

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gensulin N, 100 IU/ml, suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Gensulin N suspension contains 100 IU of isophane human insulin (*Insulinum humanum*) obtained by *E.coli* DNA recombination.

The vial contains 10 ml of suspension, corresponding to 1000 IU of isophane insulin.

Gensulin N contains human insulin only. The products are 100% consistent with the amino acid composition of the insulin produced by humans – unlike animal insulin or other insulin analogues obtained by genetic recombination whose compositions differ from human insulin to various extents.

Full list of excipients, see: 6.1.

3. PHARMACEUTICAL FORM

Gensulin N: suspension for injection in a vial.

Gensulin N is a sterile suspension of white crystalline isophane human insulin precipitate in an isotonic phosphate buffer, adjusted to the pH range of 7-7.6.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Diabetes of patients requiring insulin administration in order to maintain proper glucose metabolism. Gestational diabetes.

4.2. Posology and method of administration

Posology

Dosage is determined by the doctor on the basis of patient's insulin requirement. In type 2 diabetes the average initial dose is 0.2 IU/kg body weight.

Gensulin N should be administered by subcutaneous injection. It is not recommended, however, possible to be administered intramuscularly. These forms of insulin must not be administered intravenously. Gensulin N can be used in intensive insulin therapy to ensure basic insulin secretion. Gensulin N can be used at initiation of insulin therapy in type 2 diabetes. The most popular scheme is a once daily injection in the evening time. Subcutaneous injections should be made in the abdominal area, buttocks, thigh or upper arm. The injection site should be changed to prevent skin thickening.

Injections should be made at different sites in the same anatomic area, the same site should not be used more than once a month.

While making an injection, caution should be used to prevent needle insertion into a blood vessel. Do not massage the injection site after insulin administration. Inform your patients how to make the injection correctly.

Gensulin N can be administered together with Gensulin R (see: Drug preparation for use – Insulin mixing).

Gensulin N products can be used in combination with oral diabetes medications, e.g. metformin or glimepiride.

Method of administration

Drug preparation for use

Immediately before administering Gensulin N, roll the vial in your hands 10 times and then turn it 10 times by 180° to obtain uniformly turbid or milky suspension. If the effect is not obtained, repeat the procedure till the ingredients are mixed. Do not shake as foam formed in the container can make it difficult to properly measure the insulin dose. Check insulin appearance in vials often. Do not use the product, when lumps or white particles adhering to walls or bottom are visible or when the glass looks mat.

Each package contains the Patient Information Leaflet with an instruction on how to make an injection.

Administering Gensulin N with a syringe

Insulin should be administered with special syringes marked with insulin units. It is recommended to use syringes of the same type and from the same manufacturer. Always check whether the syringe you are using is scaled for the strength of insulin used.

a) Dose preparation

- Remove the plastic cap from the cap (do not break the cap).
- Wipe the vial stopper with alcohol. Do not take the stopper out!
- Draw into the syringe a volume of air equal to the insulin dose.
- Pierce the rubber stopper with a needle placed on the syringe and inject the air into the vial.
- Invert the vial with the syringe.

- Make sure that the needle tip is immersed in insulin suspension.
- Draw into the syringe the appropriate volume of insulin.
- Remove air bubbles from the syringe.
- Check the recommended dose again and withdraw the needle from the vial.

b) Making the injection:

- Disinfect the skin at the injection site.
- Stabilise the skin with one hand by lifting or pinching big surface to form a skin fold.
- Take the syringe with the other hand and keep it like a pencil. Pierce the needle into the skin (at 90° angle). Make sure the needle is fully inserted and well placed in subcutaneous fat and not in deeper skin layers (in very slim patients it may be necessary to place the needle not perpendicularly but at an angle).
- To inject insulin, push the plunger to the very end during less than 5 seconds.
- Keep a cotton pad with alcohol close to the needle and remove the needle from the skin. For a couple of seconds press the cotton pad with alcohol to the injection site. Do not rub the skin!
- To prevent tissue damage, change the injection site every time you administer the drug. The new injection site should be at least 1-2 cm away from the old one.

Mixing Gensulin N solution with Gensulin R suspension

Gensulin N can be used in the mixture with Gensulin R.

The decision on mixing Gensulin N with solution of Gensulin R can be made only by a doctor. While making the mixture, always introduce short-acting Gensulin R first into the syringe. Apply the above procedure to administer the drug.

4.3. Contraindications

Hypoglycaemia.

Hypersensitivity to insulin or to any of the excipients listed in section 6.1, unless it is a part of a desensitisation programme.

4.4. Special warnings and precautions for use

A change of the type or brand of insulin used requires doctor's supervision. A change of insulin strength, brand (manufacturer), type (soluble, isophane, biphasic), origin (animal, human, human insulin analogue) and/or production method (DNA recombination or animal origin) may require dose modification.

