PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Schedule D

NOVOLIN®GE

Insulin, Human Biosynthetic

Injectable Solution/Suspension, 3.5 mg (100 IU)

Manufacturer's Standard

Antidiabetic Agent

Novolin®**ge** Toronto ATC code: A10AB01, fast-acting

Novolin®**ge** NPH ATC code: A10AC01, intermediate-acting

Novolin®**ge** Premixed Insulin Preparations ATC code: A10AD01, intermediate- or long-acting combined with fast-acting

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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

4.4 Administration	03/2021
7 Warnings and Precautions	03/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Novolin®**ge** (Insulin, Human Biosynthetic) is indicated for:

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia.

When administered in appropriate regular doses to patients with diabetes mellitus and who follow a controlled diet and exercise program, Novolin®**ge** (Insulin, Human Biosynthetic) temporarily restores their ability to metabolize carbohydrates, protein and fats.

The Novolin®**ge** formulations differ with respect to onset, peak and duration of action. These times reflect averages and can vary depending upon the individual patient. The standard time action characteristics are as follows:

Novolin®**ge** Toronto (Insulin Injection, Human Biosynthetic) is a water-clear, colourless, neutral solution of human insulin with a short duration of action. The effect of Novolin®**ge** Toronto after subcutaneous administration begins after approximately ½ hour, is maximal between 2 ½ and 5 hours and terminates after approximately 8 hours.

Novolin®**ge** NPH (Insulin Isophane, Human Biosynthetic) is a cloudy, neutral suspension of human isophane insulin with an intermediate duration of action. The effect of Novolin®**ge** NPH begins after approximately 1 ½ hours, is maximal between 4 and 12 hours and terminates after approximately 24 hours.

Novolin®**ge** Premixed Insulin Preparations: Novolin®**ge** 30/70, Novolin®**ge** 40/60, Novolin®**ge** 50/50 are a series of Insulin, Human Biosynthetic mixtures containing Novolin®**ge** Toronto and Novolin®**ge** NPH, respectively, in the proportions indicated by the ratio in the product name. The Novolin®**ge** Premixed Insulin Preparations are dual-acting insulins. They have a biphasic formulation containing fast-acting and intermediate-acting insulin. The mixtures are cloudy, neutral suspensions with an intermediate duration of action. The strength of the initial effect is dependent on the amount of Novolin®**ge** Toronto in the mixture. The effect of Novolin®**ge** mixtures begins after approximately ½ hour, is maximal between 2 and about 12 hours and terminates after approximately 24 hours. Premixed insulin preparations are usually given once or twice daily when a rapid initial effect together with a more prolonged effect is desired.

Novolin®**ge** NPH insulin in vials may be mixed with Novolin®**ge** Toronto in order to meet the requirements of individual diabetics as determined by the physician.

Only Novolin®**ge** Toronto, using intravenous administration, should be used for the treatment of emergencies, such as diabetic coma and pre-coma, and in diabetics undergoing surgery. (See also *CONTRAINDICATIONS*)

1.1 Pediatrics

- Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Geriatrics (≥65 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Novolin®**ge** is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- During episodes of hypoglycemia.
- In patients who are hypersensitive to human insulin or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

- Novolin®**ge** NPH (Insulin Isophane, Human Biosynthetic) and Novolin®**ge** (Insulin, Human Biosynthetic) Premixed Insulin Preparations are never to be administered intravenously, or intramuscularly.
- Novolin®**ge** NPH (Insulin Isophane, Human Biosynthetic) and Novolin®**ge** (Insulin, Human Biosynthetic) Premixed Insulin Preparations are not suitable for the treatment of diabetic coma

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulins products, the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins. (see HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (see ENDOCRINE AND METABOLISM – HYPOGLYCEMIA)
- Any transfer of insulin products should be made cautiously and only under medical supervision. (see WARNINGS AND PRECAUTIONS)
- Some insulin products are short-acting insulin and are known for their rapid onset and short duration of action. The injection of such insulin products should be followed by a meal (within 30 minutes) (Novolin®**ge** Toronto). (see DOSAGE AND ADMINISTRATION)
- Short-acting insulins should be combined with longer-acting insulin to maintain adequate glucose control (Novolin®**ge** Toronto).
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision. (see WARNINGS AND PRECAUTIONS)
- Novolin®**ge** Toronto shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge. (see DOSAGE AND ADMINISTRATION)
- Novolin®**ge** NPH and Novolin®**ge** 30/70, Novolin®**ge** 40/60 and Novolin®**ge** 50/50 shall not be used if the resuspended liquid does not appear uniformly white and cloudy or if it has formed a deposit of solid particles on the wall of the vial or cartridge which is present after resuspending. (see DOSAGE AND ADMINISTRATION)
- Due to the risk of precipitation in some pump catheters, Novolin®**ge** Toronto is

not recommended for use in insulin pumps.
- Long-acting insulin products and/or suspensions as Novolin®**ge** NPH and Novolin®**ge** Premix MUST NOT be administered intravenously (IV) or be used in insulin infusion pumps.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Concomitant stress or illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. In these instances, patients should contact their physicians and carefully control their blood glucose.

4.2 Recommended Dose and Dosage Adjustment

Novolin®**ge** (Insulin, Human Biosynthetic) is made in one strength in Canada, 100 units per mL. The dosage is determined by the physician in accordance with the needs of the patient.

The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty in the young or due to obesity) and lower in patients with residual, endogenous insulin production.

Novolin®ge Toronto
Novolin®**ge** Toronto when used alone is usually given three or more times daily. Novolin®**ge** Toronto may also be used in combination with longer-acting insulins of equal purity to suit the needs of the individual patients. It may be given subcutaneously, intramuscularly or intravenously. The injection of Novolin®**ge** Toronto should be followed by a meal no later than 30 minutes after injection.

Novolin®ge NPH
Novolin®**ge** NPH is usually given once or twice daily. It is administered by subcutaneous injection.

Novolin®**ge** NPH may be used alone or mixed with fast-acting soluble insulin. In intensive insulin therapy the suspensions may be used as basal insulin (evening and/or morning injection) with fast-acting or rapid-acting insulin given at meals.

Novolin®ge Premixed Insulin Preparations
Novolin®**ge** 30/70, Novolin®**ge** 40/60, Novolin®**ge** 50/50 are usually given once or twice daily, especially when a strong initial effect is desired. They are administered by subcutaneous injection. The injection of Novolin®**ge** Premixed Insulins Preparations should be followed by a meal no later than 30 minutes after injection.

Dosage Adjustments
- Renal or hepatic impairment may reduce insulin requirement.
- Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet.
- In insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher.

The following are general prescribing guidelines:

New Patients
Although each patient must be assessed individually, initial stabilization on multiple injections of Novolin®**ge** Toronto is recommended. Following this, most patients will respond well to a regimen of Novolin®**ge** NPH once or twice daily. Usually small amounts of Novolin®**ge** Toronto are added to cover the morning and evening meals.

Alternatively, Novolin®**ge** Premixed Insulin Preparations may be given once or twice daily.

4.4 Administration

Before each injection, check that the right preparation is being used.

Novolin®ge in vials
A U-100 syringe should always be used. Failure to use the correct syringe can lead to dosage errors.

Novolin®ge Toronto
Insulin solution should not be used if it does not appear water-clear and colourless.

Novolin®ge NPH and Novolin®ge Premixed Insulin Preparations
An insulin suspension should not be used if it does not appear uniformly white and cloudy after re-suspension.

Novolin®**ge** NPH and Novolin®**ge** Premixed Insulin suspensions should not be used if the precipitate has become lumpy or granular in appearance or has formed a deposit of solid particles on the wall of the vial or cartridge. These insulin suspensions should also not be used if the contents remain clear after the vial or cartridge has been shaken carefully.

To avoid possible transmission of disease, Penfill® cartridge in insulin delivery systems must not be used by more than one person.

Insulin should not be used after the expiration date printed on the package.

Routine Injection Procedure

Syringes
If sterile disposable syringes and needles are not used, sterile glass syringes and appropriate sterile needles may be used.

- The surface of the vial-stopper and the site of injection should be wiped with a suitable antiseptic, such as alcohol, and allowed to dry.
- If only one insulin type is used, a volume of air equal to the dose of insulin to be injected is drawn into the syringe, and then introduced into the vial. The vial and syringe is turned upside down and the correct insulin dose is drawn into the syringe. Then the needle is removed from the vial, any air is expelled from the syringe and the dose is checked.
- Insulins of different types should be mixed only on the recommendation of the physician. The order of mixing of insulins and brand or model of syringe should not be changed,

otherwise dosage errors may result. This is because insulin hypodermic syringes may vary in the amount of space between the bottom line and the needle (dead space).

- The skin is pinched between the thumb and forefinger and the needle pushed into the fold at an angle of approximately 45 degrees. The insulin is injected under the skin (subcutaneously). Care should be taken not to inject into a muscle or vein. The needle is removed and the injection spot pressed gently for a few seconds to prevent any insulin seeping out.
- Successive injections at any one site should be avoided. The site of injection should be altered routinely as advised by the physician.

Insulin suspensions should be carefully shaken to ensure that the contents are uniformly mixed before injecting each dose.

Novo Nordisk Insulin Delivery Devices

Penfill® cartridges are only for use in Novo Nordisk insulin delivery devices described in the *DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING* section. If treatment involves two insulins in Penfill® cartridges, a separate Novo Nordisk Insulin Delivery Device should be used for each type of insulin.

Novolin®**ge** Penfill® must not be refilled.

