INSULINAGYPT 70/30 (100 IU/ml) Suspension for injection in vial

30 % human Insulin Injection / 70 % Human Insulin Isophane protamine Suspension

1. Name of the medicinal product

Insulinagypt 70/30 (100 IU/ml) Suspension for Injection in Vial.

2. Qualitative and quantitative composition

Each 1 ml contains 100 IU insulin human (r DNA Origin):

30 % human Insulin Injection / 70 % Human Insulin Isophane protamine Suspension

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Suspension for subcutaneous injection in a vial.

a white suspension which on standing deposite white sediment and leaves a colorless to almost colorless supernatant liquid. The sediment is readily suspended by gentle shaking.

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

Insulinagypt 70/30 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.

Care should be taken when injecting Insulinagypt N 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.

Insulinagypt 70/30 is a ready-made defined mixture of soluble and 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 desensitisation programme.

Insulinagypt 70/30 should not be administered 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 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.

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.

Excipients

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

4.5 Interaction 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 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 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 Insulinagypt, 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 side effects

Reporting adverse reactions after authorization 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.

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*:* Insulins and analogues for injection, intermediate acting combined with fast acting. ATC code: A10A C01

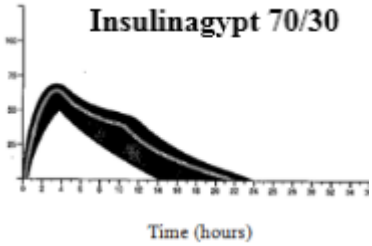
Insulinagypt 70/30 is a premixed suspension of rapid and intermediate acting insulin.

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.



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

Insulinagypt 70/30 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

- Metacresol Distilled
- Glycerol
- Phenol
- Protamine sulfate
- Dibasic Sodium Phosphate (heptahydrate)
- Zinc oxide
- Water for Injection
- Hydrochloric Acid Solution 10% used to adjust pH

6.2 Incompatibilities

Insulinagypt 70/30 should not be mixed with insulins produced by other manufacturers or with animal insulin preparations.

6.3 Shelf life

Unopened vials: 3 years.
After first use: 28 days at 30°C

6.4 Special precautions for storage

Unopened vials: Store in a refrigerator (2°C - 8°C). Do not freeze.
After first use: Store below 30°C. Do not expose to excessive heat or direct sunlight.

6.5 Nature and contents of container

Carton box contains one vial contains 4 or 10 ml insulin suspension (100 IU/ml) and an inner leaflet. The vial glass is made from type I flint glass, stoppered with rubber closure (made from off-white halo butyl formulation) and sealed with aluminum seal combined with a plastic flip flop.

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 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 10 ml vial to be used in conjunction with an appropriate syringe (100 IU/ml markings).

a) Preparing a dose

Vials containing Insulinagypt 70/30 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.

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.

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

7. Marketing authorisation holder

Medical Union Pharmaceuticals Co.

36. Dr. Mohamed Hassan El-Gamal St., 6th District- Nasr City – Cairo – A.R.E

Tel: +202 22 70 9324

Fax: +202 22 70 9315

Web: www.mupeg.com

8. Date of revision of the text

08/04/2019