FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY

Rx

# *Isophane Insulin Injection I.P. 100 IU/ml (r-DNA origin)*

**3ml multi-dose cartridge**

100 IU/ml

## Wosulin® N

**NPH Monocomponent Insulin HUMAN**

*For SC use only*

WOCKHARDT

**1. Generic Name**

Isophane Insulin Injection IP 100 IU/mL
(r-DNA origin), NPH-Monocomponent Insulin Human

**2. Qualitative and quantitative composition**

Each mL of Isophane suspension contains
Human Insulin IP .....100 IU
m-Cresol USP .....0.16% w/v (as preservative)
Phenol IP .....0.065% w/v (as preservative)
Water for Injections IP .....q.s.

**3. Dosage form and strength**

It is a 3 mL cartridge containing 100 IU/mL, Isophane Insulin Injection for subcutaneous use.

**4. Clinical particulars**

**4.1 Therapeutic indication**

Isophane Insulin Injection is indicated for the following:

- For the treatment of type-I diabetes mellitus
- For the treatment of type-II diabetes who are not adequately controlled by diet and or oral hypoglycaemic agent
- For the initial stabilization of Type II diabetes patients with diabetic ketoacidosis, hyperosmolar non-ketotic syndrome and in diabetes during pregnancy.

**4.2 Posology and method of administration**

Inspect WOSULIN-N visually before use. It should not contain particulate matter and should appear uniformly cloudy after mixing. Do not use WOSULIN-N if particulate matter is seen.

WOSULIN-N should only be administered subcutaneously. Administer in the subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks. To reduce the risk of lipodystrophy, rotate the injection site within the same region from one injection to the next.

Do not administer WOSULIN-N intravenously or intramuscularly and do not use it in an insulin infusion pump.

Individualize and adjust the dosage of WOSULIN-N based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.

Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness.

The average range of total daily insulin requirement for maintenance therapy in insulin-treated patients without severe insulin resistance lies between 0.5 and 1 unit/kg/day. For Neonates it is 0.01 – 0.1 IU/kg/hr by continuous infusion or SC 0.1 –0.2 IU/kg 6 –12 hr. For children it is 0.5 – 1 IU/kg/24hr (Adjust doses to blood glucose and haemoglobin A1c results) and for adolescents it is 0.8 – 1.2 IU/kg/24hr. However, in pre-pubertal children it usually varies from 0.7 to 1 unit/kg/day, but can be much lower during the period of partial remission. In situations of insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher. Initial dosages for patients with diabetes are often lower, e.g., 0.2 to 0.4 units/kg/day. In patients with type 2 diabetes, the requirements of insulin are lower i.e. approximately 0.3 – 0.6 IU / kg / day.

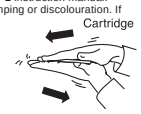
WOSULIN-N should not be used after the printed expiration date.

**INSTRUCTIONS FOR USE**

a. Disinfect the rubber surface of the insulin Cartridge with alcohol. Insert the Cartridge in the Pen as shown in the **mypen®2** instruction manual. Before inserting the Cartridge, inspect the Cartridge of **WOSULIN-N** after removing from the sealed pack for any crystallization, clumping or discolouration. If present, discard and use a new Cartridge.

b. Before you insert the Cartridge into the **mypen®2**, roll it between your palms at least 10 times. (Ref Fig. 1).

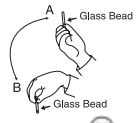
Fig. 1




Then hold the Cartridge at one end and move between position "A" to position "B" slowly so that the glass ball travels from one end of the Cartridge to the other end. (Ref Fig. 2).

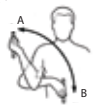
This must be done at least 10 times until the liquid appears uniformly cloudy or milky. Discard the Cartridge if clumps are seen after mixing.

Fig. 2




c.If the Cartridge is already inside the **mypen®2**, turn the Pen up and down gently at least 10 times until the liquid appears uniformly cloudy or milky. This has to be done before each injection. (Ref Fig. 3).

Fig. 3




d. After you attach the needle, dial 2 units on the dose selector to remove any air that may be inside the needle.
e. Wash your hands and clean the skin with alcohol where the injection is to be made.
f. With one hand, lightly pinch up the skin, insert the needle as advised by your doctor or educator. Push and hold the release button of the Pen. Count to 10 and pull out the needle. Do not massage the area as this may cause back leakage of insulin
g. Dispose off the needle in the recommended way.
h. For additional information, read the instruction manual of **mypen®2** and also log on to www.wockhardtdiabetes.com

**4.3 Contraindications**

WOSULIN-N is contraindicated during episodes of hypoglycemia and in patients hypersensitive to WOSULIN-N or any of its excipients.

**4.4 Special warnings and precautions for use**

Needles or syringes must never be reused or shared between patients. Sharing poses a risk for transmission of blood-borne pathogens.

Any change in insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog, etc.), species, or method of administration may result in the need for a change in dosage.

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-N, 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.