Follow carefully the instructions for assembly and use of the Novo Nordisk Insulin Delivery Devices

- Before use check that the Penfill® cartridge is intact (e.g., no cracks). Do not use Penfill® if any damage is seen, or if more of the rubber stopper (plunger) is visible than equal to the width of the white barcode label.
- Check that sufficient insulin remains in the cartridge, prefilled syringe or delivery system to complete the injection and that the insulin is the correct preparation.
- Wipe the rubber membrane of the Penfill® cartridge and the site of injection with a suitable antiseptic, such as alcohol, and allow to dry.
- Remove the paper tab from a NovoFine®, NovoFine®Plus and/or a NovoTwist® needle and screw it firmly onto the Novo Nordisk Insulin Delivery Device. Pull off the outer and inner needle caps.
- For insulin suspensions, before insertion into Novo Nordisk Insulin Delivery Device, the Penfill® cartridge should be carefully shaken up and down at least 10 times (except for Novolin®**ge** Toronto Penfill® which is a clear solution), until the liquid appears uniformly white and cloudy. The glass ball inside the cartridge should move from one end to the other during mixing.
- Before each injection, Novo Nordisk Insulin Delivery Device with the inserted cartridge should be carefully shaken up and down at least 10 times (except for Novolin®**ge** Toronto which is a clear solution), until the liquid appears uniformly white and cloudy. The glass ball inside the cartridge should move from one end of the cartridge to the other during mixing.
- When making an injection using a Novo Nordisk insulin delivery device, allow the needle to remain under the skin for at least 6 seconds. Keep the push button fully depressed until after the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood or other body fluids into the needle or insulin reservoir.
- NovoFine®, NovoFine®Plus and/or NovoTwist® needles should be removed after each injection. If the needle is not removed, changes in ambient temperature can result in some liquid being expelled from the cartridge. In the case of insulin suspensions, removal of

supernatant liquid can cause an increase in insulin concentration (i.e., strength) within the cartridge, which can cause inaccurate dosing.

Novolin®**ge** Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

NovoFine®, NovoFine®Plus and/or NovoTwist® needles are designed for use with Novo Nordisk Insulin Delivery Devices.

Novolin®**ge** Toronto is usually administered subcutaneously by injection in the abdominal wall. The thigh, the buttocks or the deltoid region may also be used. Injection sites should always be rotated within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

Novolin®**ge** NPH are usually administered subcutaneously by injection in the thigh. If convenient, the abdominal wall, the buttocks or the deltoid region may also be used. Injection sites should always be rotated within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). Subcutaneous injection into the thigh results in a slower and less variable absorption compared to the other injection sites.

Novolin®**ge** Premixed Insulin Preparations are usually administered subcutaneously by injection in the thigh or abdominal wall. If convenient, the buttocks or the deltoid region may also be used. Injection sites should always be rotated within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

5 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

Mild episodes of hypoglycemia can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes always carry some sugar candy.

Severe hypoglycemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or

glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse. Hypokalemia must be corrected appropriately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Novolin®**ge** (Insulin, Human Biosynthetic) preparations are available in 10 mL vials and 3mL Penfill® cartridges. Novolin®**ge** preparations are available in the following presentations:

10 mL vials	3.0 mL Penfill® cartridges
Novolin®**ge** Toronto Novolin®**ge** NPH Novolin®**ge** 30/70	Novolin®**ge** Toronto Novolin®**ge** NPH Novolin®**ge** 30/70 Novolin®**ge** 40/60 Novolin®**ge** 50/50

Novo Nordisk Delivery devices are insulin delivery devices designed for use with Novolin®**ge** Penfill® insulin cartridges and NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Penfill®: Needles and Novolin®**ge** Penfill® in a Novo Nordisk Insulin Delivery Device should never be shared between patients, even if the needle is changed.

Non-medicinal ingredients:

Novolin®**ge** Toronto
Glycerol, metacresol, zinc chloride and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH.

Novolin®**ge** NPH
Disodium phosphate dihydrate, glycerol, metacresol, phenol, protamine sulphate, zinc chloride and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH.

Novolin®**ge** 30/40/50
Disodium phosphate dihydrate, glycerol, metacresol, phenol, protamine sulphate, zinc chloride and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Novolin®ge Toronto Subcutaneous, intramuscular, or intravenous injection	injectable solution, 3.5 mg (100 IU)	Zinc chloride, glycerol, metacresol, sodium hydroxide and/or hydrochloric acid, water for injections
Novolin®ge NPH Subcutaneous injection	injectable suspension 3.5 mg (100 IU)	Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide and/or hydrochloric acid, protamine sulphate, water for injections
Novolin®ge 30/70 **Novolin®ge 40/60** **Novolin®ge 50/50** Subcutaneous injection	injectable suspension 3.5 mg (100 IU)	Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide and/or hydrochloric acid, protamine sulphate, water for injections

Description

The active substance in Novolin®**ge**, Insulin, Human Biosynthetic, is a polypeptide that is structurally identical to natural human insulin. Insulin human is produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with all insulin products, the duration of Novolin®**ge** NPH, Novolin®**ge** Toronto and Novolin®**ge** Premixed Insulin preparations may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including Insulin), can cause heart failure and oedema. The combination of Insulin with a TZD is not indicated for the treatment of Type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including Novolin®**ge**, is contemplated.

Never Share a Novolin®ge Penfill® in a Novo Nordisk Insulin Delivery Device Between Patients:

Novolin® **ge** Penfill® in a Novo Nordisk Insulin Delivery Device should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne

pathogens.

Avoidance of accidental mix-ups/medication errors
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Novolin®**ge** Toronto, Novolin®**ge** NPH, or Novolin®**ge** Premixed Insulin Preparations and other insulin products.

Carcinogenesis and Mutagenesis

See Part II – Scientific Information – NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia
As with other insulins, hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. Such reactions following treatment with Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations are mostly mild and easily managed.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.
Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. (see ADVERSE REACTIONS and HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions, loss of consciousness, temporary or permanent impairment of brain function, or, in extreme circumstances, even death which can occur without recognizable symptoms.

Some people may not recognize when their blood sugar drops low.

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 be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Glucose monitoring is recommended for all patients with diabetes.

Hepatic/Biliary/Pancreatic

There is no experience of the treatment with Novolin®**ge** patients with hepatic impairment. As with other insulins, Novolin®**ge** requirements may need to be adjusted in patients with hepatic impairment (see CLINICAL PHARMACOLOGY – Pharmacokinetics). As Novolin®**ge** is used for treatment of diabetes mellitus, there is experience with treatment of pancreatic impairment concerned with diabetes mellitus, but not with other types pancreatic impairment.

Hyperglycemia

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

Hypokalemia

All insulin products, including Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin , cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. 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, patients receiving intravenously administered insulin or patients losing potassium through other means (e.g., diarrhea)]. (see ADVERSE REACTIONS)

Immune

Local Allergic Reaction

As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in Novolin®**ge** NPH, Novolin®**ge** Toronto and Novolin®**ge** Premixed Insulin. (see Skin and subcutaneous tissue disorders)

Systemic Allergic Reaction

Systemic allergic reactions have not been reported during the clinical development of Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations. Systemic allergic reactions have rarely occurred with Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations as with other insulin treatment. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be

life threatening.

Antibody Production
Immune responses can occur in response to insulin. This may be associated with elevated IgG levels however this does not appear to affect HbA1c.

Human insulin is known to be antigenic, with low titres of antibodies developing in most patients (up to 80%). The effect of insulin antibodies on insulin pharmacokinetics, with the presence of binding IgG in serum, may delay time to peak levels of free insulin. Antibodies may be cross-reactive between different types of insulin.

Mixing of Insulins
Mixing of Novolin®**ge** Premixed Insulin (30/70, 40/60 and 50/50) preparations is generally not recommended. Mixing of one insulin formulation with another insulin formulation may change the pharmacokinetic and/or pharmacodynamic profile of action of the combined mixture in an unpredictable manner.

Insulin should only be mixed as directed by the physician. Novolin®**ge** Toronto should be mixed in the syringe with insulin of equal purity (e.g., Novolin®**ge** NPH). The order of mixing and brand or model of syringe should be specified by the physician. In general, when longer-acting insulins are mixed with short-acting soluble insulins, the short-acting insulin should be drawn into the syringe first.

Monitoring and Laboratory Tests

In patients with diabetes mellitus optimised metabolic control delays the onset and slows the progression of late diabetic complications. Optimised metabolic control, including glucose monitoring, is therefore recommended.

Renal

There is no experience of the treatment with Novolin®**ge** patients with renal impairment. As with other insulins, Novolin®**ge** requirements may need to be adjusted in patients with renal impairment (see CLINICAL PHARMACOLOGY – Pharmacokinetics).

Reproductive Health: Female and Male Potential

- **Function**

  There is no information available on teratogenicity of human insulin products.

- **Reproduction**

  There is no information available on teratogenicity of human insulin products.

Transferring Patients from Other Insulins
When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may have changed or become less pronounced than those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g. regular, NPH or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral anti-diabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first weeks or months and under medical supervision.

Patients currently on self-prepared mixtures should be transferred to the closest available Novolin®**ge** fixed mixture preparation.

Any patient on a total daily dose of greater than 100 units of insulin may need to be closely monitored by the physician when transferring to a different insulin preparation, preferably in hospital.

Skin and subcutaneous tissue disorders

Subcutaneous administration of insulin products, including Novolin®ge can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (thickening of adipose tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

7.1 Special Populations

7.1.1 Pregnant Women

During pregnancy and lactation, diabetes may become more difficult to manage. However, optimal metabolic control not only during pregnancy, but also prior to conception has proven to be beneficial in reducing the risk of miscarriage and malformation of the fetus. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. Diabetics who have become pregnant or desiring to become pregnant should consult their doctor for advice. Insulin ingested with the mother's milk has not been associated with any risk for the baby.

