SCHEDULING STATUS **S3**

PROPRIETARY NAME AND DOSAGE FORM

HUMULIN R (Solution for Injection)

HUMULIN N (Suspension for Injection)

HUMULIN 30/70 (Suspension for Injection)

COMPOSITION

HUMULIN injections contain biosynthetic human insulin (recombinant DNA origin) 100 I.U./ml and have a pH of 7,0 - 7,8. Composition details of HUMULIN R, N and 30/70 are as follows:

HUMULIN presentation	**Type of biosynthetic human insulin (rDNA)**	**Preservatives**	**Other excipients**
HUMULIN R (Solution for Injection)	Regular	m-cresol 0,25 % m/v	Glycerol, Hydrochloric acid (solution, 10 %), and/or Sodium hydroxide (solution, 10 %), Water for injection.
HUMULIN N (Suspension for Injection)	Isophane	m-cresol 0,16 % m/v phenol 0,06 % m/v	Dibasic sodium phosphate (heptahydrate crystals), Glycerol, Protamine sulphate (purified), Hydrochloric acid (solution, 10 %) and/or Sodium hydroxide (solution, 10 %), Water for injection, Zinc oxide.
HUMULIN 30/70 (Suspension for Injection)	30 % Regular 70 % Isophane	m-cresol 0,16 % m/v Phenol 0,06 % m/v	Dibasic sodium phosphate (crystals), Glycerin, Protamine sulphate (purified), Hydrochloric acid (solution, 10 %) and/or Sodium hydroxide (solution, 10 %), Water for injection, Zinc oxide.

PHARMACOLOGICAL CLASSIFICATION

A 21.1 Insulin Preparations

PHARMACOLOGICAL ACTION

HUMULIN replaces the insufficiency of insulin secreted by the β-cells of the pancreas.

HUMULIN R is a short-acting preparation.

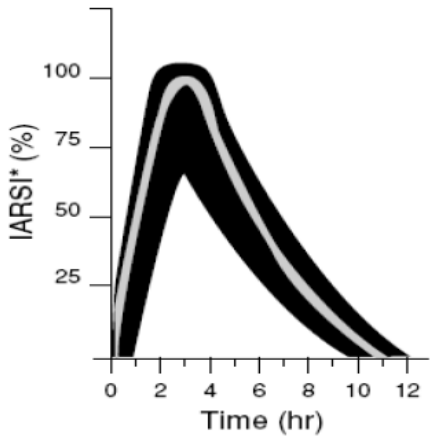
HUMULIN N is an intermediate-acting preparation.

HUMULIN 30/70 is a mixture of a short-acting and an intermediate-acting preparation.

Typical activity profiles (glucose utilisation curves) following subcutaneous injection of the abovementioned HUMULIN presentations are illustrated below by the light-coloured lines within the shaded areas. Variations that a patient may experience in timing and/or intensity of insulin activity are illustrated by the shaded areas.

It should be noted that the time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. The duration of action of the HUMULIN range of products is dependent on dose, site of injection, blood supply, temperature, and physical activity.

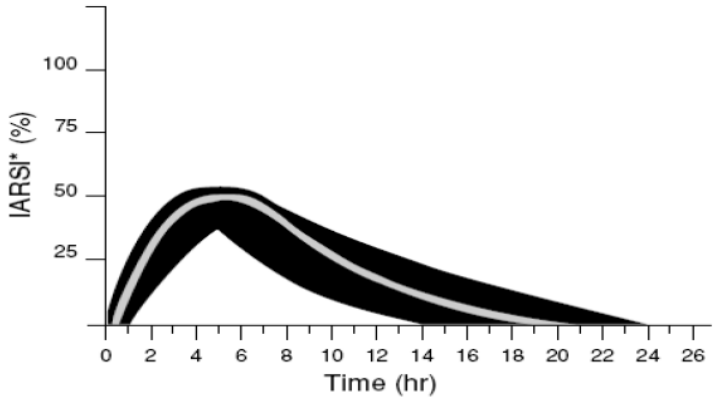
HUMULIN R



*** Insulin Activity Relative to Soluble Insulin**

Soluble insulin injection takes effect rapidly and has a relatively short duration of activity.

