottom or wall of the cartridge, 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: glycerol, metacresol, water for injection.

Humulin N, Humulin 70/30: glycerol, dibasic sodium phosphate (heptahydrate), metacresol, phenol, protamine sulphate, 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 5 X 3.0 ml cartridges

- **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.

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

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