SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Wosulin N 100 IU/ml suspension for injection in vial

2. QUALITATIVE A ND QUANTITATIVE COMPOSITION

1 ml suspension contains 100 international units isophane (NPH) insulin human*.
1 vial contains 10 ml equivalent to 1,000 international units.
*Human insulin is produced in *Hansenula Polymorpha* by recombinant DNA technology.

Sr. No.	Ingredients	Specifications	Theoretical Quantity per mL	Reason for inclusion
1.	Insulin Human (Recombinant)	USP	100 IU*	Active
2.	Disodium hydrogen phosphate anhydrous	USP	2.08 mg	Buffering agent
3.	Glycerol (98%)	USP	16.32 mg	Isotonic agent
4.	Zinc (as Zinc oxide)	USP	0.025 mg	Stabilizer
5.	m-Cresol	USP	1.60 mg	Preservative
6.	Phenol	USP	0.65 mg	Preservative
7.	Protamine sulphate	USP	0.37 mg	Complexing agent
8.	Sodium hydroxide	USP	q.s. to pH	pH modifier
9.	Hydrochloric acid	USP	q.s. to pH	pH modifier
10.	Water for Injection	USP	q.s. to 1 mL	Vehicle

USP: United States national formulary

Note:

1. The amount of Zinc oxide added to the formulation is dependent on the amount of zinc in the Human Insulin used. The target amount for Zinc in the formulation is 25 µg per 100 IU Insulin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for subcutaneous injection.The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

WOSULIN-N is indicated for treatment of diabetes mellitus.

4.2 Posology and method of administration

Route of administration: Subcutaneous Injection

Posology

The potency of human insulin is expressed in international units.

WOSULIN-N dosing is individual and determined in accordance with the needs of the patient. The physician determines whether one or several daily injections are necessary. WOSULIN-N may be used alone or mixed with fast-acting insulin. In intensive insulin therapy the suspension may be used as basal insulin (evening and/or morning injection) with fast-acting insulin given at meals. Blood glucose monitoring is achieve optimal glycaemic control.

The individual insulin requirement is usually between 0.3 and recommended to 1.0 unit/kg/day.

Adjustment of dose may be necessary if patients undertake increased international physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly (> 65 years old)

WOSULIN-N can be used in elderly patients.

In elderly patients, glucose monitoring should be intensified and the insulin dose adjusted on an individual basis.

Renal and hepatic impairment

Renal or hepatic impairment may reduce the patient's insulin requirements.

In patients with renal or hepatic impairment, glucose monitoring should be intensified and the human insulin dose adjusted on an individual basis.

Paediatric population

WOSULIN-N can be used in children and adolescents.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products, adjustment of the WOSULIN-N dose and timing of administration may be necessary.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

WOSULIN-N is a human insulin with gradual onset and long duration of action.

WOSULIN-N is administered subcutaneously by injection in the thigh, the abdominal wall, the gluteal region or the deltoid region. Insulin suspensions are never to be administered intravenously. Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.

The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
Insulin suspensions are not to be used in insulin infusion pumps.
WOSULIN-N vials are for use with insulin syringes with a corresponding unit scale.
WOSULIN-N vial is accompanied by a package leaflet with detailed instructions for use to be followed.

4.3 Contraindications

Isophane insulin human suspension - WOSULIN-N is contraindicated in the following conditions:

- Hypersensitivity to insulin or any other component of the formulation

4.4 Special warnings and special precautions for use

Before travelling between different time zones, the patient should seek the doctor's advice since this may mean that the patient has to take the insulin and meals at different times.

Hyperglycaemia
Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, Wosulin must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.8 and 4.9).
Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients

with longstanding diabetes.
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.
When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.
Transfer from other insulin medicinal products
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, 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.
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.
Treatment with human insulin may cause formation of antibodies, but titers 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.

Injection site reactions
As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of WOSULIN-N.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including WOSULIN-R, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

4.5 Interactions with other medicaments and other forms of Interaction

Insulin requirements may be increased by medications with hyperglycemic activity such

as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g. niacin), estrogens, oral contraceptives, phenothiazines, sympathomimetics, growth hormone, danazol and thyroid replacement therapy. Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors, beta adrenergic blockers, and anabolic steroids. Beta adrenergic blockers may mask the symptoms of hypoglycemia in some patients. Octreotide/lanreotide may either increase or decrease the insulin requirement. Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Renal Impairment:
The requirements for insulin may be reduced in patients with renal impairment.
Hepatic Impairment:

Although impaired hepatic function does not affect the absorption or disposition of Isophane insulin human suspension - WOSULIN-N, careful glucose monitoring and dose adjustments of insulin may be necessary.

4.6 Fertility, Pregnancy and Lactation

Pregnancy: There are no restrictions on the use of insulin during pregnancy since insulin does not cross the placental barrier. Published studies with human insulin suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers: There are no restrictions on the use of insulin in lactating mothers as insulin treatment of nursing mothers does not involve any risk to the baby. However, caution should be exercised when administered to nursing mothers and the dosage of insulin may be reduced.

