1. NAME OF THE MEDICINAL PRODUCT

Humulin R (Soluble Insulin Injection) Solution for Injection	(100 IU/ml, 10 ml vials; 100 IU/ml 3.0 ml cartridges for use in a reusable pen
Humulin N (Isophane Insulin Injection) Suspension for Injection	(100 IU/ml 10 ml vials; 100 IU/ml, 3.0 ml cartridges for use in a reusable pen).
Humulin 70/30 (Biphasic Isophane Insulin Injection) (30% soluble insulin/70% isophane insulin) Suspension for Injection	(100 IU/ml, 3.0 ml cartridges for use in a reusable pen)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 IU human Insulin (produced in *E. coli* by recombinant DNA technology).

One vial contains 10 ml equivalent to 1000 IU.

or

One cartridge contains 3 ml equivalent to 300 IU.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Humulin R:
A solution for injection in a vial or in a cartridge.
Humulin R (Soluble) is a sterile, clear, colorless, aqueous solution of human insulin.

Humulin N:
A suspension for injection in a vial or in a cartridge.
Humulin N (Isophane) is a sterile suspension of a white, crystalline precipitate of isophane human insulin in an isotonic phosphate buffer.

Humulin 70/30:
A suspension for injection in a cartridge.
Humulin 70/30 (Mixture) is a sterile suspension of human insulin in the proportion of 30% soluble insulin to 70% isophane insulin.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis.

4.2 Posology and method of administration

Posology
The dosage should be determined by the physician, according to the requirement of the patient.

Pediatric population

No data are available

Method of administration
Cartridges:
Humulin Soluble in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe or intravenous injection is necessary, a vial should be used.

Humulin Isophane in cartridges is only suitable for subcutaneous injections from a reusable pen. This formulation should not be administered intravenously.

Humulin Mixtures in cartridges is only suitable for subcutaneous injections from a reusable pen. This formulation should not be administered intravenously.

Vials:
Humulin Soluble should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. It may also be administered intravenously.
Humulin Isophane in vials should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. This formulation should not be administered intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Care should be taken when injecting any Humulin insulin preparations to ensure that a blood vessel has not been entered. After any insulin injection, the injection site should not be massaged. Patients must be educated to use proper injection techniques.

Humulin Isophane may be administered in combination with Humulin Soluble. (See Section 6.6 Instructions for use and handling - for Mixing of Insulins).

Humulin Mixture formulation is a ready-made defined mixture of Humulin Soluble and Humulin Isophane insulin designed to avoid the need for the patient to mix insulin preparations. A patient's treatment regimen should be based on their individual metabolic requirements.

Each pack contains a patient information leaflet with instructions on how to inject insulin.

4.3 Contraindications

Hypoglycemia.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, unless used as part of a desensitization programme.

Under no circumstances should any Humulin formulation other than Humulin Soluble be given intravenously.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (soluble, isophane, mixture), species (animal, human, human insulin analogue), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Some patients taking human insulin may require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

A few patients who experienced hypoglycemic reactions after transfer to human insulin have reported that the early warning symptoms were less pronounced or different from those experienced with their previous animal insulin. Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycemia and should be advised accordingly. Other conditions which may make the early warning symptoms of hypoglycemia different or less pronounced include long duration of diabetes, diabetic nerve disease, or medications such as beta blockers. Uncorrected hypoglycemic and hyperglycemic reactions can cause loss of consciousness, coma or death.

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.

Treatment with human insulin may cause formation of antibodies, but titres of antibodies are lower than those to purified animal insulin.

Insulin requirements may change significantly in diseases of the adrenal, pituitary or thyroid glands and in the presence of renal or hepatic impairment.

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of insulin dosage may also be necessary if patients change their level of physical activity or change their usual diet.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Combination of human insulin with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind, if treatment with the combination of pioglitazone and human insulin is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and edema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

Instructions for use and handling

To prevent the possible transmission of disease, each cartridge must be used by one patient only, even if the needle on the delivery device is changed.

Pens to be used with Humulin cartridges
The cartridges should only be used in conjunction with a Lilly reusable insulin pen and should not be used with any other reusable pen as the dosing accuracy has not been established with other pens.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially "sodium-free".

4.5 Interactions with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism and therefore the physician should be consulted when using other medications in addition to human insulin (see section 4.4). The physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

Insulin requirements may be increased by substances with hyperglycemic activity, such as, glucocorticoids, thyroid hormones, growth hormone, danazol, beta$_2$-sympatomimetics (such as ritodrine, salbutamol, terbutaline), thiazides.