7.1.2 Breast-feeding

There are no restrictions on the treatment of diabetes with Novolin®**ge** Toronto, Novolin®**ge** NPH, or Novolin®**ge** Premixed Insulin Preparations during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the dosage of Novolin®**ge** Toronto, Novolin®**ge** NPH, or Novolin®**ge** Premixed Insulin Preparations and/or diet may need to be adjusted.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No data is available.

Others
The presence of diseases such as Acromegaly, Cushing's syndrome, Hyperthyroidism and Pheochromocytoma can complicate the control of diabetes mellitus.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

At institution of insulin therapy, oedema and refraction anomalies may occur. These conditions are usually of a transitory nature.

Occasionally, transitory redness, swelling, and itching at the injection site can either be caused by the insulin as such or the preservative used in the preparation. These reactions will often be of a non-specific and transitory nature. In very rare cases, lipoatrophy or lipohypertrophy can develop at the injection site. Patients should rotate the injection site to avoid this side effect.

If, in exceptional cases, redness at the injection site quickly spreads as rash and blisters over the whole body, immediate medical attention is required. This is extremely rare with the use of Novolin®**ge** (Insulin, Human Biosynthetic).

Hypoglycemia is the most frequent undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimes. Therefore, no specific frequency can be presented. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events were reported in three comparative studies. In one study, one patient in the Novolin®**ge** treatment group experienced pain at the injection site. In one study, two patients in the Novolin®**ge** treatment group had suspected insulin allergy. However, skin tests showed no evidence of a response to either Novolin®**ge** or Novolin®, Insulin Human Semi-synthetic (ss). One patient receiving Novolin®**ge** was hospitalized with mild ketoacidosis but fully recovered after hospital treatment. In one study seven patients receiving Novolin®**ge** and two Novolin® (ss) reported headaches. There was no clear etiology for these. In addition, eight patients receiving Novolin®**ge** and one receiving Novolin® (ss) experienced pain and burning after injection. These latter findings are difficult to interpret as they are currently seen in clinical practice. They were not related to insulin allergy except in one patient who tested positive to protamine.

8.3 Less Common Clinical Trial Adverse Reactions

No clinical trials, where human insulin has been used as the primary investigational medicinal

products (IMP), have been conducted recently. However, human insulin has been used as comparator or concomitant medication in clinical trials where other products have been the IMP.

The overall profile of adverse events – frequency, severity or type of adverse events – reported on human insulin during these clinical trials, has not caused any safety concern. No specific clustering of less common adverse drug reactions have been seen and no changes to the core safety information have been necessary for safety reasons.

8.5 Post-Market Adverse Reactions

The following are adverse drug reactions based on post-marketing experience.

Metabolism and Nutrition Disorders
Rare (<1/1000)
Change in blood glucose: hypoglycemia / hyperglycemia.

Hypoglycemia:
Symptoms of hypoglycemia usually occur suddenly. They may include cold sweats; cool pale skin; fatigue; nervousness or tremor; anxiousness; unusual tiredness or weakness; confusion; difficulty in concentration; drowsiness; excessive hunger; vision changes; headache; nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Hyperglycemia:
Usually the first symptoms of hyperglycemia set in gradually, over a period of hours or days. They include thirst; increased frequency of urination; nausea; vomiting; drowsiness; flushed dry skin; dry mouth; loss of appetite as well as acetone odour of breath.

In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis which is potentially lethal.

Immune system disorder
Uncommon (>1/1000, <1/100) – Urticaria, rash.
Very rare (<1/10 000) – Anaphylactic reactions.
Symptoms of generalized hypersensitivity may include generalized skin rash; itching; sweating; gastrointestinal upset; angioneurotic oedema; difficulties in breathing; palpitation; reduction in blood pressure and fainting/loss of consciousness. Generalized hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Uncommon (>1/1000, <1/100) – Peripheral neuropathy for Novolin®**ge** Toronto and Novolin®**ge** Premix Insulin.
Very rare (<1/10 000) – Peripheral neuropathy for Novolin®**ge** NPH.
Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Uncommon (>1/1000, <1/100) – Diabetic retinopathy for Novolin®**ge** NPH and Novolin®**ge** Premix Insulin.
Very rare (<1/10 000) – Diabetic retinopathy for Novolin®**ge** Toronto.

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

Very rare (<1/10 000) – Refraction disorders for Novolin®**ge** NPH and Novolin®**ge** Premix Insulin.
Uncommon (>1/1000, <1/100) – Refraction disorders for Novolin®**ge** Toronto.
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually transitory in nature.

Skin and subcutaneous tissue disorders
Uncommon (>1/1000, <1/100) – Lipodystrophy.
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon (>1/1000, <1/100) - Injection site reactions.
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are usually transitory and disappear during continued treatment.

Uncommon (>1/1000, <1/100) – Oedema.
Oedema may occur upon initiation of insulin therapy. These symptoms are usually transitory in nature.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

As with insulin in general, concomitant use of other drugs may influence insulin requirements.

9.4 Drug-Drug Interactions

The following substances may reduce the insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulphonamides and alcohol.

The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.

Octreotide/lanreotide may either increase or decrease insulin requirements.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with Novolin®**ge** is not indicated. (see WARNINGS AND PRECAUTIONS)

9.5 Drug-Food Interactions

Please refer to CLINICAL PHARMACOLOGY, Mechanism of Action and DOSAGE AND ADMINISTRATION for interactions with food and timing of food consumption, respectively.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Changes in insulin therapy or changes in lifestyle (i.e. diet, exercise/physical activity) may require a change in dosage.

Patients should be informed about the potential advantages and disadvantages of Novolin®**ge** therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using Novolin®**ge** NPH, Novolin®**ge** Toronto or Novolin®**ge** Premixed Insulin preparations to obtain optimal glycemic control.

Female patients should be advised to discuss with their physician if they intend to or if they become pregnant.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The primary activity of Novolin®**ge** Toronto, Novolin®**ge** NPH, Novolin®**ge** 30/70, Novolin®**ge** 40/60 and Novolin®**ge** 50/50 is the regulation of glucose metabolism. The blood glucose lowering effect of insulins, inlcuding Novolin®**ge** Toronto, Novolin®**ge** NPH, Novolin®**ge** 30/70, Novolin®**ge** 40/60 and Novolin®**ge** 50/50 is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

10.2 Pharmacodynamics

Novolin®**ge** Toronto – fast-acting insulin. Onset of action is within ½ hour, reaches maximum effect within 1.5-3.5 hours and entire time of duration is approximately 7-8 hours.

Novolin®**ge** NPH – intermediate-acting insulin. Onset of action is within 1½ hour, reaches maximum effect within 4-12 hours and the entire time of duration is approximately 24 hours.

Novolin®**ge** Premixes – dual-acting insulin. Onset of action is within ½ hour, reaches a maximum effect within 2-8 hours and the entire time of duration is up to 24 hours.

This profile is similar in children and adolescents.

10.3 Pharmacokinetics

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin is therefore affected by significant intra- and inter-individual variation.

In general, the absorption after subcutaneous administration of Novolin®**ge** products is different, dependant on the injection site. The absorption is fastest from the abdomen and slowest from the thigh. An approximate action profile following subcutaneous administration indicates:

	Novolin®ge Toronto	**Novolin®ge NPH**	**Novolin®ge Premixed**
Onset	0.5 hour	1.5 hours	0.5 hour
Maximum	1.5-3.5 hours	4-12 hours	2-8 hours
Duration	approx. 7-8 hrs	approx. 24 hours	up to 24 hours

Absorption

Novolin®ge Toronto
The maximum plasma concentration is reached within 1.5-2.5 hours after subcutaneous administration.

Novolin®ge NPH
The maximum plasma concentration of the insulin is reached within 2-18 hours after subcutaneous administration.

Novolin®ge Premixed Insulin Preparations
The absorption profile is due to the product being a mixture of insulins with fast and protracted absorption respectively. The maximum plasma concentration of the fast-acting insulin is reached within 1.5-2.5 hours after subcutaneous administration.

Distribution:

Novolin®**ge** Toronto, Novolin®**ge** NPH, Novolin®**ge** Premixed Insulin Preparations.

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism:

Novolin®**ge** Toronto, Novolin®**ge** NPH, Novolin®**ge** Premixed Insulin Preparations.

Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination

The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{1/2}$) is therefore a measure of the terminal absorption rather than of the

elimination *per se* of insulin from plasma (insulin in the blood stream has a $t_{1/2}$ of a few minutes).

Novolin®ge Toronto
Trials have indicated a $t_{1/2}$ of about 2-5 hours.

Novolin®ge NPH and Premixed Insulin Preparations
Trials have indicated a $t_{1/2}$ of about 5-10 hours.

Special Populations and Conditions

No specific pharmacokinetic data on Novolin®**ge** products in special patient populations are available. The approved indication covers "Treatment of insulin requiring diabetics" (see *Indications and Clinical* use) without any restrictions regarding age, gender or ethnicity of the diabetes patients.

Dosage is individual and is determined by the physician in accordance with the needs of the patients. However, renal or hepatic impairment may reduce insulin requirements.

Detailed Pharmacology

Animal Pharmacology
Novolin®ge, Insulin, Human Biosynthetic was tested in a number of pharmacological models in order to exclude secondary effects different from those which could be expected with Novolin®, Insulin, Human Semi-synthetic (ss). In a similar series of tests, Novolin® (ss) was compared with pork insulin of equal purity in doses up to 50 U/kg. The models used for both comparisons covered a wide range of target systems and can be seen in the following table:

Table 2 - Animal pharmacological models tested to exclude secondary effects from Novolin®ge different from those expected with Novolin® (ss).