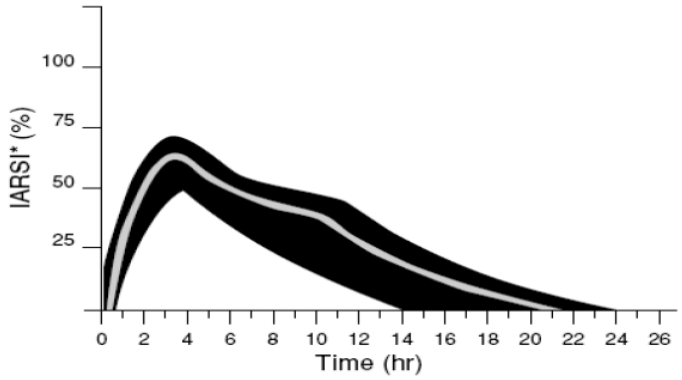
HUMULIN N



*** Insulin Activity Relative to Soluble Insulin**

Isophane insulin human suspension is an intermediate-acting insulin with a slower onset of action and a longer duration of activity.

HUMULIN 30/70



Biphasic isophane insulin injection are intermediate-acting insulins combined with the more rapid onset of action of soluble insulin injection.

INDICATIONS

HUMULIN R, HUMULIN N and HUMULIN 30/70 are indicated in the treatment of diabetes mellitus.

CONTRAINDICATIONS

- Hypoglycaemia.
- Allergy to any of the ingredients.

Under no circumstances should HUMULIN N or 30/70 be given intravenously.

WARNINGS and SPECIAL PRECAUTIONS

Insulin changes:

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, type (e.g insulin human injection, human insulin isophane suspension), species (beef, pork, beef-pork, human, human insulin analog), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Some patients transferring from insulins of animal source to HUMULIN may require a change in dosage from that used with animal source insulins. Patients who are very tightly controlled and bordering on hypoglycaemia may require a reduced dosage. The dosage reduction may occur immediately after transfer or be a gradual process lasting for several weeks or months. There is a risk of hypoglycaemia if insulin requirement is decreased and both the healthcare professional and the patient should be aware of this possibility. Patients who experienced hypoglycaemic reactions after being transferred to HUMULIN have reported that the early warning symptoms of hypoglycaemia were less pronounced than they were with animal-source insulin. The risk can be considered minimal if the daily dosage is less than 40 I.U. Insulin-resistant patients receiving more than 100 I.U. daily should be referred to hospital for transfer.

In some patients, to improve glycaemic control, it may be necessary to split the HUMULIN 30/70 dose. This may be done as follows: Administer one-half to two-thirds of the daily dose of HUMULIN in the morning, with the remainder of the dose before supper or later in the evening (i.e. sometime after supper).

Insulin requirements may be increased during illness or emotional disturbances, or by concurrent administration of medicines with hyperglycaemic activity, e.g. oral contraceptives, corticosteroids or thyroid replacement therapy. (See “Interactions”).

Insulin requirements may be reduced in the presence of renal or hepatic impairment, or by the concurrent administration of medicines with hypoglycaemic activity, e.g. monoamine oxidase and ß adrenergic blockers. (See “Interactions”).

ß blocker therapy may mask the symptoms of insulin induced-hypoglycaemia and impair the body’s response to hypoglycaemia (See “Interactions”).

Adjustment of HUMULIN R, HUMULIN N or HUMULIN 30/70 dosage may also be necessary if patients change physical activity or change their usual diet.

Thiazolidinediones (TZDs) used in combination with HUMULIN R, HUMULIN N or HUMULIN 30/70: TZDs in combination with insulin, are associated with an increased risk of oedema and heart failure; especially in patients with underlying cardiac disease.