Hypoglycemia: Hypoglycemia is the most common adverse reaction of all insulin therapies, including WOSULIN-N. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Concomitant antihyperglycemic agents may need to be adjusted. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Hyperglycemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome: Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less WOSULIN-N than needed to control blood glucose levels. This could be due to increases in insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses or use of drugs that affect glucose metabolism or insulin sensitivity.

Hypokalemia: Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia, that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypokalemia is necessary. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including WOSULIN-N. Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

**4.5 Drugs interactions**

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood-glucose-lowering effect of WOSULIN-N and susceptibility to hypoglycemia: Oral antihyperglycemic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors [SSRIs]), pramlintide, disopyramide, fibrates, fluoxetine, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.

Drugs that may reduce the blood-glucose-lowering effect: Corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents, somatropin, atypical antipsychotics, glucagon, protease inhibitors and thyroid replacement therapy.

Drugs that may increase or decrease blood-glucose-lowering effect: Beta-adrenergic blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Drugs that may mask the signs of hypoglycemia: Beta-adrenergic blockers, clonidine, guanethidine, and reserpine.

**4.6 Use in special populations**

**Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

**Use in Pregnancy:** Pregnancy Category B. All pregnancies have a background risk of birth defects, miscarriage, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and is decreased with good glucose control. It is important for patients to maintain good control of diabetes before conception and during pregnancy. Special attention should be paid to diet, exercise and insulin regimens. Insulin requirements may decrease during the first trimester, usually increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking WOSULIN-N. While there are no adequate and well-controlled studies of WOSULIN- N in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.

**Labor and Delivery:** Careful glucose monitoring and management of patients with diabetes during labor and delivery are required.

Nursing Mothers: Endogenous insulin is present in human milk. Insulin orally ingested is degraded in the gastrointestinal tract. No adverse reactions have been associated with infant exposure to insulin through the consumption of human milk. Good glucose control supports lactation in patients with diabetes. Women with diabetes who are lactating may require adjustments in their insulin dose.

**Pediatric Use:** Safety and effectiveness of WOSULIN-N in patients less than 18 years of age has not been established.

**Geriatric Use:** The effect of age on the pharmacokinetics and pharmacodynamics of WOSULIN-N has not been studied. Patients with advanced age using any insulin, including WOSULIN-N, may be at increased risk of hypoglycemia due to co-morbid disease and polypharmacy.

**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 a car 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**

Hypoglycemia: Hypoglycemia is one of the most frequent adverse events experienced by insulin users. Symptoms of mild to moderate hypoglycemia may occur suddenly and can include sweating, drowsiness, dizziness, sleep disturbances, palpitation, anxiety, tremor, blurred vision, hunger, slurred speech, restlessness, depressed mood, tingling in the hands, feet, lips, or tongue, irritability, lightheadedness, abnormal behavior, inability to concentrate, unsteady movement, headache and personality changes. Signs of severe hypoglycemia can include disorientation, seizures, unconsciousness, coma and death.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, autonomic diabetic neuropathy, use of medications such as beta-adrenergic blockers, changing insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes. Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose more frequently, especially prior to activities such as driving. Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as hard candy, non-diet carbohydrate-containing drinks or glucose tablets.

Hypokalemia: See section 4.4 Special warnings and precautions for use.

Lipodystrophy: Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue).

Allergy

Local Allergy – Patients occasionally experience erythema, local edema, and pruritus at the site of injection. This condition usually is self-limiting. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic Allergy – Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy (anaphylaxis) may be life threatening.

Weight Gain: Weight gain can occur with some insulin therapies and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Peripheral Edema: Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Immunogenicity: Development of antibodies that react with human insulin have been observed with all insulin, including WOSULIN-N

Insulin resistance

When insulin requirement is increased (> 200 IU / day), insulin resistance is said to have developed. The following are the different grades of insulin resistance:

Acute:

Acute insulin resistance develops rapidly and is usually a short term problem. It usually occurs due to an underlying infection, trauma, surgery and emotional stress. Treatment is to overcome the precipitating factor and to give high doses of regular insulin.

Chronic:

This type of insulin resistance is generally seen in patients treated for years with conventional preparations of beef or pork insulins and it is more common in patients with Type 2 diabetes. Development of such a type of insulin resistance is an indication for switching patients to the newer preparations of insulin. After instituting the newer preparations, insulin requirement gradually declines over weeks and months and majority of patients stabilize at approximately 60 IU / day.

**4.9 Overdose**

Excess insulin may cause hypoglycemia and hypokalemia, particularly after intravenous administration. 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. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

**5. Pharmacological properties**

**5.1 Mechanism of Action**

Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat following binding the insulin receptors, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis, proteolysis, and gluconeogenesis, and enhance protein synthesis and conversion of excess glucose into fat. Administered insulin, including WOSULIN-N, substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of insulin. When administered in appropriate doses at prescribed intervals to patients with diabetes mellitus, WOSULIN-N restores their ability to metabolize carbohydrates, proteins and fats.

**5.2 Pharmacodynamic properties**

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.