Target System	Pharmacological Model		Secondary Effects Seen (Yes/No)	
			Novolin® ge compared with Novolin® (ss)	Novolin® (ss) compared with pork insulin
1. Central Nervous System	Mice	Ataxia (animex and rotarod) and narcosis potentiation	Yes	Yes
2. Autonomic Nervous System	Cat	Ganglionic Transmission	No	No
3. Neuromuscular Transmission	Rat	Tibial nerve-gastrocnemius muscle preparation	No	No
4. Cardiovascular	Cat	General Hemodynamics, respiration and ECG	No	No
	Rat (conscious)	Blood pressure	No	No
5. Kidneys	Rat	Diuresis and antidiuresis	No	Yes
6. Liver	Pig	Bromsulfophthalein test	No	No
7. Blood Sugar	Rat	Effects on streptozocin induced diabetes	Yes	Yes

Target System	Pharmacological Model		Secondary Effects Seen (Yes/No)	
			Novolin® ge compared with Novolin® (ss)	**Novolin® (ss) compared with pork insulin**
8. Isolated Smooth Muscle Preparations	Guinea-Pig	Illuem stimulated with acetylcholine, histamine, serotonim and nicotine	No	No
	Guinea-Pig	Vas deferens stimulated with noradrenaline (concentration of the insulins 50 U/l)	No	No

When comparing Novolin®**ge** and Novolin® (ss), effects were seen in two of the tests (1 and 7). When comparing Novolin® (ss) and pork insulin, in addition to tests 1 and 7, effects were also seen in test 5. This may be due to the dose given or minor differences in experimental design. In all cases, these effects were the same for the two insulin preparations being compared. In other tests no effects were observed with any of the insulin preparations being compared. In other tests no effects were observed with any of the insulin preparations. The immunogenicity of Novolin®**ge** was compared with Novolin® (ss) insulin. The immunization was performed in rabbits with 20 IU per injection in incomplete Freund's adjuvant. No statistically significant difference between the immunogenicity of Novolin®**ge** and Novolin® (ss) insulins was found.

Human Pharmacology

Owens compared the bioavailability of Novolin-Toronto® semi-synthetic with Novolin®**ge** Toronto following subcutaneous injection in ten normal male volunteer subjects. The study was undertaken with both U40 and U100 insulin preparations. All subjects participated in four separate study days, approximately one week apart. The subjects received, in random order, 0.1 IU/kg body weight of the following: Novolin®**ge** Toronto 40 IU/ml, Novolin®**ge** Toronto 100 IU/ml, and the equivalent Novolin® (ss) insulin preparations following a ten-hour overnight fast prior to each study day. Only the results from the study with U100 insulin are reviewed. No statistically significant differences were observed in terms of plasma insulin and plasma glucose profiles between the two insulin preparations following subcutaneous injections. Plasma glucose and immunoreactive insulin levels were virtually identical. The two comparative preparations were well tolerated by all subjects and no untoward side effects were reported.

Table 3 - Human pharmacological model tested to exclude secondary effect from Novolin®ge that differ from those expected with Novolin® (ss).

Target System	Pharmacological Model		Secondary Effects Seen (Yes/No)	
			Novolin® ge compared with Novolin® (ss)	**Novolin® (ss) compared with pork insulin**
Thrombocytes	Man	In vitro aggregation (In this test concentrations up to 7.3 U/mL were	No	No

Target System	Pharmacological Model		Secondary Effects Seen (Yes/No)	
			Novolin® ge compared with Novolin® (ss)	Novolin® (ss) compared with pork insulin
		used)		

11 STORAGE, STABILITY AND DISPOSAL

Novolin®**ge** that is not being used should be stored in a refrigerator between 2ºC-10ºC not in or too near the freezer section or cooling element. Do not freeze. Insulin preparations which have been frozen must not be used.

After removing the vial of Novolin®**ge** NPH and Novolin®**ge** 30/70 from the refrigerator it is recommended to allow it to reach room temperature before resuspending the insulin as instructed for first time use.

After removing the Novolin®**ge** NPH Penfill® cartridge and Novolin®**ge** Penfill® cartridge Premixed insulin preparation, (Novolin®**ge** 30/70, Novolin®**ge** 40/60, Novolin®**ge** 50/50) from the refrigerator it is recommended to allow it to reach room temperature before resuspending the insulin as instructed for first time use.

During use: Do not refrigerate. Do not store Novolin®**ge** above 25ºC (vial) or 30ºC (Penfill®).

Novolin®**ge** Penfill® when used in Novo Nordisk Delivery Devices can be in-use or carried as a spare for up to one month at room temperature (not above 30ºC). When in use, Novo Nordisk insulin delivery devices are to be maintained at room temperature.

Keep the vial or cartridge in the outer carton in order to protect the insulin from light. Keep the pen cap on Penfill® in order to protect the insulin from light. Protect from excessive heat and light.

Insulin should not be used after the expiry date printed on the package.

12 SPECIAL HANDLING INSTRUCTIONS

For intravenous use, infusion systems with Novolin®**ge** Toronto at concentrations from 0.05 IU/ml to 1.0 IU/ml insulin human in the infusion fluids: 0.9% sodium chloride, 5% dextrose and 10% dextrose inclusive 40 mmol/L potassium chloride, using polypropylene infusion bags, are stable at room temperature for 24 hours. Although stable over time, a certain amount of insulin will initially be absorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the infusion.

Penfill®: Cartridges should only be used in combination with products that are compatible with them and allow the cartridge to function safely and effectively.

Penfill®: Needles and Novolin®**ge** Penfill®: must not be shared. The container must not be refilled.

Insulin preparations which have been frozen must not be used.

Insulin solutions should not be used if they do not appear water-clear and colourless.

Insulin suspensions should not be used if they do not appear uniformly white and cloudy after resuspension.

Novolin®**ge** should not be used in insulin pumps for continuous subcutaneous insulin infusion.

Penfill®: The patient should be advised to discard the needle after each injection.

After removing Novolin®**ge** NPH and Novolin®**ge** 30/40/60 vial/ Penfil®: from the refrigerator, it is recommended to allow vial/Penfil®: to reach room temperature before resuspending the insulin as instructed for first time use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

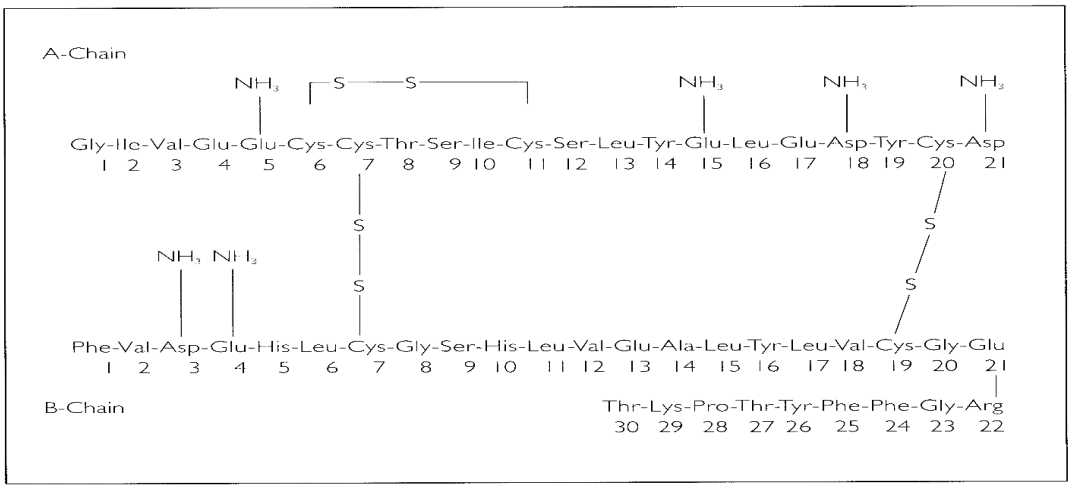
Proper name: Insulin, Human Biosynthetic

Chemical name: TBC

Molecular formula and molecular mass: $C_{257}\ H_{383}\ N_{65}\ O_{77}\ S_6$, approximately 6000

Structural formula:

Figure 1. Human insulin - molecular structure.



Physicochemical properties:

Description:
Novolin®**ge** Toronto is a water-clear, colourless, aqueous solution of human insulin.

Novolin®**ge** NPH is a cloudy, white, aqueous suspension of human insulin.

Novolin®**ge** Premixed Insulin Preparations are cloudy, white, aqueous suspension of human insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

The homogeneity of Novolin®**ge** (Insulin, Human Biosynthetic) has been confirmed by amino acid analysis, disc electrophoresis, gel filtration and reverse phase HPLC.

The structure of Novolin®**ge** has been confirmed by chain separation, amino acid composition, enzymatic degradation and Edman degradation.

Product Characteristics
Novolin®**ge** Insulin, Human Biosynthetic is produced by recombinant DNA technology, using *Saccharomyces cerevisiae* (baker's yeast). During fermentation, the organism secretes a single peptide chain insulin precursor directly into the growth medium. The insulin precursor is then converted to human insulin via an enzyme-mediated reaction and subsequently purified. Novolin®**ge** is purified to a high degree resulting in no detectable (less than 1 ppm by weight of dry insulin) immunoreactive peptides derived from *Saccharomyces cerevisiae* as determined by enzyme linked immunoabsorbent assay.

