

SUMMARY OF PRODUCT CHARACTERISTICS

1 INDICATIONS AND USAGE

HUMULIN N is an intermediate-acting recombinant human insulin indicated to improve glycemic control in adults and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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

2.2 Route of Administration

HUMULIN N should only be administered subcutaneously.

Administer in the subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6)]. During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring [see *Warnings and Precautions* (5.2)].

+Do not administer HUMULIN N intravenously or intramuscularly and do not use HUMULIN N in an insulin infusion pump.

2.3 Dosage Information

Individualize and adjust the dosage of HUMULIN 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 [see *Warnings and Precautions* (5.2, 5.3), and *Use in Specific Populations* (8.6, 8.7)].

2.4 Dosage Adjustment due to Drug Interactions

Dosage adjustment may be needed when HUMULIN N is coadministered with certain drugs [see *Drug Interactions* (7)].

Dosage adjustment may be needed when switching from another insulin to HUMULIN N [see *Warnings and Precautions* (5.2)].

Instructions for Mixing with Other Insulins

HUMULIN N may be used with a prandial insulin if indicated. HUMULIN N may be mixed with HUMULIN R or HUMALOG before injection.

- If HUMULIN N is mixed with HUMULIN R, HUMULIN R should be drawn into the syringe first. Injection should occur immediately after mixing.
- If HUMULIN N is mixed with HUMALOG, HUMALOG should be drawn into the syringe first. Injection should occur immediately after mixing.

3 DOSAGE FORMS AND STRENGTHS

HUMULIN N injectable suspension: 100 units per mL (U-100) is a white and cloudy suspension available as:

- 10 mL multiple-dose vial
- 3 mL multiple-dose vial

Not all strengths, packs sizes or presentations may be marketed.

4 CONTRAINDICATIONS

HUMULIN N is contraindicated:

- During episodes of hypoglycemia [*see Warnings and Precautions (5.3)*], and
- In patients who have had hypersensitivity reactions to HUMULIN N or any of its excipients [*see Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a HUMULIN N Syringe Between Patients

Patients using HUMULIN N vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [*see Warnings and Precautions (5.3)*] or hyperglycemia.

Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia [*see Adverse Reactions (6)*].

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant antidiabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including HUMULIN N. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [*see Drug Interactions (7)*], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of HUMULIN N may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [*see Clinical Pharmacology (12.2)*]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [*see Drug Interactions (7)*]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [*see Use in Specific Populations (8.6, 8.7)*].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and

patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMULIN N. If hypersensitivity reactions occur, discontinue HUMULIN N; treat per standard of care and monitor until symptoms and signs resolve [see *Adverse Reactions (6)*]. HUMULIN N is contraindicated in patients who have had hypersensitivity reactions to HUMULIN N or any of its excipients [see *Contraindications (4)*].

5.5 Hypokalemia

All insulin products, including HUMULIN N, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.6 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 HUMULIN 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypoglycemia [see *Warnings and Precautions (5.3)*].
- Hypokalemia [see *Warnings and Precautions (5.5)*].

The following additional adverse reactions have been identified during post-approval use of HUMULIN N. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Allergic Reactions

Some patients taking HUMULIN N have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting. Severe cases of generalized allergy (anaphylaxis) have been reported [see *Warnings and Precautions (5.4)*].

Peripheral Edema

Some patients taking HUMULIN N have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy

Administration of insulin subcutaneously, including HUMULIN N, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) [see *Dosage and Administration (2.2)*] in some patients. Localized Cutaneous Amyloidosis

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous

amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

Weight gain

Weight gain has occurred with some insulin therapies including HUMULIN N and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Immunogenicity

Development of antibodies that react with human insulin have been observed with all insulin, including HUMULIN N.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with HUMULIN N use may be increased when co-administered with antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, disopyramide, fibrates, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide). Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN N is co-administered with these drugs.

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of HUMULIN N

The glucose lowering effect of HUMULIN N may be decreased when co-administered with corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN N is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of HUMULIN N

The glucose lowering effect of HUMULIN N may be increased or decreased when co-administered with beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN N is co-administered with these drugs.

