1. NAME OF THE MEDICINAL PRODUCT

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

Humulin is a trade name referred to in this document.

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 excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Humulin R (Soluble) is a sterile, clear, colourless, aqueous solution of human insulin.
Humulin Soluble is a rapidly acting insulin preparation.

Humulin N (Isophane) is a sterile suspension of a white, crystalline precipitate of isophane human insulin in an isotonic phosphate buffer.
Humulin Isophane is an intermediate acting insulin preparation.

Humulin 70/30 (Mixture) is a sterile suspension of human insulin in the proportion of 30 % soluble insulin to 70 % isophane insulin.
Humulin Mixtures are both rapid and intermediate acting insulin preparations.

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

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

Paediatric population

No data are available

Method of administration
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 and Mixtures in vials and Humulin Isophane and Mixtures in cartridge presentations should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. These formulations 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.

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 / handling - for Mixing of Insulins).

Humulin Mixture formulations are ready-made defined mixtures 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

Hypoglycaemia.

Hypersensitivity to Humulin or to the formulation excipients, unless used as part of a desensitisation 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, etc.), 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 hypoglycaemic 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 hypoglycaemia and should be advised accordingly. Other conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, diabetic nerve disease, or medications such as beta blockers. Uncorrected hypoglycaemic and hyperglycaemic 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 hyperglycaemia 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.

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 oedema. 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.

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 hyperglycaemic activity, such as, glucocorticoids, thyroid hormones, growth hormone, danazol, beta$_2$-sympatomimetics (such as ritodrine, salbutamol, terbutaline) and thiazides.

Insulin requirements may be reduced in the presence of substances with hypoglycaemic activity, such as oral hypoglycaemics (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 hypoglycaemia. 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 hypoglycaemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia 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 generalised 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 generalised allergy may be life-threatening. In the rare event of a severe allergy to Humulin, treatment is required immediately. A change of insulin or desensitisation may be required.

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

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 be using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.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. Hypoglycaemia may occur as a result of an excess of insulin relative to food intake and energy expenditure.

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

Mild hypoglycaemic episodes will respond to oral administration of glucose or sugar products. Correction of moderately severe hypoglycaemia 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 hypoglycaemia may occur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group:

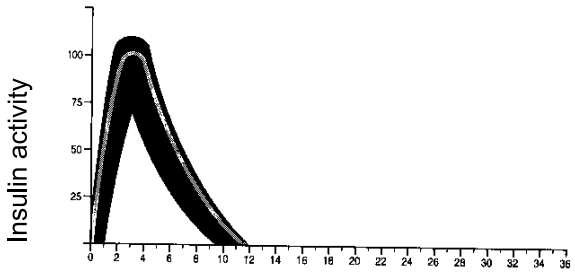
Humulin Soluble	ATC code A10A B01
Humulin Isophane	ATC code A10A C01
Humulin Mixtures	ATC code A10A D01

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.

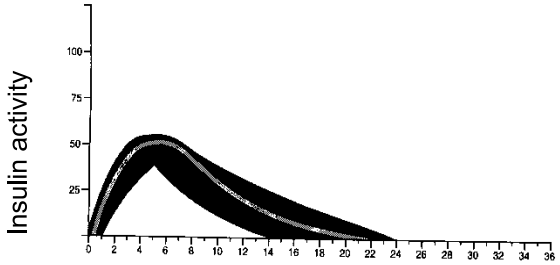
The typical activity profile (glucose utilisation curve) following subcutaneous injection is illustrated below by the heavy line. Variations that a patient may experience in timing and/or intensity of insulin activity are illustrated by the shaded area. Individual variability will depend on factors such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

Humulin Soluble



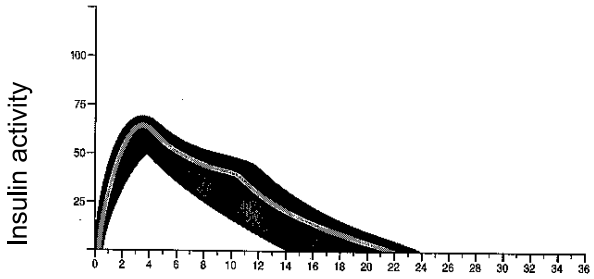
Time (hours)

Humulin Isophane



Time (hours)

Humulin 70/30



Time (hours)

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 utilisation 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:
m-cresol
glycerol
water for injections

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

For Humulin Isophane and Mixture preparations:
m-Cresol
glycerol
phenol
protamine sulphate
dibasic sodium phosphate $7H_2O$
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
Humulin R cartridges: 2 years
Humulin R, N, 70/30 vials, Humulin N, 70/30 cartridges: 3 years.

In-use
The in-use shelf life is 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.

In 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.

In use Cartridge
Once in use the cartridges may be used for up to 28 days. Do not use beyond this period. Store below 30°C. 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 (aluminium) 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 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 10ml vial to be used in conjunction with an appropriate syringe (100IU/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.

A solution or suspension for injection in a 3 ml cartridge to be used with a Lilly pen.

a) Preparing a dose

Vials or cartridges containing Humulin Soluble formulation do not require resuspension and should only be used if it is clear, colourless, 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.
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 P.O Box 2160, Herzliya Pituach 4672511.

Registration number: 054432271400/22, 057952695900/11, 054122271500/22

This leaflet format was set by MOH and its content has been reviewed and approved on April 2017.

X HUMUCTVL AF 08