Pharmaceutical standard: Manufacturer's Standard

14 CLINICAL TRIALS

***NOTE**:* There have been no clinical trials conducted with human insulin since 2002.

14.1 Trial Design and Study Demographics

Clinical studies have been designed not only to compare the safety and efficacy of Novolin®**ge** with Novolin® (ss) insulins, but also to screen for the formation of antibodies to *S. cerevisiae.* In order to do this a very sensitive ELISA technique has been developed. Evaluation of sera from 216 healthy volunteers without any history of atopy has been used to establish a normal range for antibodies to yeast and to provide a reference for comparison with samples from clinical trials with Novolin®**ge**.

Fourteen clinical studies investigating the safety and efficacy of Novolin®**ge** have been undertaken. All studies were of twelve months duration. A total of 396 diabetic patients, all previously treated with Novolin® (ss), completed their respective studies. One study was uncontrolled and sequential. Twelve were open, randomized, parallel, asymmetrical comparisons of Novolin®**ge** with the corresponding Novolin® (ss) preparations employing a similar protocol. One study was a multicentre, double blind, randomized, parallel, asymmetrical comparison of Novolin®**ge** with the corresponding Novolin® (ss) preparations.

The safety and efficacy of treatment with a series of premixed preparations of Novolin®**ge** Toronto and Novolin®**ge** NPH was compared with individual mixtures of biosynthetic human insulin manufactured by Eli Lilly in a 12-week crossover study of 38 insulin requiring diabetics. Metabolic control (as judged by HbA1c), 8 point blood glucose profiles (laboratory and home

monitored), fasting blood sugar, occurrence and severity of hypoglycemic episodes, and complaints were recorded at predetermined intervals

14.2 Study Results

No significant differences were found between the two groups for mean 8 point blood glucose profiles (laboratory or home monitored), fasting blood glucose, or the occurrence of hypoglycemic episodes at week 6 or week 12 (crossover and completion). Metabolic control, as judged by HbA1c, remained unchanged between the 2 study groups irrespective of treatment order and no significant differences were found between the 2 groups at week 6 or week 12.

Two studies evaluated the bioequivalence of four different Novolin®**ge** premixed preparations and fresh admixtures of Novolin®**ge** Toronto / Novolin®**ge** NPH of similar proportions in 12 normal volunteers. In each study the serum concentration of immunoreactive insulin, C-peptide and blood glucose were compared after subcutaneous injection of 12 units according to a randomized 4-way crossover design. Bioequivalence was concluded to exist between all four premixed Novolin®**ge** preparations and the comparable admixture of Novolin®**ge** Toronto and Novolin®**ge** NPH as assessed by T_{max}, C_{max}, and AUC.

In both studies some subjects experienced hypoglycemia after administration of insulin especially in the study with Novolin®**ge** 40/60 and Novolin®**ge** 50/50. However, there were no differences between the premixed insulins and the admixtures in this regard. This is not unexpected in view of the proportion of regular insulin given and the fact that the subjects were fasting.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Animal Toxicity

Table 4 - Details of Animal Toxicity Studies.

	Animal Species			
	Mice and Rats	**Rats**	**Rabbits**	**Beagles**
Objective	Compare Novolin®**ge** (Insulin, Human Biosynthetic) with Novolin®(ss) (Insulin, Human Semi-synthetic) insulin	Compare Novolin®**ge** (Insulin, Human Biosynthetic) with Novolin® (ss) (Insulin, Human Semi-synthetic) insulin		Inject 3.0 U/kg/day over a 13 week period.
Route	Subcutaneous	Subcutaneous	Intermuscular injection	Subcutaneous Injection
Dosage Regimen	Acute	4 week		13 week Period

	Animal Species			
	Mice and Rats	**Rats**	**Rabbits**	**Beagles**
Results	No differences observed between Novolin®**ge** and Novolin® (ss)	No differences observed between Novolin®**ge** and Novolin® (ss)		No evidence of toxicity

Local irritation in rabbits after intermuscular injection with Novolin®**ge** was similar to that caused by isotonic saline.
Novolin®**ge** has been shown to be pyrogen free.

Carcinogenicity
Preclinical data with Novolin®**ge** reveal no special hazard for humans based on conventional studies of carcinogenic potential.

Mutagenicity
In a series of sensitive tests designed to evaluate mutagenic activity Novolin®**ge** has been shown to be non-mutagenic. Preclinical data with Novolin®**ge** reveal no special hazard for humans based on conventional studies of genotoxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NOVOLIN®GE TORONTO

Penfill®/vial

Insulin Injection

Human Biosynthetic

Read this carefully before you start taking **Novolin®ge Toronto** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Novolin®ge Toronto**.

This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist. If you have trouble reading this, ask a family member or a friend for help.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin including Novolin®ge.
- If hypoglycemic or hyperglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Novolin®ge Toronto should be given before a meal because of the fast onset of action (start of the meal should be within 30 minutes of injection).
- Novolin®ge Toronto should not be used if it is not water-clear and colourless. Due to the risk of precipitation in some pump catheters, Novolin®ge Toronto is not recommended for use in insulin pumps.

What is Novolin®ge Toronto used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does Novolin®ge Toronto work?

Novolin®ge Toronto is human insulin used to treat diabetes.

Novolin®ge Toronto is an antidiabetic agent used for the treatment of diabetes mellitus as it reduces the level of sugar in the blood and urine. To control your diabetes, your doctor has prescribed Novolin®ge Toronto injections.

Novolin®ge Toronto is a fast-acting insulin. This means that it will start to lower your blood sugar about ½ an hour after you take it, and the effect will last for approximately 8 hours. Novolin®ge Toronto is often given in combination with longer-acting insulin products.

What are the ingredients in Novolin®ge Toronto?

Medicinal ingredients: The active ingredient in Novolin®ge Toronto is Insulin Injection, Human Biosynthetic, (Regular). Novolin®ge Toronto is a solution for injection containing Biosynthetic Human Insulin produced by recombinant DNA methods using S. cerevisiae (baker's yeast) and followed by unique purification processes. Human Insulin (biosynthetic) is structurally identical to natural human insulin.

Non-medicinal ingredients: Zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

Novolin®ge Toronto comes in the following dosage forms:

Novolin®ge Toronto is available from Novo Nordisk Canada in the following formats:

- Novolin®ge Toronto 10 mL vial
- Novolin®ge Toronto Penfill® 3 mL cartridge

Novolin®ge Toronto Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Novolin®ge Toronto Penfill® insulin cartridges in combination with products that do not meet the same specifications or quality standards as NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Do not use Novolin®ge Toronto if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see 'What are possible side effects from using Novolin®ge Toronto?' for more about hypoglycemia).
- You are allergic (hypersensitive) to Insulin, Human Biosynthetic, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see 'What are possible side effects from using Novolin®ge Toronto?').
- In insulin infusion pumps.
- The Penfill® cartridge or the Novo Nordisk Insulin Delivery Device containing the insulin is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The protective cap on the vial is loose or missing. Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- The insulin has not been stored correctly or if it has been frozen (see 'How to store Novolin®ge Toronto?').
- The insulin does not appear water-clear and colourless.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Novolin®ge Toronto. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) watch for signs your need for insulin may change as your blood sugar level may rise or fall.

- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemia coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypoglycemic reactions or if you find it hard to recognize hypoglycemias.

Before you travel, check with your physician or pharmacist on the availability of Novolin®ge Toronto insulin in other countries. If possible, bring enough Novolin®ge Toronto with you on your trip.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

Other warnings you should know about:

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)

- Other medicines for the treatment of diabetes.
- Monoamine oxidase inhibitors (MAOI) (used to treat depression).
- Beta-blockers (used to treat high blood pressure).
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure).
- Salicylates (used to relieve pain and lower fever).
- Anabolic steroids (such as testosterone).
- Sulphonamides (used to treat infections).

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)

- Oral contraceptives (birth control pills).
- Thiazides (used to treat high blood pressure or excessive fluid retention).
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation).
- Thyroid hormones (used to treat thyroid gland disorders).
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma).
- Growth hormone (medicine for stimulation of skeletal and somatic growth and

pronounced influence on the body's metabolic processes).
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Novolin®ge Toronto:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

Before using Novolin®ge Toronto
- Check the label to make sure you have the right type of insulin.
- Remove the protective cap [vial].
- Always check the Penfill® cartridge, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1-800-465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- Always use a new needle for each injection to prevent contamination. [Penfill®]
- Do not share your Novolin®ge Penfill® in a Novo Nordisk Insulin Delivery Device with another person, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.

Do not refill a Novolin®ge Toronto Penfill® insulin cartridge.

Novolin®ge Toronto Penfill® cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices NovoFine®, NovoFine®Plus and/or NovoTwist® needles as part of The All-In-One System®.

If you are treated with Novolin®ge Toronto Penfill® insulin and another insulin in Penfill® cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

As a precautionary measure, you should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin,

such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted or thickened area (see 'How to take Novolin®ge Toronto'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Injecting Novolin®ge Toronto on its own

- Draw air into the syringe, in the same amount as the dose of insulin you need.
- Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
- Turn the vial and syringe upside down.
- Draw the right dose of insulin into the syringe.
- Pull the needle out of the vial.
- Make sure there is no air left in the syringe: point the needle upwards and push the air out.
- Check that you have the right dose.
- Inject immediately.

