AUSTRALIAN PRODUCT INFORMATION

HUMULIN® R (REGULAR – NEUTRAL – SOLUBLE HUMAN INSULIN (RBE) INJECTION)

HUMULIN® NPH (ISOPHANE – NPH – HUMAN INSULIN (RBE) SUSPENSION)

HUMULIN® 30/70 (30% REGULAR HUMAN INSULIN (RBE) INJECTION AND 70% ISOPHANE HUMAN INSULIN (RBE) SUSPENSION)

1. NAME OF THE MEDICINE

Insulin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

There are three different presentations in the HUMULIN range:

HUMULIN R (regular-neutral-soluble) – neutral human insulin of recombinant DNA origin.

HUMULIN NPH (isophane) – isophane human insulin of recombinant DNA origin.

HUMULIN 30/70 – a mixture consisting of 30% Regular (neutral human insulin of recombinant DNA origin) and 70% NPH (isophane human insulin of recombinant DNA origin.

For the full list of excipients, see section **6.1 List of excipients**

HUMULIN is found to be chemically, physically, biologically and immunologically equivalent to pancreatic human insulin, which differs slightly from porcine or bovine insulin in amino acid composition.

3. PHARMACEUTICAL FORM

HUMULIN R: A sterile, clear colourless, aqueous solution of neutral human insulin (rbe) adjusted to pH 6.6 to 8.0.

HUMULIN NPH: A sterile suspension of white, crystalline precipitate of isophane human insulin (rbe) in an isotonic phosphate buffer adjusted to pH 6.9 to 7.5

HUMULIN 30/70: A sterile mixture of 30% Regular and 70% NPH human insulin (rbe) adjusted to pH 6.9 to 7.5

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

HUMULIN is indicated for the treatment of insulin-dependent diabetic patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage should be determined by the physician, according to the requirements of the patient. During changes to a patient's insulin regimen, increase the frequency of glucose monitoring. Subcutaneous administration, preferably by the patient, 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 frequently than once a month, in order to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localised cutaneous amyloidosis.

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

Vials

HUMULIN R is a short acting insulin which may be administered by subcutaneous, intramuscular or intravenous injection. HUMULIN NPH and HUMULIN 30/70 should only be administered by subcutaneous or intramuscular injection.

HUMULIN R may be administered in combination with HUMULIN NPH, depending on individual metabolic requirements of the patients as determined by the physician. A mixture of HUMULIN R and NPH is usually administered as a twice-daily regimen.

HUMULIN NPH may be given as a single daily dose before breakfast, usually the most satisfactory injection time.

The effects of mixing these products with insulins of animal source have not been studied, and this practice is not recommended.

HUMULIN NPH and HUMULIN 30/70 - The vial should be rotated in the palms of hands before use in order to resuspend.

Mixing of Insulins: The shorter-acting (HUMULIN R) insulin should be drawn into the syringe first to prevent contamination of the vial by the longer-acting (HUMULIN NPH) preparation. It is advisable to inject immediately after mixing.

Cartridges

HUMULIN R, NPH and 30/70 are supplied as 3.0 mL Cartridges (100 Units/mL) for use in HumaPen. HUMULIN 3.0mL Cartridges are not designed to allow any other insulin to be mixed in the cartridge.

HUMULIN NPH and 30/70 Cartridges should be rotated in the palms of hands before use in order to resuspend.

HUMULIN R, NPH and 30/70 Cartridges should be used only for subcutaneous administration.

Instructions for Use/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.

4.3 CONTRAINDICATIONS

HUMULIN R, HUMULIN NPH and HUMULIN 30/70 are contraindicated in hypoglycaemia.

Human insulin is contraindicated in patients with hypersensitivity to human insulin or any of its excipients (unless used as part of a desensitisation program).

Vials

HUMULIN NPH and 30/70 vials should not be administered by the intravenous route.

Cartridges

HUMULIN R, NPH and 30/70 cartridges should not be administered by the intramuscular or intravenous route.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Any change in an insulin or human insulin analogue regimen should be made cautiously and only under medical supervision with increased frequency of glucose monitoring. Changes in strength, brand (manufacturer), type (regular, NPH, lente, 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.