In some patients, a change from animal insulin to human insulin may require dose modification. If dose modification is required, it should be done at the administration of the first dose of the new insulin or during the first weeks or months following the change.

In some patients changing from animal insulin to human insulin, early warning symptoms of hypoglycaemia can be less distinctive or totally different from those developed during application of animal insulin. With better glycaemia control (e.g. with intensive insulin therapy), the warning symptoms of hypoglycaemia can be less distinctive or may not develop at all. Patients should be informed about the risk. Other factors changing or weakening early warning symptoms of hypoglycaemia are: long-lasting diabetes, diabetic neuropathy, some medications, e.g. β -adrenolytics. Uncontrolled hypoglycaemia or hyperglycaemia may lead to loss of consciousness, coma or death.

Inappropriate dosing or therapy discontinuation, especially in insulin-dependent diabetes, may cause hyperglycaemia and ketoacidosis – life threatening conditions.

Human insulin administration can lead to production of antibodies, however their titre is lower than in the case of purified animal insulin.

Insulin requirement can change significantly with pancreatic, adrenal, pituitary and thyroid disease, renal or hepatic dysfunction.

Insulin requirement can increase during high fever, severe infection, diseases and disorders of the alimentary tract with nausea, vomiting, diarrhoea, delayed gastric emptying and absorption disorders and also during emotional disturbances.

Dose modification can also be required when the patient changes their physical activity or diet.

Patients intending to cross at least two time zones should consult their doctor with respect to the modification of the insulin administration mode. During an air trip, insulin should be kept in the hand luggage and not in a luggage hatch (it must not be frozen).

During long-term insulin therapy insulin-resistance can develop. In such a case the insulin dose should be increased.

Concomitant administration of Gensulin N with pioglitazone:

Cardiac insufficiency cases have been reported with concomitant administration of insulin with pioglitazone, especially in patients with cardiac insufficiency risk factors. This should be considered

before using any combination treatment with Gensulin N and pioglitazone. When combination treatment is administered, patients should be monitored for signs and symptoms of cardiac insufficiency, increased body weight and oedema. If cardiovascular symptoms occur, pioglitazone should be discontinued.

4.5. Interactions with other medicaments and other forms of interaction

Some medicinal products can change glucose metabolism. The doctor should take the potential interaction into account and ask the patient about other medicaments used by them.

Insulin requirement can be increased by substances showing hyperglycaemic action, such as glucocorticosteroids, thyroid hormone, growth hormone, danazol, β_2 -sympathomimetics (ritodrine, salbutamol, terbutaline), diuretic thiazides and niacin.

Insulin requirement may decrease when hypoglycaemic agents are used, e.g. oral hypoglycaemic medications, salicylates (e.g. acetylsalicylic acid), some antidepressants (monoamine oxidase inhibitors), some angiotensin convertase inhibitors (captopril, enalapril), non-selective beta-adrenolytic drugs and alcohol.

Insulin requirement may be changed by somatostatin analogues (octreotide, lanreotide).

4.6. Fertility, pregnancy and lactation

Pregnancy

In women treated with insulin (insulin-dependent diabetes or gestational diabetes) it is necessary to maintain the right control throughout the pregnancy. Insulin requirement usually decreases during the first trimester of pregnancy and increases during the second and third trimester. Diabetic women should be informed that pregnancy or planned pregnancy require consultation with the managing doctor.

In diabetic pregnant women it is necessary to closely monitor the glucose levels and general health conditions.

Immediately after the delivery, insulin requirement decreases abruptly.

Breastfeeding

In diabetic breastfeeding mothers insulin dose modification and/or diet change can be necessary as during lactation insulin requirement drops below the pre-pregnancy level. It comes back to the initial level after 6-9 months.

4.7. Effects on ability to drive and use machines

Due to hypoglycaemia, patient's concentration and ability to react can be reduced. Situations requiring these abilities (e.g. driving and using machines) can be dangerous to the patient.

Patients should be informed to be cautious to prevent hypoglycaemia while driving. It is especially important for individuals that do not experience intensive warning symptoms of hypoglycaemia or are not aware of them and who often develop hypoglycaemia. In such cases the necessity of driving should be considered.

4.8. Undesirable effects

In insulin therapy, the most frequent undesirable effect is hypoglycaemia. Severe hypoglycaemia may lead to loss of consciousness and even death. The frequency of hypoglycaemia is not determined since hypoglycaemia can be a consequence of insulin administration as well as other factors, e.g. diet or physical activity.

A topical allergic reaction is a frequent (1/100 to <1/10) undesirable effect. At insulin injection site erythema, oedema and itching may occur. The symptoms usually disappear in a couple of days or weeks. In some cases topical reactions can be caused by factors other than insulin, e.g. irritating substances included in skin disinfectants or a wrong injection technique.