7.4 Drugs That May Blunt Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia [see *Warnings and Precautions (5.3)*] may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with HUMULIN N.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Animal reproduction studies were not performed.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7% and has been reported to be as high as 20-25% in women with a HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from retrospective studies, open-label, randomized, parallel studies and meta-analyses over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. All available studies have methodological limitations, including lack of blinding, unclear methods or randomization, and small sample size.

8.2 Lactation

Risk Summary

Available data from published literature suggests that exogenous human insulin products, including HUMULIN N, are transferred into human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including HUMULIN N on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMULIN N and any potential adverse effects on the breastfed child from HUMULIN N or from the underlying maternal condition.

8.4 Pediatric Use

HUMULIN N has not been studied in pediatric patients. As in adults, the dosage of HUMULIN N in pediatric patients must be individualized based on metabolic needs, treatment goal and blood glucose monitoring results.

8.5 Geriatric Use

The effect of age on the pharmacokinetics and pharmacodynamics of HUMULIN N has not been studied [see *Clinical Pharmacology* (12.3)]. Patients with advanced age using any insulin, including HUMULIN N, may be at increased risk of hypoglycemia due to co-morbid disease and polypharmacy [see *Warnings and Precautions* (5.3)].

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics and pharmacodynamics of HUMULIN N has not been studied [see *Clinical Pharmacology* (12.3)]. Patients with renal impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN N dose adjustment and more frequent blood glucose monitoring.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of HUMULIN N has not been studied [see *Clinical Pharmacology* (12.3)]. Patients with hepatic impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN N dose adjustment and more frequent blood glucose monitoring.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see *Warnings and Precautions* (5.3, 5.5)]. Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level 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.

11 DESCRIPTION

HUMULIN N (isophane insulin human injection) is an intermediate-acting human insulin. Human insulin is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. HUMULIN 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 HUMULIN N is identical to human insulin and has the empirical formula C₂₅₇H₃₈₃N₆₅O₇₇S₆ with a molecular weight of 5808.

HUMULIN N is a sterile preserved aqueous suspension that contains isophane insulin human injection (NPH) for subcutaneous use. Each milliliter of HUMULIN N contains 100 units of insulin human, protamine sulfate, the amount is variable in order to attain 0.27 mg protamine base per 100 units of insulin, 16 mg of glycerol, 3.78 mg of dibasic sodium phosphate (heptahydrate), 1.6 mg of metacresol, phenol, amount is variable in order to attain 0.65 mg/mL phenol, zinc oxide content adjusted to provide 0.025-0.035 mg zinc ion per 100 units of insulin, and water for injections. The pH is 7.0 to 7.5. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HUMULIN N lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

HUMULIN N is an intermediate-acting insulin with a slower onset of action and a longer duration of activity than that of regular human insulin. In a study in which healthy subjects (n=16) received subcutaneous injections of HUMULIN N (0.4 unit/kg) on 4 occasions, the median maximum effect occurred at 6.5 hours (range: 2.8 to 13 hours). In this study, insulin activity was measured by the rate of glucose infusions.

The time course of action of insulin, such as HUMULIN N may vary in different individuals or within the same individual. The parameters of HUMULIN N activity (time of onset, peak time, and duration) as designated in Figure 1 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, physical activity level, and other variables [see *Warnings and Precautions* (5.3)].

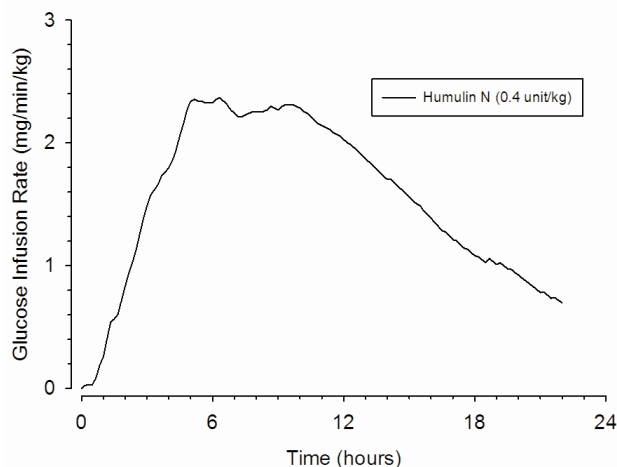


Figure 1: Mean Insulin Activity Versus Time Profile After Subcutaneous Injection of HUMULIN N (0.4 unit/kg) in Healthy Subjects.