Prompt recognition and appropriate management of the complications of insulin therapy are essential for the safe and effective control of diabetes mellitus.

The number and size of daily doses and the time of administration, as well as diet and exercise, are problems that require direct and continuous medical supervision.

Under special circumstances (such as increased physical effort, insufficient food, etc.) the daily dose of insulin administered to the patient may represent an overdose. Patients should always carry some glucose with them. For symptoms, see section **4.9 Overdose**.

Insulin requirements may be increased during illness or emotional disturbances. In the event of infectious diseases such as colds, boils, etc., the insulin requirements increase, in which case the patient must consult his physician in time to prevent the development of dangerous complications.

Patients whose glycaemic control is greatly improved, e.g. by flexible 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 a long duration of diabetes, diabetic nerve disease or medications such as beta blockers. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma or death.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and phaeochromocytoma complicate the control of diabetes.

Thiazolidinediones (TZDs) in combination with insulin are associated with an increased risk of oedema and heart failure; especially in patients with underlying cardiac disease.

Visual disturbances in uncontrolled diabetes due to refractive changes are reversed during the early phase of effective management. However, since alteration in osmotic equilibrium between the lens and ocular fluids may not stabilise for a few weeks after initiating therapy, it is wise to postpone prescribing new corrective lenses for 3 to 6 weeks.

Patients who are travelling overseas (or to destinations with substantially different time zones) should contact their doctor/ pharmacist/ diabetes educator for information.

Patients who receive insulin, which contains protamine, have an increased risk of severe reactions simulating anaphylaxis when protamine is used to reverse systemic heparinisation after cardiac catheterisation.

Injection technique

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 glycaemic 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 hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Use in hepatic impairment

Insulin requirements may be reduced in the presence of hepatic impairment.

Use in renal impairment

Insulin requirements may be reduced in the presence of renal impairment.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The physician should be consulted when using other medication in addition to human insulin (see section **4.4 Special warnings and precautions for use**).

Insulin requirements can increase, decrease, or remain unchanged in patients receiving diuretics. Insulin requirements may be increased if the patient is receiving concurrent administration of drugs with hyperglycaemic activity, e.g., oral contraceptives, corticosteroids, thyroid replacement therapy, growth hormone, glucagon, adrenaline, isoniazid, phenothiazines or beta-2 stimulants (such as salbutamol, terbutaline). The hypoglycaemic action of insulin may also be antagonised by phenytoin.

Insulin requirements may be reduced if the patient is receiving concurrent administration of drugs with hypoglycaemic activity, e.g., anabolic steroids, MAO inhibitors, guanethidine, propranolol (masking effect), oral hypoglycaemics, salicylates (for example, aspirin), sulphonamides, antidepressants, angiotensin converting enzyme inhibitors (captopril and enalapril), angiotensin II receptor blockers, other beta blockers, octreotide and alcohol.

Transferring from Other Insulins

A small number of patients transferring from insulins of animal source to insulins of recombinant DNA origin may require a reduced dosage especially if they are tightly controlled and bordering on hypoglycaemia. The dosage reduction may occur with the first dose or over a period of several weeks. There is a risk of hypoglycaemia if the insulin requirement is decreased, and both the physician and the patient should be aware of this possibility. The risk can be considered to be minimal if the daily dose is less than 40 units. Insulin-resistant patients receiving more than 100 units daily should be hospitalised for transferring from other insulins.

Pharmacological studies suggest that these human insulins may have a quicker onset of action and a shorter duration of effect than their beef or pork counterparts in patients already stabilised on a mixture of neutral and isophane insulin. Some adjustment of the proportions may be needed after transfer to human insulin.

A few patients who experienced hypoglycaemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Carcinogenicity or fertility studies with HUMULIN have not been conducted.

Use in pregnancy

It is essential to maintain good control of the insulin-dependent diabetic patient throughout pregnancy. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of the patient is required throughout pregnancy.