Mixing Novolin®ge Toronto with intermediate-acting insulin

- Roll the vial of intermediate-acting insulin between your hands. Do this until the liquid is uniformly white and cloudy.
- Draw as much air into the syringe as the dose of intermediate-acting insulin you need. Inject the air into the intermediate-acting insulin vial, then pull out the needle.
- Draw as much air into the syringe as the dose of Novolin®ge Toronto you need. Inject the air into the Novolin®ge Toronto vial. Then turn the vial and syringe upside down.
- Draw the right dose of Novolin®ge Toronto into the syringe.
- Pull the needle out of the vial. Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose.
- Now push the needle into the vial of intermediate-acting insulin. Then turn the vial and syringe upside down.
- Draw the right dose of intermediate-acting insulin into the syringe.
- Pull the needle out of the vial.
- Make sure there is no air left in the syringe and check the dose.
- Inject the mixture immediately.

Always mix fast-acting and intermediate-acting insulin in this order.

How to inject this insulin

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device manual.
- Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered. [vial]
- Keep the needle under your skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir. [Penfill®]
- After each injection be sure to remove the needle and store Novolin®ge Toronto without

the needle attached. Otherwise, insulin may leak out, which can cause inaccurate dosing.

How to take Novolin®ge Toronto:

Novolin®ge Toronto is for injection under the skin (subcutaneously).

Always vary the site you inject within the same region, to avoid lumps (see 'What are possible side effects from using Novolin®ge Toronto?'). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

Novolin®ge Toronto vials are for use with insulin syringes which are marked for use with IU-100 insulin. Failure to use the correct syringe can lead to dosage errors.

Novolin®ge Toronto may also be administered intravenously in special situations by medical professionals.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection

Causes of a hyperglycemia
You get a hyperglycemia if your blood sugar gets too high.

This might happen:
- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Overdose:

Causes of a hypoglycemia
You get a hypoglycemia if your blood sugar gets too low.

This might happen:
- If you take too much insulin.

- If you eat too little or miss a meal.
- If you exercise more than usual.

The warning signs of a hypoglycemia may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon: you need to find the reason for your hypoglycemia in order to avoid getting more.

- If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

If you think you, or a person you are caring for, have taken too much Novolin®ge Toronto, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Novolin®ge Toronto?

These are not all the possible side effects you may have when taking Novolin®ge Toronto. If you experience any side effects not listed here, tell your healthcare professional.

These are not all the possible side effects you may feel when taking Novolin®ge Toronto. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, Novolin®ge Toronto can cause side effects, although not everybody gets them. Novolin®ge Toronto may cause low blood sugar (hypoglycemia) (see the advice in ‘How to take Novolin®ge Toronto’).

Less commonly reported side effects
(1 to 10 users in 1000)

Signs of allergy
Hives and rash may occur.

Seek medical advice immediately

- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Novolin®ge Toronto or one of its ingredients (called a generalized allergic reaction) (see also the warning in 'Do not use Novolin®ge Toronto if').

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

Changes at the injection site (Lipodystrophy)
If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

Swollen joints
When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

Painful neuropathy (nerve related pain)
If your blood glucose levels improve very fast it may cause burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

Very rarely reported side effects
(less than 1 in 10,000)

Diabetic retinopathy (eye background changes)
If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Not known
Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

If any of the side effects get serious, or if you notice any side effects, including those not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy: hives and rash		√	√
Vision problems	√		
Changes at the injection site (Lipodystrophy)		√	
Swollen joints	√		
Painful neuropathy (nerve related pain)		√	√
RARE (less than 1 in 10,000)			
Diabetic retinopathy (eye background changes)		√	√
UNKNOWN			
Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Novolin®ge Toronto [vial] [Penfill®] that is not being used is to be stored in a refrigerator between 2°C-10°C, not in or too near the freezer section or the cooling element and is to be kept in the original carton. Do not freeze.

Novolin®ge Toronto [vial] [Penfill®] that is being used or is about to be used is not to be kept in a refrigerator.

Novolin®ge Toronto vial
You can carry the vial with you and keep it at room temperature (not above 25°C) for up to 4

weeks.

Novolin®ge Toronto Penfill®
You can carry the [cartridge] [insulin delivery device] with you and keep it at room temperature (not above 30°C) for up to 4 weeks.

Always keep your [vial] [Penfill® cartridge] in the outer carton when you are not using it, in order to protect it from light.

Novolin®ge Toronto [vial] [Penfill® cartridge] must be protected from excessive heat and light.

Do not use Novolin®ge Toronto [vial] [Penfill® cartridge] after the expiry date which is printed on the label and the carton.

Novolin®ge Toronto [vial] [Penfill® cartridge] should not be disposed of in waste water or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help protect the environment.

What Novolin®ge Toronto [vial][Penfill®] looks like and package content
The solution for injection comes as a water-clear, colourless, aqueous solution in packs of:

- 1 x 10 mL vial.
- 1 x 5 x 3 mL Penfill® cartridges.
- 1 mL contains 100 IU (International Units) of insulin human.
- 1 vial contains 10 mL equivalent to 1000 IU.
- 1 Penfill® contains 3 mL equivalent to 300 IU.

Keep out of reach and sight of children.

If you want more information about Novolin®ge Toronto:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NOVOLIN®GE NPH

Penfill®/vial

Insulin Isophane

Human Biosynthetic

Read this carefully before you start taking **Novolin®ge NPH** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Novolin®ge NPH**.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist. If you have trouble reading this ask a family member or a friend for help.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin including Novolin®ge.
- If hypoglycemic or hyperglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Insulin suspensions as Novolin®ge NPH are not to be used in insulin infusion pumps.
- Insulin suspensions as Novolin®ge NPH are never to be administered intravenously.
- Novolin®ge NPH should not be used if it is not uniformly white and cloudy after resuspension.

What is Novolin®ge NPH used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does Novolin®ge NPH work?

Novolin®ge NPH is human insulin used to treat diabetes.

Novolin®ge NPH is an antidiabetic agent used for the treatment of diabetes mellitus as it reduces the level of sugar in the blood and urine. To control your diabetes, your doctor has prescribed Novolin®ge NPH injections.

Novolin®ge NPH is an intermediate-acting insulin. This means that it will start to lower your blood sugar about 1½ hours after you take it, and the effect will last for approximately 24 hours. Novolin®ge NPH is often given in combination with fast-acting insulin products.

What are the ingredients in Novolin®ge NPH?

Medicinal ingredient: The active ingredient in Novolin®ge NPH is Insulin Isophane, Human Biosynthetic. It is a cloudy suspension of human insulin particles (the cloudy material) with protamine and zinc. Novolin®ge NPH is a suspension for injection containing Biosynthetic Human Insulin produced by recombinant DNA methods using S. cerevisiae (baker's yeast) and followed by unique purification processes. Human Insulin (biosynthetic) is structurally identical to natural human insulin.

Non-medicinal ingredients: Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid, protamine sulphate and water for injections.

Novolin®ge NPH comes in the following dosage forms:

Novolin®ge NPH insulin is available from Novo Nordisk Canada in the following format:

- Novolin®ge NPH 10 mL vial
- Novolin®geNPH Penfill® 3 mL cartridge

Novolin®ge NPH Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Novolin®ge NPH [Penfill® insulin cartridges] in combination with products that do not meet the same specifications or quality standards as NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Do not use Novolin®ge NPH if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see 'What are possible side effects from using Novolin®ge NPH?') for more about hypoglycemia.
- You are allergic (hypersensitive) to insulin isophane, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see 'What are possible side effects from using Novolin®ge NPH?').
- In insulin infusion pumps.
- The Penfill® cartridge or the Novo Nordisk Insulin Delivery Device containing the insulin is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The protective cap on the vial is loose or missing. Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- The insulin has not been stored correctly or if it has been frozen (see 'How to store Novolin®ge NPH?').
- The insulin does not appear uniformly white and cloudy after resuspension.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Novolin®ge NPH. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) watch for signs your need for insulin may change as your blood sugar level may rise or fall.

- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemia coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypoglycemic reactions or if you find it hard to recognize hypoglycemias.

Before you travel, check with your physician or pharmacist on the availability of Novolin®ge NPH insulin in other countries. If possible, bring enough Novolin®ge NPH with you on your trip.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

Other warnings you should know about:

<u>If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)</u>

- Other medicines for the treatment of diabetes.
- Monoamine oxidase inhibitors (MAOI) (used to treat depression).
- Beta-blockers (used to treat high blood pressure).
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure).
- Salicylates (used to relieve pain and lower fever).
- Anabolic steroids (such as testosterone).
- Sulphonamides (used to treat infections).

<u>If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)</u>

- Oral contraceptives (birth control pills).
- Thiazides (used to treat high blood pressure or excessive fluid retention).
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation).
- Thyroid hormones (used to treat thyroid gland disorders).
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma).
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes).

- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Novolin®ge NPH:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

How to take Novolin®ge NPH:

Novolin®ge NPH is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle.

Always vary the site you inject within the same region, to avoid lumps (see 'What are possible side effects from using Novolin®ge NPH?'). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.
Novolin®ge NPH vials are for use with insulin syringes which are marked for use with IU-100 insulin. Failure to use the correct syringe can lead to dosage errors.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Before using Novolin®ge NPH

- Check the label to make sure you have the right type of insulin.
- Remove the protective cap [vial].
- Always check the Penfill® cartridge, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1-800-465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- Always use a new needle for each injection to prevent contamination.
- Do not share your Novolin®ge Penfill® in a Novo Nordisk Insulin Delivery Device with another person, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.

Do not refill a Novolin®ge NPH Penfill® insulin cartridge.

Novolin®ge NPH Penfill® cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles as part of The All-In-One System®.

