EUSPC12AUG2020

1. NAME OF THE MEDICINAL PRODUCT

Humulin N 100 IU/ml suspension for injection in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial contains 10 ml equivalent to 1000 IU of isophane insulin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A suspension for injection in a vial.

Humulin N is a sterile suspension of a white, crystalline precipitate of isophane human insulin in an isotonic phosphate buffer.

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.

Paediatric population

No data are available

Method of administration

Humulin N 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 N may be administered in combination with Humulin R. (See Instructions for use and handling for Mixing of Insulins).

4.3 Contraindications

Hypoglycaemia.

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

Under no circumstances should any Humulin formulation other than Humulin R 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 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.

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.

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.

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 hyperglycaemic 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 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).

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 oedema 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 authorisation 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 via the Drug Office, Department of Health.

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

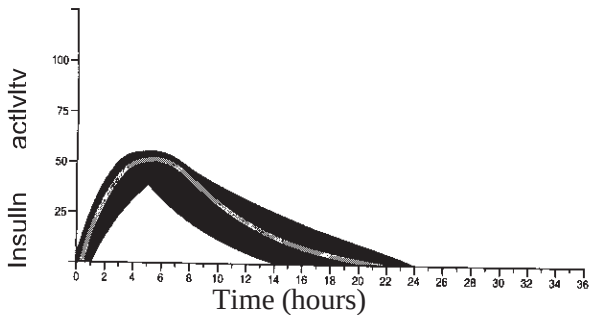
Pharmacotherapeutic group: Insulins and analogues for injection, intermediate-acting,
ATC code: A10A C01.
Humulin N is an intermediate acting insulin preparation.

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 N



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

m-cresol glycerol
phenol
protamine sulfate
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

Do not dilute or mix with any solution or with any other insulin except Humulin® R insulin.

6.3 Shelf life

Unopened vials
The shelf life is 36 months when stored at 2°C to 8°C and when protected from light.

After first use

- Store drug product in a refrigerator at 2°C to 8°C until time of use.
- Store in-use drug product (after the stopper has been punctured) refrigerated for up to 28 days.
- If refrigeration is not possible, store in-use drug product unrefrigerated at a maximum temperature of 30°C.

6.4 Special precautions for storage

- Do not freeze.
- Store unopened containers refrigerated at 2°C to 8°C until time of use.
- The drug product should be stored and used protected from freezing, from direct heat, and from direct light or sunlight.

6.5 Nature and content of container

10 ml of 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 or 2 or 5 (5 x 1). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not reuse needles. Dispose of the needle in a responsible manner. Needles must not be shared. Vials 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
A suspension for injection in a 10ml vial to be used in conjunction with an appropriate syringe (100 IU/ml markings).

a) Preparing a dose

Vials containing Humulin N formulation 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.
Do not shake vigorously as this may cause frothing, which may interfere with the correct measurement of the dose.

The 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 vial, giving a frosted appearance.

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 R and N, can be used for administration of the correct amount of each formulation**.**

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.

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.