During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Use in lactation

Patients with diabetes who are lactating may require adjustments in insulin dose, diet or both.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The patient's ability to concentrate and to 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 while 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The use of preparations of HUMULIN should minimise the incidence of side effects which have been associated with insulins of animal source. However, there have been rare reports of

patients with hypersensitivity reactions to human insulins who have tolerated insulins of animal origin.

The following reactions have been reported:

Hypoglycaemia

Hypoglycaemia is the most frequent undesirable effect of insulin therapy. Severe hypoglycaemia may lead to loss of consciousness and, in extreme cases, death.

Local Allergy

including pruritus, rash, erythema, induration. Local allergy in patients occasionally occurs as redness, swelling and itching at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic Allergy

including anaphylactoid reaction, urticaria. Systemic allergy, less common 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.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy or lipohypertrophy. A change in injection technique may help alleviate the problem.

Insulin resistance

Spontaneous data

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy (see section **4.4 Special warnings and precautions for use**).

Lipodystrophy and localised cutaneous amyloidosis at the injection site have occurred. Hyperglycaemia has been reported with repeated insulin injections into areas of lipodystrophy or localised cutaneous amyloidosis; hypoglycaemia has been reported with a sudden change to an unaffected injection site (see section **4.4 Special warnings and precautions for use**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Hypoglycaemia can occur if the patient takes too much insulin, misses meals, exercises or works too hard just before a meal, or has an infection or becomes ill (especially with diarrhoea or vomiting) or if the body need for insulin changes for other reasons.

Symptoms include listlessness, confusion, palpitations, sweating, vomiting, hunger, faintness and dizziness. Patients also may experience headache, drowsiness, fatigue, anxiety, blurred vision, diplopia, or numbness of the lips, nose or fingers.

Symptoms are likely to appear when the blood sugar concentration falls below 2.22 mmol/L but may occur with a sudden drop in blood glucose even when the value remains above 2.22 mmol/L.

The clinical manifestations of hypoglycaemia can be masked by the concomitant administration of propranolol or other beta adrenergic blockers.

Treatment

Mild hypoglycaemic episodes will respond to oral administration of glucose or sugar and rest.

Correction of moderately severe hypoglycaemia can be accomplished by the intramuscular or subcutaneous administration of glucagon, 1 unit every 20 minutes for 2 or 3 doses, 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, intravenous administration of 10 to 20 g of dextrose in sterile solution is required.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The administration of suitable doses of insulin to patients with diabetes mellitus, along with controlled diet and exercise, temporarily restores their ability to metabolise carbohydrates, fats and proteins; to store glycogen in the liver; and to convert glucose to fat. When given in suitable doses at regular intervals to a patient with diabetes mellitus, the blood glucose is maintained within a reasonable range, the urine remains relatively free of glucose and ketone bodies, and diabetic acidosis and coma are prevented.

Studies indicate that immunogenicity problems with biosynthetic human insulin produced by recombinant DNA technology are no more likely to occur than with insulin that is derived from animal origin. Biosynthetic human insulin is devoid of all protein contaminants of pancreatic origin normally present even in trace amounts in all insulins of pancreatic origin.

The rigid purification procedures used in the manufacture of biosynthetic human insulin remove E. coli proteins detectable by presently available methods. Even if E. coli proteins are present in trace amounts, clinical studies indicate the absence of any detectable E. coli protein antibodies ascribable to the use of biosynthetic human insulin. Biosynthetic human insulin did not elicit an antigenic response when administered to E. coli polypeptide-sensitised rats and guinea pigs.

Although human insulins appear to produce less antigenicity than beef/pork insulins, they are not free of antigenicity.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

HUMULIN R is a short-acting preparation. Onset of action occurs at approximately 30 minutes, with a duration of activity of 6 to 8 hours and peak activity at 2 to 4 hours.

HUMULIN NPH is an intermediate-acting preparation. Onset of action occurs at approximately 1 hour, with a duration of activity of 16 to 18 hours and peak activity at 4 to 10 hours.

HUMULIN 30/70 is an intermediate-acting insulin with a more rapid onset of action than NPH alone. HUMULIN 30/70 has a duration of activity of 16 to 18 hours and a peak activity at 2 to 12 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was no evidence of genotoxicity in a range of assays for gene mutations, chromosomal effects and DNA damage.