**5.3 Pharmacokinetic properties**

As with all insulin preparations, the duration of action of WOSULIN-N is dependent on dose, site of injection, blood supply, temperature, and physical activity. WOSULIN-N is an intermediate-acting insulin with a slower onset of action and a longer duration of activity than that of regular human insulin. With subcutaneous use, the pharmacologic effect of WOSULIN-N begins approximately 1-2 hours after administration. The effect is maximal at approximately 6-12 hours and terminates after approximately 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.

**6. Nonclinical properties**

**6.1 Animal Toxicology**

Single dose toxicity – There were no signs of toxicity in Swiss albino mice and Sprague Dawley rats treated at the dose level of 24IU/kg body weight of subcutaneous injections of Isophane insulin.

Repeated dose toxicity - There were no signs of toxicity in Swiss albino mice and Sprague Dawley rats during a period of 28 days with subcutaneous injections of Isophane insulin.

Dermal Toxicity - There were no signs of dermal irritation or skin sensitization in New Zealand white rabbits and Duncan Hartley guinea pigs with topical testing of Isophane insulin.

Carcinogenicity and impairment of fertility- Carcinogenicity and fertility studies were not performed in animals.

Mutagenicity - Human insulin was not mutagenic in mammalian cells and tested negative in the Ames bacterial reverse mutation assay with and without activation.

**7. Description**

WOSULIN-N (human insulin [rDNA origin] isophane suspension) is a human insulin suspension. Human insulin is produced by recombinant DNA technology synthesized in a special non-disease-producing laboratory strain of the yeast Hansenula polymorpha. This special host cell line has been genetically altered by the addition of the gene for human insulin production. WOSULIN-N is a suspension of crystals produced from combining human insulin and protamine sulfate under appropriate conditions for crystal formation. The amino acid sequence of WOSULIN-N is identical to human insulin.

**8. Pharmaceutical particulars**

**8.1 Incompatibilities**

These medicinal products should not be mixed with any other insulin or any other medicinal product.

**8.2 Shelf-life**

36 months

**8.3 Packaging information**

PACK: WOSULIN-N 100 IU/ml – 3 mL multi-dose cartridge

**8.4 Storage and handing instructions**

WOSULIN-N should be stored in a refrigerator (2°C to 8°C) but not allowed to freeze. When in use, cartridge may be kept at room temperature up to 30 °C for up to four weeks. Do not expose to excessive heat or direct sunlight. WOSULIN-N must be kept out of reach of children. Insulin preparations, which have been frozen, must not be used. Once opened, insulin is kept at room temperature. Cold insulin can be irritating to inject. Remove the needle after each injection, otherwise temperature changes may cause liquid to leak out of the needle and the insulin concentration may increase. Do not refill the Cartridge. Do not use WOSULIN-N after the expiration date stamped on the label or if it has been frozen.

**9. Patient Counselling Information**

***Important Risks and Adverse drug reactions***

**Never Share a Wosulin N cartridge or syringe between patients**

Advise patients using Wosulin N cartridge, not to share needles, syringes, or DispoPen with another person. Sharing poses a risk for transmission of blood-borne pathogens.

**Hypoglycemia**

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of Wosulin N therapy. Instruct patients on handling of special situations such as illness, stress, or emotional disturbances, an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals,

Instruct patients on the management of hypoglycemia. Advise patients to regularly carry some sugar lumps, sweets, biscuits, or sugary fruit juice to mitigate symptoms of hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery. [see Special warnings and precautions for use(4.4)].

**Hypoglycemia due to Medication Errors**

Instruct patients that hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

**Hypersensitivity Reactions**

Advise patients that hypersensitivity reactions can occur with Wosulin. Inform patients on the symptoms of hypersensitivity reactions and advice the patient to discontinue Wosulin and to seek medical attention if they occur [see Undesirable effects (4.8)].

***Use in Special Population***

**Pregnant females**

Advise pregnant patients that insulin requirements usually fall during the first trimester and increase during second and third trimesters of pregnancy. Careful monitoring is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

**Nursing Mothers**

Advise the nursing mothers that dosage of insulin may be reduced.

**Renal and Hepatic Impairment**

Advise the patients that dosage of insulin may be reduced and these patients are at increased risk of hypoglycemia thus requiring frequent blood glucose monitoring.

***Administration Instructions***

Instruct the patient to never use Wosulin N cartridge if it is frozen. Advise the patients on proper and safe disposal of the needle [see Instructions for use].

***Storage and Handling***

Instruct the patient that Wosulin N cartridge which is not in use, should be stored in a refrigerator (2°C to 8°C) and should never be kept in the freezer compartment.

Instruct the patient that when in use, Wosulin N cartridge may be carried at room temperature up to 30°C for up to 4 weeks.

**10. Details of manufacturer**

Manufactured in India by
**WOCKHARDT LIMITED** Biotech Park, H-14/2 MIDC, Waluj, Aurangabad 431136 Maharashtra State

**11. Details of permission or licence number**

Manufacturing License No: AD/004

**12. Date of revision**

Jan/2020.

I. I. No. m-908/5
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Front

Back

ACTUAL SIZE 110 X 218 MM
(WOSULIN-N)
Folding Size: 110 x 25

Pantone 348 C

K 100