Systemic allergic reactions indicative of generalised hypersensitivity to insulin are very rare (<1/10 000) but are potentially more dangerous. The symptoms include: eruption all over body, dyspnoea, wheezing breath, lowered arterial pressure, accelerated pulse and sweating. In serious cases, generalised allergy symptoms can be life threatening. Rare cases of severe allergy to Gensulin N require immediate treatment. Insulin change or desensitisation can be necessary.

Infrequently (1/1000 to < 1/100) lipodystrophy at injection site occurs.

Following adverse reactions have been reported during post-marketing experience:

- Cases of oedema, particularly if previous poor metabolic control is improved by intensified insulin therapy;
- Cases of weight gain;
- Injection site reactions: injection site discoloration, injection site bleeding, injection site induration, injection site mass, injection site nodule, injection site pain, injection site rash, injection site urticaria, injection site pustule;
- Cases of pruritus and generalized pruritus;
- Cases of dizziness.

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 national reporting system**

4.9. Overdose

There is no single definition of insulin overdosing because serum glucose is a result of the complex dependence between insulin levels, glucose availability and metabolic processes. Excessive insulin activity in relation to food consumption and energy expenditure may lead to hypoglycaemia.

Hypoglycaemia symptoms include: apathy, confusion, palpitation, headache, sweating and vomiting. Moderate hypoglycaemia subsides upon administration of oral glucose or other sugar-rich products.

Moderate hypoglycaemia can be controlled by intramuscular or subcutaneous administration of glucagon followed by oral administration of carbohydrates when patient's condition improves sufficiently. In case the patient does not respond to glucagon, glucose solution should be administered intravenously.

If the patient is in coma, glucagon should be administered intramuscularly or subcutaneously. In case glucagon is not available or the patient does not respond to glucagon, glucose solution should be administered intravenously. Immediately after regaining consciousness, the patient should be given a meal.

Long-term oral carbohydrate administration and patient monitoring may be necessary since hypoglycaemia can recur after a short clinical improvement.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gensulin N: intermediate-acting insulin, ACT code: A10AC01

The fundamental insulin action is regulating glucose metabolism.

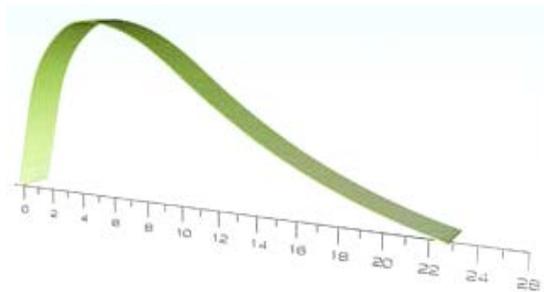
Moreover, insulin has several anabolic and anti-catabolic actions, depending on the type of tissue. In muscular tissue insulin intensifies synthesis of glycogen, fatty acids, glycerol and proteins. It increases

amino acid uptake and simultaneously reduces the intensity of glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid consumption.

A typical activity profile (glucose consumption curve) on subcutaneous insulin administration is shown below. During therapy, deviations from the mean value in time and depending on insulin action intensity are recorded. Individual deviations may be associated with such factors as: dose size, injection site, body temperature and physical activity.

Gensulin N

Insulin activity



Time (hours)

5.2. Pharmacokinetic properties

Insulin pharmacokinetics do not reflect metabolic activity of the hormone. Thus, while assessing insulin activity, it is more appropriate to analyse glucose consumption curves (as explained above).

5.3. Preclinical safety data

Limited non-clinical data did not show toxicity with clinical relevance for humans other than the activity associated with the pharmacodynamic activity consisting in blood glucose lowering (hypoglycaemia).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Gensulin N:

Phenol

Glycerol

Protamine sulphate

m-cresol

Zinc oxide

Hydrochloric acid (solution 0,1M)
Disodium hydrogen phosphate dodecahydrate
Water for injections

6.2. Incompatibilities

Gensulin N products must not be mixed with insulins of other manufacturers and insulins of animal origin.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Upon opening the package, the product is stable for 28 days at temp. up to 25°C. Gensulin N should be protected from light.

Vials that are used or intended to be used should not be kept in a refrigerator. The patient can carry them on themselves. Gensulin N should be protected from high temperature.

6.5. Nature and contents of the container

Glass vial, closed with aluminum cap with double-layered rubber disc and polypropylene cap, containing 10 ml of Gensulin N, packed in carton box.

6.6. Special precautions for drug reconstitution and elimination

Used needles must not be reused. They should be disposed of in a safe way. Needles and syringes must not be shared with other people. Any remains of unused product or waste should be eliminated in compliance with local regulations.

7. MARKETING AUTHORISATION HOLDER

BIOTON S.A.,
5 Staroscinska St.,
02-516 Warsaw

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF THE REVISION OF THE TEXT