If you are treated with Novolin®ge NPH Penfill® insulin and another insulin in Penfill® cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

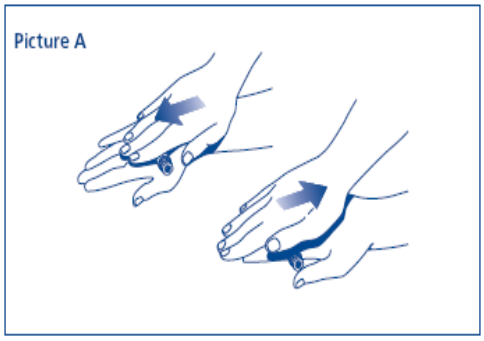
As a precautionary measure, you should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

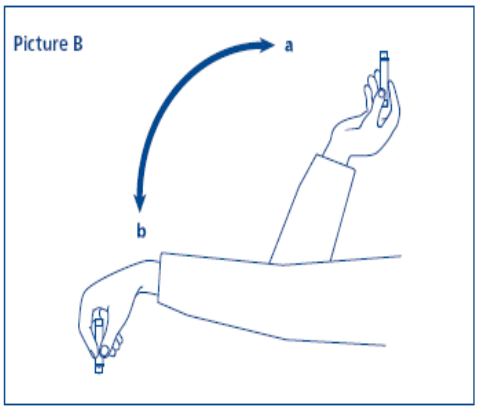
Resuspending the insulin
The first time you use Novolin®ge NPH Penfill® roll the cartridge between your palms 10 times – it is important that the cartridge is kept horizontal (see picture A).

Move the cartridge up and down between positions a and b (see picture B) 10 times so that the glass ball moves from one end of the cartridge to the other. Repeat the rolling and moving procedure until the liquid appears uniformly white and cloudy.

Mixing is easier when the insulin has reached room temperature. Complete the other stages of injection without delay.

For all subsequent injections move the insulin delivery device, with the cartridge inside it, up and down between a and b (see picture B) at least 10 times until the liquid appears uniformly white and cloudy.





Check there are at least 12 units of insulin left in the cartridge to allow even resuspending. If there are less than 12 units left, use a new Penfill®.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted or thickened area (see 'How to take Novolin®ge NPH'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Injecting Novolin®ge NPH on its own

- Just before injecting this insulin, roll the vial between your hands until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.
- Draw air into the syringe, in the same amount as the dose of insulin you need.
- Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
- Turn the vial and syringe upside down.
- Draw the right dose of insulin into the syringe.
- Pull the needle out of the vial.
- Make sure there is no air left in the syringe: point the needle upwards and push the air out.
- Check you have the right dose.
- Inject immediately.

Mixing Novolin®ge NPH with fast-acting insulin

- Roll the vial of Novolin®ge NPH between your hands. Do this until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.
- Draw as much air into the syringe as the dose of Novolin®ge NPH you need. Inject the air into the Novolin®ge NPH vial, then pull out the needle.
- Draw as much air into the syringe as the dose of fast-acting insulin you need. Inject the air into the fast-acting insulin vial. Then turn the vial and syringe upside down.
- Draw the right dose of fast-acting insulin into the syringe.

- Pull the needle out of the vial.
- Make sure there is no air left in the syringe: point the needle upwards and push the air out. Check the dose.
- Now push the needle into the vial of Novolin®ge NPH. Then turn the vial and syringe upside down.
- Draw the right dose of Novolin®ge NPH into the syringe.
- Pull the needle out of the vial.
- Make sure there is no air left in the syringe and check the dose.
- Inject the mixture immediately.

Always mix fast-acting and intermediate-acting insulin in this order.
How to inject this insulin

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device manual.
- Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered. [vial]
- Keep the needle under your skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir. [Penfill®]
- After each injection be sure to remove and discard the needle and store Novolin®ge NPH without the needle attached. Otherwise, insulin may leak out, which can cause inaccurate dosing.

Overdose:

Causes of a hypoglycemia
You get a hypoglycemia if your blood sugar gets too low.

This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

The warning signs of a hypoglycemia may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need

to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon: you need to find the reason for your hypoglycemia in order to avoid getting more.

- If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

If you think you, or a person you are caring for, have taken too much Novolin®ge NPH, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Causes of a hyperglycemia
You get a hyperglycemia if your blood sugar gets too high.

This might happen:
- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

What are possible side effects from using Novolin®ge NPH?

These are not all the possible side effects you may have when taking Novolin®ge NPH. If you experience any side effects not listed here, tell your healthcare professional.

These are not all the possible side effects you may feel when taking Novolin®ge NPH. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, Novolin®ge NPH can cause side effects, although not everybody gets them. Novolin®ge NPH may cause low blood sugar (hypoglycemia). (see the advice in ‘How to take Novolin®ge NPH?’)

Less commonly reported side effects
(1 to 10 users in 1000)

Signs of allergy
Hives and rash may occur.

Seek medical advice immediately

- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Novolin®ge NPH or one of its ingredients (called a generalized allergic reaction). (see also the warning in 'Do no use Novolin®ge NPH if').

Changes at the injection site (Lipodystrophy)
If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

Diabetic retinopathy (eye background changes)
If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Swollen joints
When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

Very rarely reported side effects
(less than 1 in 10,000)

Vision problems
When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Painful neuropathy (nerve related pain)
If your blood glucose levels improve very fast it may cause burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

Not known
Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

If any of the side effects get serious, or if you notice any side effects, including those not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy: hives and rash,		√	√
Changes at the injection site (Lipodystrophy)		√	√
Swollen joints	√		
Diabetic retinopathy (eye background changes)		√	√
VERY RARE (less than 1 in 10,000 users)			
Vision problems		√	
Painful neuropathy (nerve related pain)		√	√
UNKNOWN			
Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Novolin®ge NPH [vial] [Penfill®] that is not being used is to be stored in a refrigerator between 2°C to 10°C, not in or too near the freezer section or the cooling element and is to be kept in the original carton. Do not freeze.

Novolin®ge NPH [vial] [Penfill®] that is being used or is about to be used is not to be kept in a refrigerator. After removing Novolin®ge NPH [vial] [Penfill®] from the refrigerator let the [vial]

[Penfill® cartridge] [insulin delivery device] reach room temperature before resuspending the insulin as instructed for first time use. (see 'How to take Novolin®ge NPH').

Novolin®ge NPH vial
You can carry the vial with you and keep it at room temperature (not above 25°C) for up to 4 weeks.

Novolin®ge NPH Penfill®
You can carry the [cartridge] [insulin delivery device] with you and keep it at room temperature (not above 30°C) for up to 4 weeks.

Always keep your [vial] [Penfill® cartridge] in the outer carton when you are not using it, in order to protect it from light.

Novolin®ge NPH [vial] [Penfill® cartridge] must be protected from excessive heat and light.

Do not use Novolin®ge NPH [vial] Penfill® cartridge] after the expiry date which is printed on the label and the carton.

Novolin®ge NPH [vial] [Penfill® cartridge] should not be disposed of in wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help protect the environment.

Keep out of reach and sight of children.

What Novolin®ge NPH [vial][Penfill®] looks like and package content
The suspension for injection comes as a cloudy, white, aqueous suspension in packs of:

- 1 x 10 mL vial.
- 1 x 5 x 3 mL Penfill® cartridges.
- 1 mL contains 100 IU (International Units) of insulin human.
- 1 vial contains 10 mL equivalent to 1000 IU.
- 1 Penfill® contains 3 mL equivalent to 300 IU.

If you want more information about Novolin®ge NPH:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NOVOLIN®GE PREMIXED INSULIN PREPARATIONS

Penfill®/vial

Insulin Injection 30% and Insulin Isophane 70%
Insulin Injection 40% and Insulin Isophane 60%
Insulin Injection 50% and Insulin Isophane 50%
Human Biosynthetic

Read this carefully before you start taking **Novolin®ge premixed insulin** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Novolin®ge premixed insulin**.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist. If you have trouble reading this, ask a family member or a friend for help.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin including Novolin®ge.
- If hypoglycemic or hyperglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Insulin suspensions as Novolin®ge 30/70, Novolin®ge 40/60 and Novolin®ge 50/50 are not to be used in insulin infusion pumps.
- Insulin suspensions as Novolin®ge 30/70, Novolin®ge 40/60 and Novolin®ge 50/50 are never to be administered intravenously.
- Novolin®ge30/70, Novolin®ge40/60 and Novolin®ge 50/50 should not be used if it is not uniformly white and cloudy after resuspension.

What is Novolin®ge premixed insulin used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does Novolin®ge premixed insulin work?

Novolin®ge premixed is human insulin used to treat diabetes.

Novolin®ge premixed insulin is an antidiabetic agent used for the treatment of diabetes mellitus as it reduces the level of sugar in the blood and urine. To control your diabetes, your doctor has prescribed Novolin®ge premixed insulin injections.

Novolin®ge premixed is a mixture of fast-acting and intermediate-acting insulin. This means that it will start to lower your blood sugar about ½ an hour after you take it and the effect will last for approximately 24 hours.

What are the ingredients in Novolin®ge premixed insulin?

Medicinal ingredients: The active ingredient in Novolin®ge premixed insulin preparations is Insulin Isophane, Human Biosynthetic with increasing proportions of Insulin Injection, Human Biosynthetic (Novolin®ge 30/70, Novolin®ge 40/60, Novolin®ge 50/50).

Novolin®ge premixed insulin is a suspension for injection containing Biosynthetic Human Insulin produced by recombinant DNA methods using S. cerevisiae (baker's yeast) and followed by unique purification processes. Human Insulin (biosynthetic) is structurally identical to natural human insulin.

Non-medicinal ingredients: Zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid, protamine sulphate and water for injections.