HUMULIN R solutions should be clear and colourless. Do not use the insulin if it appears cloudy, thickened, slightly coloured or if solid particles are visible.

HUMULIN N and 30/70 suspensions should look uniformly cloudy or milky. If the insulin substance (the cloudy material) settles at the bottom of the cartridge in the pen injector, it must be rotated or carefully shaken before injection so that the contents are uniformly mixed. Do not use if a deposit of solid particles remains on the bottom or wall of the cartridge, giving it a frosted appearance, or if there are clumps floating in the insulin after the pen injector has been rotated or carefully shaken. Also, an insulin suspension should not be used if it is clear and remains clear after it is rotated or shaken.

After the dose is prepared, the injection should be made promptly to avoid clogging of the needle.

INTERACTIONS

Insulin requirements may be increased by concurrent administration of medicines with hyperglycaemic activity, e.g. oral contraceptives, corticosteroids or thyroid replacement therapy.

Insulin requirements may be decreased in the presence of, agents such as oral antidiabetic agents, salicylates, sulpha antibiotics, and certain antidepressants (monoamine oxidase inhibitors), β-adrenergic blockers, angiotensin converting enzyme inhibitors and angiotensin II

receptor blockers. β-blocker therapy may mask the symptoms of insulin-induced hypoglycaemia and impair the body's response to hypoglycaemia.

PREGNANCY AND LACTATION

Pregnancy

The blood glucose of the mother should be as normal as possible from the time of conception until delivery. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. Diabetic patients who contemplate pregnancy should seek medical advice and should be monitored medically with particular regard to adjustment of insulin dosage throughout their pregnancy.

Lactation

Diabetic patients who are nursing may require adjustments in insulin and/or in their diet.

DOSAGE AND DIRECTIONS FOR USE

The dosage should be determined by the healthcare professional, according to the requirements of the patient.

HUMULIN R may be administered alone or in combination with HUMULIN N.

HUMULIN N is usually administered as a twice daily regimen. HUMULIN N may be given as a single dose before breakfast, but some patients may require concurrent administration of short acting insulin.

HUMULIN 30/70 is a ready-made mixture designed to avoid the need for mixing of insulins by patients. It should normally be administered twice daily, usually with two-thirds of the daily requirement being given in the morning and the remainder in the evening. In general, for any one injection the dose should not exceed 50 I.U.

HUMULIN R may be administered by subcutaneous, intramuscular or intravenous injection.

HUMULIN N and 30/70 should be administered by subcutaneous or intramuscular injection only.

Under no circumstances should HUMULIN N or 30/70 be given intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks or abdomen. Use of injection sites should be rotated so that the same exact site is not used more than once a month. Patients must be educated to use proper injection techniques.

Care should be taken to ensure that a blood vessel has not been entered. The injection site should not be massaged.

Mixing of insulin

Vials: HUMULIN R from vials may be administered in combination with HUMULIN N from vials as required, and usually as a twice daily regimen.

When mixing insulins the short acting insulin should be drawn into the syringe first to prevent contamination of the vial by the longer-acting preparation (i.e. HUMULIN N). It is advisable to inject immediately after mixing. Such mixtures should not be administered intravenously.

The effects of mixing with insulin of animal source have not been studied and this practice is not recommended.

Cartridges: HUMULIN cartridges are not designed to allow any other insulin to be mixed in the cartridges and disposable pen injectors.

Before starting therapy, patients should read the “User Manual” that accompanies the delivery device, to ensure the correct use thereof. Before using Lilly cartridges in any other manufacturer’s insulin delivery device, the user must check the device manufacturer’s literature to verify that Lilly cartridges are compatible with that device.

SIDE EFFECTS

Lipodystrophy, insulin resistance, hypoglycaemia and hypersensitivity reactions are among the side effects associated with the use of HUMULIN.

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.

Local allergy at the site of injection in patients is common (≥1/100 to < 1/10). Redness, swelling, and itching can occur at the site of 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.

