HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMULIN N safely and effectively. See full prescribing information for HUMULIN N.

HUMULIN N (human insulin [rDNA origin] isophane suspension), injectable suspension, for subcutaneous use

Initial U.S. Approval: 1982

------------------------- RECENT MAJOR CHANGES -------------------------

None.

------------------------ 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. (1)

----- DOSAGE AND ADMINISTRATION -----------

• Only administer subcutaneously (in abdominal wall, thigh, upper arm, or buttocks). (2.2)
• Individualize and adjust dosage based on metabolic needs, blood glucose monitoring results and glycemic control goal. (2.3)
• See Full Prescribing Information for dosage adjustments due to drug interactions and patients with renal and hepatic impairment. (2.3, 2.4)
• May use with a meal-time insulin if indicated. (2.4)

----- DOSE FORMS AND STRENGTHS -----

Injectable suspension 100 units per mL (U-100) available as 10 mL vials, 3 mL vials, and 3 mL HUMULIN N KwikPen® (prefilled). (3)

----- CONTRAINDICATIONS -------

• During episodes of hypoglycemia. (4)
• In patients with hypersensitivity to HUMULIN N or any of its excipients. (4)

----- WARNINGS AND PRECAUTIONS ----- 

• Never share a HUMULIN N KwikPen or syringe between patients, even if the needle is changed. (5.1)
• Changes in Insulin Regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)
• Hypoglycemia: May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3, 7, 8.6, 8.7)
• Hypersensitivity Reactions: May be life-threatening. Discontinue HUMULIN N, monitor and treat if indicated. (5.4)
• Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.5)
• Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.6)

--------- ADVERSE REACTIONS ---------

Adverse reactions observed with HUMULIN N include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, weight gain, and edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Drugs that Affect Glucose Metabolism: Adjustment of insulin dosage may be needed. (7.1, 7.2, 7.3)
• Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent. (5.3, 7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2017

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FULL PRESCRIBING INFORMATION

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. To reduce the risk of lipodystrophy, rotate the injection site within the same region from one injection to the next [see Adverse Reactions (6)]. 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 available as:
• 10 mL vials
• 3 mL vials
• 3 mL HUMULIN N KwikPen (prefilled)

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 KwikPen or Syringe Between Patients
HUMULIN N KwikPens must never be shared between patients, even if the needle is changed. 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 Changes in Insulin Regimen
Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.3)] or hyperglycemia. These changes should be made cautiously and under close medical supervision and the frequency of blood glucose monitoring should be increased.

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.

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, propoxyphene, 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
Pregnancy Category B

Risk Summary
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control 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 HUMULIN N.

Human Data
While there are no adequate and well-controlled studies of HUMULIN 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.

Animal Data
Reproduction and fertility toxicity studies were not performed in animals.

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

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 (human insulin [rDNA origin] isophane suspension) is a human insulin suspension. 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 \( C_{257}H_{383}N_{65}O_{77}S_6 \) with a molecular weight of 5808.

HUMULIN N is a sterile white suspension. Each milliliter of HUMULIN N contains 100 units of insulin human, 0.35 mg of protamine sulfate, 16 mg of glycerin, 3.78 mg of dibasic sodium phosphate, 1.6 mg of metacresol, 0.65 mg of phenol, zinc oxide content adjusted to provide 0.025 mg zinc ion, and Water for Injection. 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.](image)

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 100 units per mL (U-100) is available as:

10 mL vials NDC 0002-8315-01 (HI-310)
3 mL vials NDC 0002-8315-17 (HI-313)
5 x 3 mL HUMULIN N KwikPen (prefilled) NDC 0002-8805-59 (HP-8805)

Each prefilled HUMULIN N KwikPen is for use by a single patient. HUMULIN N KwikPens must never be shared between patients, even if the needle is changed. Patients using HUMULIN N vials must never share needles or syringes with another person.

16.2 Storage and Handling
Protect from heat and light. Do not freeze. Do not use after the expiration date.

Not In-Use (Unopened) HUMULIN N Vials

Refrigerated
Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen.
Room Temperature
If stored at room temperature, below 86°F (30°C) the vial must be discarded after 31 days.

In-Use (Opened) HUMULIN N Vials

Refrigerated
Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen. Vials must be used within 31 days or be discarded, even if they still contain HUMULIN N.
Room Temperature
If stored at room temperature, below 86°F (30°C) the vial must be discarded after 31 days, even if the vial still contains HUMULIN N.

Not In-Use (Unopened) HUMULIN N KwikPen

Refrigerated
Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen.
Room Temperature
If stored at room temperature, below 86°F (30°C) the pen must be discarded after 14 days.

In-Use (Opened) HUMULIN N KwikPen

Refrigerated
Do NOT store in a refrigerator.
Room Temperature
Store at room temperature, below 86°F (30°C) and the pen must be discarded after 14 days, even if the pen still contains HUMULIN N. See storage table below:

<table>
<thead>
<tr>
<th></th>
<th>Not In-Use (Unopened)</th>
<th>Not In-Use (Unopened)</th>
<th>In-Use (Opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refrigerated</td>
<td>Room Temperature</td>
<td></td>
</tr>
<tr>
<td>10 mL vial</td>
<td>Until expiration date</td>
<td>31 days</td>
<td>31 days, refrigerated/room temperature</td>
</tr>
<tr>
<td>3 mL vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mL HUMULIN N</td>
<td>Until expiration date</td>
<td>14 days</td>
<td>14 days, room temperature. Do not refrigerate.</td>
</tr>
<tr>
<td>KwikPen (prefilled)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17  PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share a HUMULIN N KwikPen or Syringe Between Patients
Advise patients that they must never share a HUMULIN N KwikPen with another person, even if the needle is changed. 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.

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)].

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)].

Females with Reproductive Potential
Advise females of reproductive potential with diabetes to inform their doctor if they are pregnant or are contemplating pregnancy [see Use in Specific Populations (8.1)].

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)].

Expiration Date
Instruct patients not to use HUMULIN N after the printed expiration date.