Carcinogenicity

Carcinogenicity or fertility studies with HUMULIN have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

HUMULIN R (regular-neutral-soluble) – This product consists of zinc-insulin crystals dissolved in a clear fluid. It also contains glycerol, hydrochloric acid, metacresol, sodium hydroxide and water for injection.

HUMULIN NPH (isophane) – HUMULIN NPH is a crystalline suspension of human insulin with protamine sulfate and zinc oxide. It also contains dibasic sodium phosphate heptahydrate, glycerol, hydrochloric acid, metacresol, phenol, sodium hydroxide and water for injection.

HUMULIN 30/70 – It also contains dibasic sodium phosphate heptahydrate, glycerol, hydrochloric acid, metacresol, phenol, protamine sulfate, sodium hydroxide, water for injection and zinc oxide.

6.2 INCOMPATIBILITIES

HUMULIN 3.0mL Cartridges are not designed to allow any other insulin to be mixed in the cartridge.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

For information on the in-use shelf life, see section **6.4 Special precautions for storage.**

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Vials

Preparations of HUMULIN (unopened or new vials) should be stored in a refrigerator between 2°and 8°C. They should not be frozen or exposed to excessive heat or sunlight. Under these conditions, potency should be maintained for 24 months from the date of manufacture for HUMULIN R, HUMULIN NPH and HUMULIN 30/70.

Vials of HUMULIN preparations while in use may be kept at room temperature for up to 28 days without loss of potency. Insulin opened and stored at room temperature which has not been used for a month or more should be discarded. Insulin which is used only occasionally is best kept refrigerated.

Cartridges

Cartridges of HUMULIN preparations should be stored in a refrigerator between 2°C and 8°C. HUMULIN Cartridges have a 2 year shelf-life when stored between 2°C and 8°C. Do not allow the insulin to freeze.

When inserted in HumaPen or when carried as a spare, HUMULIN R, NPH, and 30/70 Cartridges need not be refrigerated but should be kept cool (below 30°C) and away from excessive heat and direct sunlight. Unrefrigerated HUMULIN R, NPH and 30/70 Cartridges should be discarded after 21 days even if the cartridges still contain insulin.

6.5 NATURE AND CONTENTS OF CONTAINER

HUMULIN is supplied in vials, cartridges and a disposable HUMULIN Pen device containing 3.0 mL HUMULIN cartridges. For information on HUMULIN Pens, please refer to the separate HUMULIN Pen product information document.

HUMULIN R is supplied in 100 units/mL in 10 mL size rubber- stoppered vials (No. HI-210) and 100 units/mL in 3.0mL size cartridges (No. HI-219) in packs of 5. The 3.0 mL size cartridges are to be used in the HumaPen.

HUMULIN NPH is supplied in 100 units/mL in 10 mL size rubber-stoppered vials (No. HI-310) and in 3.0mL size cartridges (No. HI-319) in packs of 5. The 3.0 mL size cartridges are to be used in the HumaPen.

HUMULIN 30/70 is supplied in 100 units/mL in 10 mL size rubber-stoppered vials (No. HI-710) and in 3.0 mL size cartridges (HI-719) in packs of 5. The 3.0 mL size cartridges are to be used in the HumaPen.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active ingredient in Humulin solutions and suspensions is human insulin (recombinant DNA origin). Human insulin is a polypeptide hormone consisting of a 21 amino acid A-chain

and a 30 amino acid B-chain linked by two disulphide bonds. Its empirical formula is C257H383N65O77S6, which corresponds to a molecular weight of 5808.

CAS number

The CAS number for human insulin is 11061-68-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8. SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road, West Ryde, NSW 2114
AUSTRALIA
1800 454 559

9. DATE OF FIRST APPROVAL

5 September 1991

10. DATE OF REVISION

28 January 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2, and 4.8	Information on the relationship between injection site and localised cutaneous amyloidosis and lipodystrophy Increase frequency of glucose monitoring after changes in insulin regimen (4.2 only)
4.4	Section 'Injection technique' added
6.1	Additions to list of excipients for completeness