Insulin requirements may be reduced in the presence of substances with hypoglycemic activity, such as oral hypoglycemics (OHA), salicylates (for example, acetylsalicylic acid), certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme (ACE) inhibitors (captopril, enalapril), angiotensin II receptor blockers, non-selective beta-blocking agents and alcohol.

Somatostatin analogues (octreotide, lanreotide) may both decrease or increase insulin dose requirements.

4.6 Fertility, Pregnancy and lactation

It is essential to maintain good control of the insulin treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy.

Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycemia is presented, since hypoglycemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise.

Local allergy in patients is common (≥1/100 to < 1/10). Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, local reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy, which is very rare (< 1/10,000) but potentially more serious, is a generalized allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. In the rare event of a severe allergy to Humulin, treatment is required immediately. A change of insulin or desensitization may be required.

Lipodystrophy at the injection site is uncommon (≥1/1,000 to < 1/100).

Skin and subcutaneous tissue disorders: Frequency “unknown”: Cutaneous amyloidosis

Skin and subcutaneous tissue disorders:
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (See section 4.4).

Cases of edema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Insulin has no specific overdose definitions, because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycemia may occur as a result of an excess of insulin relative to food intake and energy expenditure.

Hypoglycemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycemic episodes will respond to oral administration of glucose or sugar products.

Correction of moderately severe hypoglycemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously, if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered.

Sustained carbohydrate intake and observation may be necessary because hypoglycemia may occur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting and intermediate acting.
Humulin Soluble ATC code A10A B01
Humulin R is a rapidly acting insulin preparation.

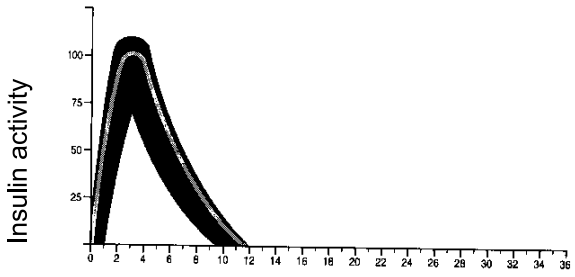
Humulin Isophane ATC code A10A C01
Humulin N is an intermediate acting insulin preparation.

Humulin Mixtures ATC code A10A D01
Humulin 70/30 is a premixed suspension of rapid and intermediate acting insulin.

The prime activity of insulin is the regulation of glucose metabolism.
In addition insulin has several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

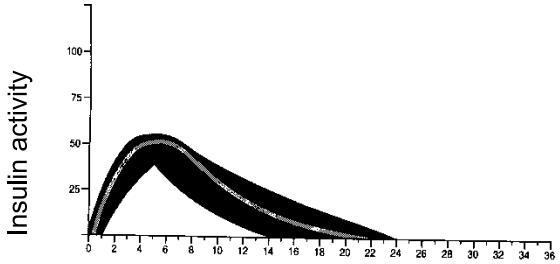
The typical activity profile (glucose utilization curve) following subcutaneous injection is illustrated below by the heavy line. Variations that a patient may experience in timing and/or intensity of insulin activity are illustrated by the shaded area. Individual variability will depend on factors such as size of dose, site of injection temperature and physical activity of the patient.

Humulin Soluble

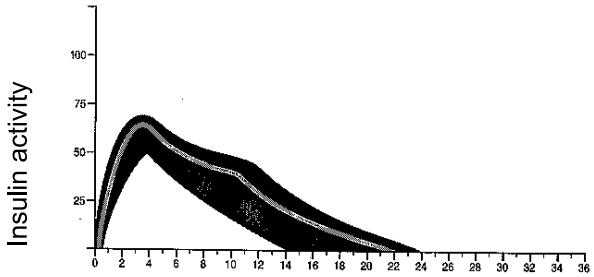


Time (hours)

Humulin Isophane



Humulin 70/30



5.2 Pharmacokinetic properties

The pharmacokinetics of insulin do not reflect the metabolic action of that hormone. Therefore, it is more appropriate to examine glucose utilization curves (as discussed above) when considering the activity of insulin.