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

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

Post-Marketing Data

Cases of general oedema have been reported with insulin therapy, mostly after initiating HUMULIN therapy or after changing the dose (See “Warnings and Special Precautions”).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage causes hypoglycaemia with accompanying symptoms that include lethargy, confusion, palpitations, sweating and vomiting.

Treatment: Mild hypoglycaemic episodes will respond to oral administration of glucose or sugar and rest. If the patient is comatose, intravenous administration of dextrose injection, with or without glucagon, is required.

IDENTIFICATION

HUMULIN R (Solution for Injection)

The vials, cartridges and disposable pens contain a sterile, clear, colourless solution for injection.

Vials (HI 0210): a 10 ml size flint-glass vial sealed with a rubber stopper and an aluminium seal.

Cartridges (HI 0219): a 3,0 ml size flint-glass cartridge sealed with a rubber plunger head at the bottom of the cartridge and a rubber disc and outer aluminium seal at the top of the cartridge. The cartridges should be used in reusable pen injectors.

Disposable pens (HP 8720 & HP 8804) are supplied as prefilled, disposable pen injectors containing 3,0 ml size cartridges.

HUMULIN N (Suspension for Injection) vials, cartridges and disposable pens, and **HUMULIN 30/70 (Suspension for Injection)** cartridges and disposable pens contain a sterile, white suspension.

HUMULIN N (Suspension for Injection)

Vials (HI 0310): a 10 ml size flint-glass vial sealed with a rubber stopper and an aluminium seal.

Cartridges (HI 0319): a 3,0 ml size flint-glass cartridge sealed with a rubber plunger head at the bottom of the cartridge and a rubber disc and outer aluminium seal at the top of the cartridge.

The cartridges should be used in reusable pen injectors. Each suspension-containing cartridge contains a small flint glass bead to assist in mixing.

Disposable pens (HP 8730 & HP 8805): Prefilled, disposable pen injectors containing 3,0 ml size cartridges.

HUMULIN 30/70 (Suspension for Injection)

Vials (HI 0710): a 10 ml size flint-glass vial sealed with a rubber stopper and an aluminium seal.

Cartridges (HI 0719): a 3,0 ml size flint-glass cartridge sealed with a rubber plunger head at the bottom of the cartridge and a rubber disc and outer aluminium seal at the top of the cartridge. The cartridges should be used in reusable pen injectors. Each suspension-containing cartridge contains a small flint glass bead to assist in mixing.

Disposable pens (HP 8770 & HP 8803): Prefilled, disposable pen injectors containing 3,0 ml size cartridges.

PRESENTATION

HUMULIN R (Solution for Injection), HUMULIN N (Suspension for Injection) and HUMULIN 30/70 (Suspension for Injection), 10 ml vials are packed as singles.

HUMULIN R (Solution for Injection), HUMULIN N (Suspension for Injection), and HUMULIN 30/70 (Suspension for Injection), 3,0 ml cartridges and disposable pen injectors containing 3,0 ml cartridges are packed in cartons containing 5.

STORAGE INSTRUCTIONS

Store in a refrigerator at (2-8 °C). Do not freeze or expose to excessive heat or sunlight.

Vials, cartridges or pens in use

Vials: If refrigeration is not possible, the vial in use can be stored at or below 25 °C for 28 days. Do not expose to excessive heat or sunlight.

Cartridges and disposable pens: The cartridge of insulin currently in use should not be refrigerated but should be kept cool (at or below 25 °C) and away from heat and sunlight. Unrefrigerated cartridges and disposable pens containing 3,0 ml cartridges should be discarded

after 28 days, even if they still contain product. Do not use after the expiration date stamped on the label.

Keep out of reach of children.

REGISTRATION NUMBERS

R/21.1/2 for HUMULIN R

R/21.1/1 for HUMULIN N

W/21.1/397 for HUMULIN 30/70

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

Date of registration:

Humulin R: 21 December 1983

Humulin N: 21 December 1983

Humulin 30/70: 17 January 1990

Date of most recently revised approved package insert: 02 June 2017