12.3 Pharmacokinetics

Absorption — In healthy subjects given subcutaneous doses of HUMULIN N (0.4 unit/kg), median peak serum concentration of insulin occurred at approximately 4 hours (range: 1 to 12 hours) after dosing.

Metabolism — The uptake and degradation of insulin occurs predominantly in liver, kidney, muscle, and adipocytes, with the liver being the major organ involved in the clearance of insulin.

Elimination — Because of the absorption-rate limited kinetics of insulin mixtures, a true half-life cannot be accurately estimated from the terminal slope of the concentration versus time curve. In healthy subjects given subcutaneous doses of HUMULIN N (0.4 unit/kg), the mean apparent half-life was approximately 4.4 hours (range: 1-84 hours).

Specific Populations

The effects of age, gender, race, obesity, pregnancy, or smoking on the pharmacokinetics of HUMULIN N have not been studied.

Careful glucose monitoring and dose adjustments of insulin, including HUMULIN N, may be necessary in patients with renal or hepatic dysfunction [see *Use in Specific Populations* (8.6, 8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and fertility studies were not performed in animals. Biosynthetic human insulin was not genotoxic in the *in vivo* sister chromatid exchange assay and the *in vitro* gradient plate and unscheduled DNA synthesis assays.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMULIN N injectable suspension 100 units per mL (U-100) is a white and cloudy suspension available as: 10 mL multiple-dose vial (HI-310)
3 mL multiple-dose vial (HI-313)

Not all strengths, packs sizes or presentations may be marketed.

Patients using HUMULIN N vials must never share needles or syringes with another

person.

16.2 Storage and Handling

Dispense in the original sealed carton with the enclosed Instructions for Use. Protect from direct heat and direct light or sunlight. Do not freeze. Do not use after the expiration date.

Not In-Use (Unopened) HUMULIN N Vials

Refrigerated

Store in a refrigerator at 2°C to 8°C [36°F to 46°F] until time of use, but not in the freezer. Do not use if it has been frozen.

In-Use (Opened) HUMULIN N Vials

Refrigerated

Store in a refrigerator at 2°C to 8°C [36°F to 46°F] until time of use but not in the freezer. Do not use if it has been frozen. Vials must be used within 28 days (after the stopper has been punctured) or be discarded, even if they still contain HUMULIN N.

Room Temperature

If refrigeration is not possible, store in-use drug product unrefrigerated at a maximum temperature of 30°C [86°F].

	Not In-Use (Unopened) Refrigerated	In-Use (Opened)
10 mL multiple-dose vial 3 mL multiple-dose vial	Until expiration date	28 days, refrigerated/room temperature

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the patient labeling (Patient Information and Instructions for Use).

Never Share a HUMULIN N Syringe Between Patients

Advise patients using HUMULIN N vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens [see *Warnings and Precautions* (5.1)].

Hyperglycemia or Hypoglycemia

Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia especially at initiation of HUMULIN N therapy. Instruct patients on handling of special situations such as intercurrent conditions (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.

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 *Warnings and Precautions* (5.3)].

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision [see *Warnings and Precautions* (5.2)].

Inform patients that accidental mix-ups between HUMULIN N and other insulins have been reported. Instruct patients to always carefully check that they are administering the correct insulin (e.g., by checking the insulin label before each injection) to avoid medication errors between HUMULIN N and other insulins.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with HUMULIN N. Inform patients on the symptoms of hypersensitivity reactions [*see Warnings and Precautions (5.4)*].

Visual Inspection Prior to Use

Instruct patients to visually inspect HUMULIN N before use and to use HUMULIN N only if it contains no particulate matter and appears uniformly cloudy after mixing [*see Dosage and Administration (2.1)*].