5.3 Preclinical safety data

Humulin is human insulin produced by recombinant technology. No serious events have been reported in subchronic toxicology studies. Human insulin was not mutagenic in a series of *in vitro* and *in vivo* genetic toxicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For Humulin Soluble preparations:
glycerol
m-cresol
water for injections

The following may be used to adjust pH; hydrochloric acid and/or sodium hydroxide

For Humulin Isophane and Mixture preparations:
glycerol
dibasic sodium phosphate $7H_2O$
m-Cresol

phenol

protamine sulphate
zinc oxide
water for injections

The following may be used to adjust pH; hydrochloric acid and/or sodium hydroxide

6.2 Incompatibilities

Humulin preparations should not be mixed with insulins produced by other manufacturers or with animal insulin preparations.

6.3 Shelf life

Unused vial/cartridge
Humulin R cartridges: 2 years
Humulin R, N, 70/30 vials, Humulin N, 70/30 cartridges: 3 years.

After first use
28 days.

6.4 Special precautions for storage

Unused vials and Cartridges
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not expose to excessive heat or direct sunlight.

After first use
Vials: Once in use the vials may be used for up to 28 days. Do not use beyond this period. Store below 30°C. Do not freeze. Do not expose to excessive heat or direct sunlight.

Cartridges: Once in use the cartridges may be used for up to 28 days. Do not use beyond this period. Store below 30°C. Do not refrigerate. The pen with the inserted cartridge should not be stored with the needle attached.

6.5 Nature and content of container

Humulin vials
10 ml of solution or suspension in a vial (type I glass) with a stopper (rubber) sealed with a seal (aluminum) combined with a flip top (plastic).
Pack size 1.

Humulin cartridges
3 ml solution or suspension in a cartridge (type I glass) with a plunger head at the bottom (rubber) and disc seal at the top (rubber).
Pack size of 5.

6.6 Special precautions for disposal and other handling

Do not reuse needles. Dispose of the needle in a responsible manner. Needles and pens must not be shared. Vials and Cartridges can be used until empty, then properly discard. Any

unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling
Vial
A solution or suspension for injection in a 10 ml vial to be used in conjunction with an appropriate syringe (100 IU/ml markings).

Cartridge
To prevent the possible transmission of disease, each cartridge must be used by one patient only, even if the needle on the delivery device is changed.

The cartridges should only be used in conjunction with a Lilly reusable insulin pen and should not be used with any other reusable pen as the dosing accuracy has not been established with other pens.

a) Preparing a dose

Vials or cartridges containing Humulin Soluble formulation do not require resuspension and should only be used if it is clear, colorless, with no solid particles visible and if it is of water-like appearance.

Vials containing Humulin Isophane and Mixtures formulations should be rotated several times in the palms of the hands before use to completely resuspend the insulin until it appears uniformly cloudy or milky. If not, repeat the above procedure until contents are mixed.

Cartridges containing Humulin Isophane and Mixture formulations should be rolled in the palms of the hands ten times and inverted 180^0 ten times immediately before use to resuspend the insulin until it appears uniform cloudy or milky. If not, repeat the above procedure until contents are mixed. 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 cartridges and vials 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 wall of the cartridge or vial, giving a frosted appearance.

The cartridges are not designed to allow any other insulin to be mixed in the cartridge. Cartridges are not designed to be refilled.

Mixing of insulins: The shorter acting insulin should be drawn into the syringe first, to prevent contamination of the vial by the longer acting preparation. It is advisable to inject directly after mixing. However, if a delay is necessary, a consistent routine must be followed.

Alternatively, a separate syringe or, separate cartridges of Humulin Soluble and Isophane, can be used for administration of the correct amount of each formulation**.**

Vials
Prepare your syringe prior to injection, as directed by your doctor or diabetes specialist nurse. Use an insulin syringe marked for the strength of insulin being administered.

Cartridges

The manufacturer's instructions with each individual pen must be followed for loading the cartridge, attaching the needle and administering the insulin injection.

b) Injecting a dose

Inject the correct dose of insulin, as directed by your doctor or diabetes specialist nurse.
Use of the injection sites should be rotated so that the same is not used more than approximately once a month.

Each pack contains a patient information leaflet with instructions on how to inject insulin.

7. MANUFACTURER:

Lilly S.A., Alcobendas, Madrid, Spain (Vials)
Or
Eli Lilly & Company Ltd., Indianapolis, Indiana, USA (Cartridges)

License Holder: Eli Lilly Israel LTD, 4 HaSheizaf St., P.O.Box 4246, Ra'anana 4366411.

Registration number: 054-43-22714-00/22, 057-95-26959-00, 054-12-22715-00/22

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