PART III: CONSUMER INFORMATION

HUMULIN® N CARTRIDGES

insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

and HUMULIN® N KWIKPEN®

insulin isophane, human biosynthetic (rDNA origin)

Suspension for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when HUMULIN® N was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HUMULIN® N. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMULIN has been produced by recombinant DNA processes. It differs from animal-source insulins because it is structurally identical to the insulin produced by your body's pancreas and because of its unique manufacturing process.

HUMULIN N – NPH (insulin isophane, human biosynthetic, rDNA origin) has been modified so that it has a different duration of action than Regular insulin. The result is an intermediate-acting insulin with a slower onset of action than Regular insulin and a longer duration of activity of up to 24 hours.

HUMULIN N cartridges and HUMULIN N KwikPen (prefilled pens) are for subcutaneous (under the skin) injection only.

What the medication is used for:

HUMULIN N is an intermediate-acting insulin used to treat patients diagnosed with diabetes mellitus.

What it does:

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood sugar at a nearly normal level and to keep your urine as free of sugar as possible.

When it should not be used:

HUMULIN N should not be used if you are allergic to this drug or any of the ingredients used to formulate this medication.

HUMULIN N should not be used during episodes of hypoglycemia (too little sugar in the blood).

HUMULIN N should not be given intravenously or used for treatment of diabetic coma.

HUMULIN N should be used only if your doctor has prescribed NPH insulin (insulin isophane). You should not attempt to add any insulin to this cartridge or KwikPen (prefilled pen).

If HUMULIN N and HUMULIN R mixtures are prescribed, the individual insulins should be mixed as instructed in the amounts recommended by your doctor or purchased as mixtures in the ratio recommended if available.

What the medicinal ingredient is:

- HUMULIN N contains insulin isophane, human biosynthetic.

What the nonmedicinal ingredients are:

Glycerol, m-cresol, water for injection, hydrochloric acid, sodium hydroxide, phenol, zinc oxide, protamine sulfate and dibasic sodium phosphate.

What dosage forms it comes in:

HUMULIN N (NPH) is a sterile suspension containing insulin isophane, human biosynthetic (rDNA origin) for subcutaneous injection. It is available in:
- Cartridges, 3 mL
- KwikPens, 3 mL prefilled pen

HUMULIN N is also available in:
- Vials, 3 mL
- Vials, 10 mL

Other available HUMULIN products include HUMULIN R (Regular) and HUMULIN 30/70 (mixture of 30% Regular and 70% NPH). These types of insulin differ mainly in the time they require to take effect and in the length of time their action lasts. Your doctor has prescribed the type of insulin that he/she believes is best for you. **Do not use any other insulin except on your doctor's advice and direction**.

When you receive your insulin from the pharmacy, always check to see that:

1. The name HUMULIN appears on the carton and cartridge or KwikPen (prefilled pen) label and is followed by the proper letter designation and name for the insulin formulation: N-NPH.
2. The carton and cartridge or KwikPen label is correct for your type of insulin.
3. The human insulin is of rDNA origin.
4. The insulin strength is U-100.
5. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia (too little sugar in the blood) is the most common adverse effect of insulin products. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN (insulin, human biosynthetic) have reported that these early warning symptoms were less pronounced than they were with animal-source insulin.

Any change of insulin should be made cautiously and only under medical supervision.

Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

HUMULIN N should not be mixed with any other insulin unless clearly indicated and done under medical supervision.

Do not use HUMULIN N if you see lumps that float or that stick to the sides of the cartridge, or if the contents of the cartridge are clear and remain clear after the bottle is shaken or rotated.

- Each case of diabetes is different. Your doctor has told you which insulin to use, how much, and when and how often to inject it. This schedule has been individualized for you. Proper control of your diabetes requires close and constant cooperation with your doctor.
- You have been instructed to test your blood and/or your urine regularly for sugar. If your blood tests consistently show above or below normal sugar levels or your urine tests consistently show the presence of sugar, your diabetes is not properly controlled and you must let your doctor know.
- If you become ill from any cause, especially with nausea and vomiting, your insulin requirements may change. Test your blood and/or urine and notify your doctor at once.
- Always keep an extra supply of insulin. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.
- Never change from the insulin that has been prescribed for you to another insulin without instructions from your doctor. Changing the type, strength, source, or manufacturer of insulin can cause problems with your blood sugar control.
- Some patients taking HUMULIN N will require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may be made with the first dose or over a period of several weeks.
- Take precautions to avoid hypoglycemia while driving or operating machinery. This is particularly important in patients who have reduced awareness of the warning signs of hypoglycemia or who have frequent episodes of hypoglycemia.
- Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. Take caution in situations that require these abilities such as driving or operating machinery.
- Your doctor will tell you what to do if you miss a dose of insulin or miss a meal because of illness. If you miss a meal, as a substitute use sugar, sugar-sweetened candy, fruit juice, or sugar-sweetened beverage according to your doctor's instructions. If a shortage of insulin appears inevitable, a temporary reduction in the size of dose may be made, accompanied by limitation of food to two-thirds its usual quantity and a liberal increase in fluids of little or no food value, such as water, tea, coffee, broths, or clear soups.
- Consult your doctor if you notice anything unusual or have doubts about your condition or your use of insulin.
- Consult your doctor concerning adjustments in your insulin schedule if you travel across more than 2 time zones.

INTERACTIONS WITH THIS MEDICATION

There may be interactions between HUMULIN N and other medicines. Tell your doctor if you are taking any other medicine which has been prescribed for you or which you bought without a prescription.