Novolin®ge premixed insulin comes in the following dosage forms:

Novolin®ge premixed insulin is available from Novo Nordisk Canada in the following format:

- Novolin®ge 30/70 10 mL vial
- Novolin®ge 30/70 Penfill® 3 mL cartridge
- Novolin®ge 40/60 Penfill® 3 mL cartridge
- Novolin®ge 50/50 Penfill® 3 mL cartridge

Novolin®ge premixed insulin cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Novolin®ge premixed Penfill® insulin cartridges in combination with products that do not meet the same specifications or quality standards as NovoFine®, NovoFine®Plus and/or NovoTwist® needles.

Do not use Novolin®ge premixed insulin if:

- You feel a hypoglycemic reaction (low blood sugar) coming on (see 'What are possible side effects from using Novolin®ge premixed insulin?' for more about hypoglycemia).
- You are allergic (hypersensitive) to insulin - human biosynthetic, insulin isophane, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see 'What are possible side effects from using Novolin®ge premixed insulin?').
- In insulin infusion pumps.
- The Penfill® cartridge or the Novo Nordisk Insulin Delivery Device containing the insulin is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The protective cap on the vial is loose or missing. Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- The insulin has not been stored correctly or if it has been frozen (see 'How to store Novolin®ge premixed insulin?').

- The insulin does not appear uniformly white and cloudy after resuspension.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Novolin®ge premixed insulin. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) watch for signs your need for insulin may change as your blood sugar level may rise or fall.
- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemia coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypoglycemic reactions or if you find it hard to recognize hypoglycemias.

Before you travel, check with your physician or pharmacist on the availability of Novolin®ge premixed insulin in other countries. If possible, bring enough Novolin®ge premixed with you on your trip.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

Other warnings you should know about:

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections)

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation)

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Novolin®ge premixed insulin:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

How to take Novolin®ge premixed insulin:

Novolin®ge premixed insulin is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle.

Always vary the site you inject within the same region, to avoid lumps (see 'What are possible side effects from using Novolin®ge premixed insulin?').The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject around the waist.

Novolin®ge 30/70 vials are for use with insulin syringes which are marked for use with IU-100 insulin. Failure to use the correct syringe can lead to dosage errors.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only.

If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Eat a meal or snack containing carbohydrates within 30 minutes of the injection.

Before using Novolin®ge premixed

- Check the label to make sure you have the right type of insulin.
- Remove the protective cap [vial].
- Always check the Penfill® cartridge, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1-800-465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- Always use a new needle for each injection to prevent contamination. [Penfill®]
- Do not share your Novolin®ge Penfill® in a Novo Nordisk Insulin Delivery Device with another person, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.

Do not refill a Novolin®ge premixed insulin Penfill® cartridge.

Novolin®ge premixed Penfill® cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine®Plus and/or NovoTwist® needles as part of The All In-One System®.

If you are treated with Novolin®ge premixed Penfill® and another insulin in Penfill® cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

As a precautionary measure, you should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

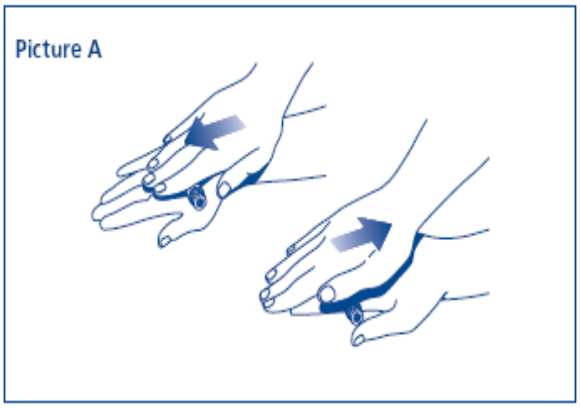
Resuspending the insulin

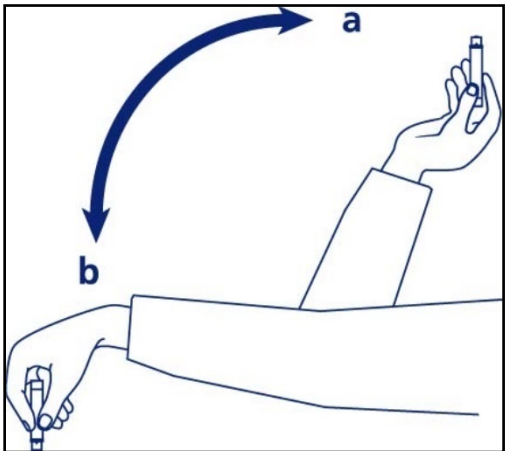
The first time you use Novolin®ge premixed Penfill® roll the cartridge between your palms 10 times – it is important that the cartridge is kept horizontal (see picture A).

Move the cartridge up and down between positions a and b (see picture B) 10 times so that the glass ball moves from one end of the cartridge to the other. Repeat the rolling and moving procedure until the liquid appears uniformly white and cloudy.

Mixing is easier when the insulin has reached room temperature. Complete the other stages of injection without delay.

For all subsequent injections move the insulin delivery device, with the cartridge inside it, up and down between a and b (see picture B) at least 10 times until the liquid appears uniformly white and cloudy.





Check there are at least 12 units of insulin left in the cartridge to allow even resuspending. If there are less than 12 units left, use a new Penfill®.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted or thickened area (see 'How to take Novolin®ge premixed insulin'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

How to use this insulin

Before injecting Novolin®ge 30/70

- Just before injecting this insulin, roll the vial between your hands until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.
- Draw air into the syringe, in the same amount as the dose of insulin you need.
- Inject the air into the vial: push the needle through the rubber stopper and press the plunger.

- Turn the vial and syringe upside down.
- Draw the right dose of insulin into the syringe.
- Pull the needle out of the vial.
- Make sure there is no air left in the syringe: point the needle upwards and push the air out.
- Check you have the right dose.
- Inject immediately.

How to inject this insulin

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device manual.
- Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered. [vial]
- Keep the needle under your skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir. [Penfill®]
- After each injection be sure to remove and discard the needle and store Novolin®ge Penfill® premixed insulin without the needle attached. Otherwise, insulin may leak out, which can cause inaccurate dosing.

Overdose:

Causes of a hypoglycemia
You get a hypoglycemia if your blood sugar gets too low.

This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

The warning signs of a hypoglycemia may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon: you need to find the reason for your hypoglycemia in

order to avoid getting more.

- If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

If you think you, or a person you are caring for, have taken too much Novolin®ge premixed insulin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Causes of a hyperglycemia
You get a hyperglycemia if your blood sugar gets too high.

This might happen:
- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

What are possible side effects from using Novolin®ge premixed insulin?

These are not all the possible side effects you may have when taking Novolin®ge premixed. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, Novolin®ge premixed insulin can cause side effects, although not everybody gets them. Novolin®ge premixed insulin may cause low blood sugar (hypoglycemia). (see the advice in ‘How to take Novolin®ge premixed insulin’).

Less commonly reported side effects
(1 to 10 users in 1000)

Signs of allergy
Hives and rash may occur.

Seek medical advice immediately
- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Novolin®ge premixed insulin or one of its ingredients (called a generalized allergic reaction). (see also the warning in 'Do not use Novolin®ge premixed insulin if').

Changes at the injection site (Lipodystrophy)
If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

Diabetic retinopathy (eye background changes)
If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Swollen joints
When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

Painful neuropathy (nerve related pain)
If your blood glucose levels improve very fast it may cause burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

Very rarely reported side effects
(less than 1 in 10,000)

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

Not known
Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

If any of the side effects get serious, or if you notice any side effects, including those not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy hives and rash,		√	√
Changes at the injection site (Lipodystrophy)		√	√
Swollen joints	√		
Diabetic retinopathy (eye background changes)		√	√
Painful neuropathy (nerve related pain)		√	√
VERY RARE (less than 1 in 10,000 users)			
Vision problems		√	
UNKNOWN			
Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Novolin®ge premixed insulin [vial] [Penfill®] that is not being used is to be stored in a refrigerator between 2°C-10°C, not in or too near the freezer section or the cooling element and is to be kept in the original carton. Do not freeze.

Novolin®ge premixed insulin [vial] [Penfill®] that is being used or is about to be used is not to be kept in a refrigerator. After removing Novolin®ge premixed [vial] [Penfill®] from the refrigerator let the [vial] [cartridge] [insulin delivery device] reach room temperature before resuspending the insulin as instructed for first time use. (see 'How to take Novolin®ge premixed insulin').

Novolin®ge 30/70 vial
You can carry the vial with you and keep it at room temperature (not above 25°C) for up to 4 weeks.

Novolin®ge 30/70, Novolin®ge 40/60, Novolin®ge 50/50 Penfill®
You can carry the [cartridge] [insulin delivery device] with you and keep it at room temperature (not above 30°C) for up to 4 weeks.

Always keep your [vial] [Penfill® cartridge] in the outer carton when you are not using it, in order to protect it from light.

Novolin®ge premixed insulin [vial] [Penfill® cartridge] must be protected from excessive heat and light.

Do not use Novolin®ge premixed insulin [vial] [Penfill® cartridge] after the expiry date which is printed on the label and the carton.

Novolin®ge premixed insulin [vial] [Penfill® cartridge] should not be disposed of in wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help protect the environment.

Keep out of reach and sight of children.

What Novolin®ge premixed insulin [vial] [Penfill®] looks like and package content
The suspension for injection comes as a cloudy, white, aqueous suspension in packs of:

- 1 x 10 mL vial.
- 1 x 5 x 3 mL Penfill® cartridges.
- 1 mL contains 100 IU (International Units) of insulin human.
- 1 vial contains 10 mL equivalent to 1000 IU
- 1 Penfill® contains 3 mL equivalent to 300 IU

If you want more information about Novolin®ge premixed insulin:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

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