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 pen cartridge contains 3 ml of suspension, corresponding to 300 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 cartridge.
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 in cartridges is indicated only for subcutaneous injections with a multiple use pen injector.

Gensulin N in cartridges must not be administered intravenously or intramuscularly. In case administration with a syringe is necessary, a vial should be used. Gensulin N in vials is available on the market.

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 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 cartridge in your hands 10 times and then turn it 10 times by 180º to obtain uniformly turbid or milky suspension. If the effect is not obtained, repeat the procedure till the ingredients are mixed. Cartridges contain a small glass bead that facilitates ingredients' mixing. Do not shake as foam formed in the container can make it difficult to properly measure the insulin dose. Check insulin appearance in cartridges 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 in pen cartridges

Some Gensulin N products are presented in pen cartridges. 3 ml cartridges are administered with a pen bearing the CE mark in accordance with the manufacture's instruction.

a) Dose preparation

Cartridge construction makes it impossible to add different insulin to the cartridge. Used cartridges cannot be refilled.

Follow manufacturer's instruction attached to the pen concerning cartridge insertion into the pen, needle putting and making the injection.

b) Making the injection

Use the insulin dose recommended by the doctor or nurse in the diabetes clinic. Change injection sites, do not inject insulin into the same area more frequently than once a month.

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- sympathicomimetics (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

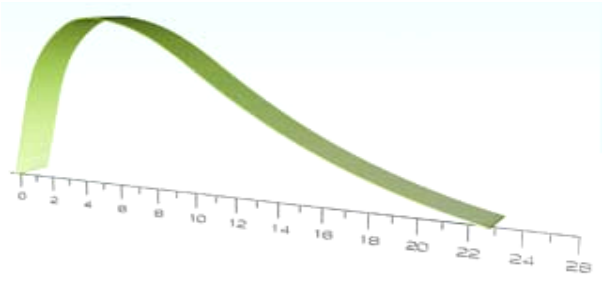
Pharmacotherapeutic group: Gensulin N: intermediate-acting insulin, ACT code: A10AC01

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:

m-cresol

Phenol

Glycerol

Protamine sulphate

Zinc oxide

Disodium hydrogen phosphate dodecahydrate

Hydrochloric acid (solution 0,1M)

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^oC - 8^oC). 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.

Cartridges 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 content of the container

5 or 10 glass cartridges for pens containing 3 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 cartridges must not be shared with other people. The cartridge can be applied till all its content has been used and then it should be disposed of in a safe way. 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

Gensulin N 100 IU/mL cartridges for pens - marketing authorization number 8524

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

Date of the first marketing authorization: 29.12.2000.
Date of the last renewal of the marketing authorization: 17.11.2009.

10. DATE OF THE REVISION OF THE TEXT