Fertility: Animal reproduction studies with human insulin have not revealed any adverse effects on fertility.

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

hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving or operating machinery). Patients should therefore be advised to avoid hypoglycemia during driving. This is particularly significant in patients who have reduced awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in

glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1,000 to < 1/100); rare (> 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Immune system disorders	Uncommon - Urticaria, rash Very rare - Anaphylactic reactions*
Metabolism and nutrition disorders	Very common - Hypoglycaemia
Nervous system disorders	Uncommon - Peripheral neuropathy (painful neuropathy)*
Eye disorders	Very rare - Refraction disorders Uncommon - Diabetic retinopathy*
Skin and subcutaneous tissue disorders	Uncommon - Lipodystrophy
General disorders and administration site conditions	Uncommon - Injection site reactions
	Uncommon - Oedema

*Not known: Anaphylactic reactions, Peripheral neuropathy (painful neuropathy) and Diabetic retinopathy.

Description of selected adverse reactions

Anaphylactic reactions

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulty in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive

hunger, vision changes, headache, nausea and palpitation.

In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area reduces the risk of developing these reactions.

Paediatric population

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

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 their respective National Pharmacovigilance and Drug Safety Centre.

As per the routine Pharmacovigilance plan, the Company will continue to monitor for any new safety information that may alter the benefit-risk profile of Wosulin N and duly take necessary steps with any new specific information that may become available.

4.9 Overdose

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. It is therefore recommended that the diabetic patient constantly carry some sugar lumps, sweets, biscuits, or sugary fruit juice. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular / subcutaneous glucagon or concentrated intravenous glucose. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for

injection, intermediate-acting, insulin (human).
ATC code: A10AC01.
Mechanism of action and pharmacodynamic effects
The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.
Wosulin - N is an amorphous and crystalline suspension of human insulin with zinc providing an intermediate - acting insulin with a slower onset and a longer duration of activity than that of regular insulin. The onset of action of Isophane insulin human suspension - WOSULIN-N is dependent on dose, site of injection, blood supply, temperature and physical activity. The onset of action is 1-2 hours, peak effect is seen at 6-12 hours and the duration of effect is about 18-24 hours. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. It is a sterile solution and is for subcutaneous injection only. It should not be used intravenously or intramuscularly.

5.2 Pharmacokinetic properties

Insulin has a half-life of a few minutes in the blood stream. Consequently, the time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the intensity and duration of action of Isophane insulin human suspension - WOSULIN-N is dependent on the dose, site of injection, blood supply, temperature, and physical activity.
An average action profile after subcutaneous injection indicates:
Onset within 1-2 hours, Peak levels attained between 6-12 hours, Duration of action approximately 18-24 hours.

5.3 Preclinical safety data

Wosulin is human insulin produced by recombinant technology. Non-clinical data reveal no special hazard for humans based on conventional sub-chronic 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

Sr No	Excipients	Specification
1	Disodium hydrogen phosphate anhydrous	USP

2	Glycerol (98%)	USP
3	Zinc oxide (as Zinc)	USP
4	m-Cresol	USP
5	Phenol	USP
6	Protamine sulphate	USP
7	Sodium hydroxide	USP
8	Hydrochloric acid	USP
9	Water for Injection	USP

USP: United States national formulary

6.2 Incompatibilities

Insulin medicinal products should only be added to compounds with which it is known to be compatible. Insulin suspensions should not be added to infusion fluids.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Isophane insulin human suspension - WOSULIN-N should be stored in a refrigerator (2 °C to 8 °C) but not allowed to freeze. When in use, vial may be kept at room temperature (15 °C to 25 °C) for up to six weeks. Do not expose to excessive heat or direct sunlight. Isophane insulin human suspension - WOSULIN-N must be kept out of reach of children. Insulin preparations, which have been frozen, must not be used. Once opened (when the stopper or seal has been punctured with a needle), insulin is kept at room temperature

Cold insulin can be irritating to inject. Patients should be asked to roll the vial in their hands 10 times for mixing the suspension prior to drawing it up in the syringe after allowing the vial to sit for 30 minutes at room temperature if the vial is stored in the refrigerator.

6.5 Nature and contents of container

White suspension of rod-shaped crystals, free from large aggregates of crystals following moderate agitation.

10 mL filled in a glass vial with bromobutyl plug and flip off seal. Vial is pasted with printed label. 1 vial packed in a printed carton with literature insert.

6.6 Special precautions for disposal and other handling

Needles and syringes must not be shared.

After removing Wosulin N vial from the refrigerator, it is recommended to allow the vial to reach room temperature before re-suspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the re-suspended liquid is not uniformly white and cloudy.

Wosulin N which has been frozen must not be used.
The patient should be advised to discard the needle and syringe after each injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Applicant/ Manufacturer

Name and address of Manufacturer
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