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), thiazides (for high blood pressure or excessive fluid retention), corticosteroids, sympathomimetics (for example salbutamol used to treat asthma or pseudoephedrine for colds), danazol (medicine acting on ovulation), or thyroid replacement therapy. Insulin requirements may also be affected by diphenylhydantoin (used to treat epilepsy).

Insulin requirements may be decreased in the presence of agents such as oral medicines for the treatment of diabetes, salicylates (Aspirin*), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers and anabolic steroids.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

The presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

PROPER USE OF THIS MEDICATION

INSTRUCTIONS FOR USE

HUMULIN N cartridges are designed for use with Lilly injector systems (reusable pens).

HUMULIN N cartridges and KwikPens (prefilled pens) are not designed to allow any other insulin to be mixed in the cartridge.

HUMULIN N cartridges and KwikPens MUST NOT be refilled and are not designed for use with a traditional syringe.

Do not reuse needles. NEEDLES, CARTRIDGES, AND PENS MUST NOT BE SHARED with anyone including family members. Never share a HUMULIN KwikPen or cartridge, even if the needle on the delivery device is changed. You may pass on a serious infection or get a serious infection from the other person.

For guidance on the use of the KwikPen (prefilled, disposable pen) or Lilly's reusable pens, please refer to the separate Instructions for Use enclosed within the pen packaging.

Preparing the Dose:

1. Wash your hands.
2. Always examine the cartridge or KwikPen (prefilled pen) of HUMULIN N after removing from the box. Re-suspend the insulin by rolling the cartridge or KwikPen between your palms 10 times and inverting it 180° 10 times. HUMULIN N should look uniformly cloudy or milky after mixing. If not, repeat the re-suspension procedure as often as necessary. DO NOT USE if the white insulin particles stick to the bottom or sides of the cartridge or KwikPen or if there are clumps floating in the insulin, or if the cartridge or KwikPen is cracked or broken.
3. Carefully load the cartridge into the reusable pen following the manufacturer's directions.
4. Wipe the exposed rubber membrane on the metal cap end of the cartridge or KwikPen (prefilled pen) with an alcohol swab and attach the needle.
5. Carefully re-suspend the HUMULIN N by rolling the cartridge and pen in your hands 10 times and inverting it 180° 10 times. This must be performed each time before you give yourself an injection even after just loading the pen.
6. Prime the pen as directed by the manufacturer. If air bubbles are present, hold the pen with the needle pointing up and tap the side of the pen until the bubbles float to the top. With the pen still vertical, purge the needle with a 2 unit dose setting of the pen. Repeat until an insulin drop appears at the end of the needle. There may be small bubbles left; the air is harmless but too large an air bubble will affect the accuracy of the insulin dose administered.
7. Set the dose as instructed by your doctor. A gauge has been provided on the side of the cartridge to help you judge the amount of insulin remaining. The distance between each mark represents approximately 20 units for 3 mL cartridges or KwikPens.

Injecting the Dose:

1. Cleanse the skin, as instructed by your healthcare professional, where the injection is to be made. To avoid tissue damage, always change the site for each injection by at least 1.5 cm (0.5 inches) from the previous site, rotating sites on the body.
2. Insert the needle under the skin, as you were taught. **Do not** inject directly into a vein.
3. To inject the insulin, follow the instructions of the pen's manufacturer.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. Immediately after injection, remove the needle from the pen. This will ensure sterility and prevent leakage, re-entry of air and potential needle clogs.

Usual Dose

The dosage will be determined by your doctor, according to the requirements of each individual patient. HUMULIN N is for subcutaneous (under the skin) injection only. Do not inject into a vein.

Use in Pregnancy

Control of the blood sugar is vital to assure the birth of a healthy child. Normalization of the blood sugar should have occurred before conception and should continue throughout the pregnancy. Since pregnancy may make diabetes worse and because of the importance of good diabetic control, patients who contemplate pregnancy or who are pregnant should seek expert medical advice.

Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Overdose:

Hypoglycemia (Insulin Reaction):

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about by:

- Taking too much insulin
- Missing or delaying meals
- Exercising or working too hard just before a meal
- An infection or illness (especially with diarrhea or vomiting)
- A change in the body's need for insulin.

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Symptoms and Treatment:

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or "shakiness", rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention.

The patient's ability to concentrate and to 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 – see Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to HUMULIN have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low.

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a diabetic becomes delirious or mentally confused, or suffers from loss of memory or delusions, corn syrup diluted or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little sugar in the blood) is one of the most frequent adverse events experienced by insulin users (see Proper Use of this Medication - Overdose).

Diabetic Acidosis and Coma

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Allergy to Insulin

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

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 may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

Lipoatrophy or Lipohypertrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of

these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

This is not a complete list of side effects. For any unexpected effects while taking HUMULIN N, contact your doctor or pharmacist.

HOW TO STORE IT

Your unused HUMULIN N cartridges or KwikPens (prefilled pens) should be stored in the refrigerator (2°-8°C). DO NOT FREEZE. The cartridge or KwikPen of insulin that you are currently using does not have to be refrigerated but should be kept at a temperature below 25°C, away from direct heat and sunlight and protected from freezing. The cartridge of insulin currently in use should be left in the pen and may be carried with you. Cartridges or KwikPens in use or not refrigerated should be discarded after 28 days even if they contain insulin.

Inspection of Cartridge/KwikPen:

DO NOT USE a cartridge or KwikPen of HUMULIN N if after re-suspending, there are clumps floating in the insulin, or if solid white particles stick to the bottom or wall of the cartridge giving it a frosted appearance (re-suspend the insulin by following instruction 2 under Preparing the Dose). A cartridge or KwikPen that appears frosted or contains clumps, or is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE AFTER EXPIRY DATE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

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You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

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