

PRODUCT MONOGRAPH

Schedule D

Novolin[®]ge

Insulin, Human Biosynthetic

Injectable Solution/Suspension

Manufacturer's Standard

Antidiabetic Agent

Novo Nordisk Canada Inc. 300-2680 Skymark Avenue Mississauga, Ontario L4W 5L6	Date of Revision: 14 March 2008
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TABLE OF CONTENTS

TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION	3
INDICATIONS AND CLINICAL USE	4
CONTRAINDICATIONS.....	5
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS	8
DRUG INTERACTIONS	11
DOSAGE AND ADMINISTRATION	13
OVERDOSAGE	17
ACTION AND CLINICAL PHARMACOLOGY.....	17
STORAGE AND STABILITY	19
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	20
PART II: SCIENTIFIC INFORMATION	22
PHARMACEUTICAL INFORMATION.....	22
CLINICAL TRIALS	23
DETAILED PHARMACOLOGY.....	24
TOXICOLOGY.....	26
REFERENCES	28
PART III: CONSUMER INFORMATION	31

Novolin[®]ge

Insulin, Human Biosynthetic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1.

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal 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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

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*.

INDICATIONS AND CLINICAL USE

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

- 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 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*)

Geriatrics:

No data is available.

Pediatrics

No data is available.

CONTRAINDICATIONS

- 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, Composition and Packaging* section of the product monograph.
- During episodes of hypoglycemia
- 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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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.
- Insulin suspensions are never to be administered intravenously.
- Insulin suspensions are not to be used in insulin infusion pumps.

General

As with all insulins, 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. 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 remains clear after the vial or cartridge has been shaken carefully.

To avoid possible transmission of disease, Penfill[®] cartridge, Novolin[®]ge FlexPen[®] prefilled insulin delivery device and Novolin[®]ge InnoLet[®] compact prefilled insulin delivery system must not be used by more than one person.

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

Stress or illness may increase insulin requirements. In these instances, patients should contact their physicians and carefully control their blood glucose.

An insulin reaction (hypoglycemia) may occur if the patient takes too much insulin, misses a

meal or exercises more than usual (see *Overdosage*).

Diabetic patients should be instructed to carry a few lumps of sugar, candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur. The diabetic should make relatives and close work-mates aware that he/she is diabetic and instruct them regarding assistance in the event of a hypoglycemic reaction. An unconscious person should not be given anything to eat or drink as choking is possible.

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetics, may lead to hyperglycaemia. Inadequate dosage could occur due to increased insulin demand during illness or infection, neglect of diet, omission or mal-administration of prescribed insulin doses. A developing ketoacidosis will be revealed by urine tests which show large amounts of sugar and acetone. The symptoms of thirst, large urine volumes, loss of appetite, fatigue, dry skin and deep and rapid breathing come on gradually, usually over a period of some hours or days. If hyperglycemia is not treated, it can cause diabetic coma or death.

Hypokalemia is among the potential clinical adverse effects associated with the use of all insulins. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs.

Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Before travelling between different time zones, the patient should seek the doctor's advice, since this may mean that the patient has to take insulin and meals at different times.

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

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.

Any change of insulin dose should be made cautiously and under medical supervision. Changes in insulin strength, manufacturer, type (e.g. regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Concomitant illness, especially infections, usually increase the patient's insulin requirements.

Endocrine and Metabolism

Hypoglycaemia

In certain cases (long duration of diabetes, diabetic nerve disease, intensified diabetes control, or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycaemia may change or be less pronounced.

Hypoglycaemia 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.

Severe hypoglycaemia can result in temporary or permanent impairment of brain function and death.

Changes in insulin therapy or changes in life style (i.e. diet, exercise/physical activity) may require a change in dosage. Inadequate dosing or discontinuation of insulin treatment may lead to hyperglycaemias and diabetic ketoacidosis. Severe sustained hyperglycaemia may result in diabetic coma and death.

Glucose monitoring is recommended for all patients with diabetes.

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).

Hepatic/Biliary/Pancreas

Hepatic impairment may reduce insulin requirements.

Immune

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 to both insulin aspart and human insulin.

Renal

Renal impairment may reduce insulin requirements.

Sexual Function/Reproduction

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

Skin

Local allergic reaction

As with other insulins, patients may experience redness, swelling or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made, or if the patient is allergic to the insulin or any excipients.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Systemic allergic reaction

Systemic allergic reactions have rarely occurred with human insulin products. These reactions may be characterized by generalized skin rash, itching, swelling, gastrointestinal

upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and loss of consciousness. Severe cases of generalized allergy include anaphylactic reaction may be life threatening.

Special Populations

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. 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.

Nursing Women:

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.

Pediatrics

No data is available.

Geriatrics

No data is available.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

At institution of insulin therapy, edema 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 lipohypotrophy 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 hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events were reported in three comparative studies^(1,2,8). In one study⁽¹⁾, one patient in the Novolin[®]ge treatment group experienced pain at the injection site. In one study⁽²⁾, 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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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.

Post-Market Adverse Drug 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 hyperglycaemia 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 hyperglycaemic 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 glycaemic 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 of 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, and 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 of transitory in nature.

DRUG INTERACTIONS

Overview

A number of medicinal products are known to interact with the glucose metabolism. The physician must therefore take possible interactions into account and should always ask their patients about any medicinal products they take.

Insulin suspensions should not be added to infusion fluids. Medicinal products added to the insulin solution may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.

However, when mixing Novolin[®]ge Toronto and Novolin[®]ge NPH the blunting effect is not observed and the rapid onset of Novolin[®]ge Toronto is preserved.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Drug Class	Ref	Effect	Clinical comment
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oral hypoglycemic agents (OHA), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides	C	May reduce insulin requirement	Therapeutic concentration monitoring is recommended
oral contraceptives, thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol	C	May increased insulin requirement	Therapeutic concentration monitoring is recommended
beta-blocking agents	C	May mask the symptoms of hypoglycemia and delay recovery from hypoglycemia	Therapeutic concentration monitoring is recommended
Octreotide/lanreotide	C	May both decrease and increase insulin requirement	Therapeutic concentration monitoring is recommended

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Please refer to the *Dosage and Administration* section for more information. Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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.

DOSAGE AND ADMINISTRATION

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.

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.

Transfer of Patients

When patients are transferred from other insulins to Novolin[®]ge, the change should be made as directed by the physician according to the following general guidelines:

- Transferring a patient to another type or brand name of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, intermediate- and long-acting insulin etc.), origin (animal, human, human insulin human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage.

If an adjustment is needed when switching the patients to Novolin[®]ge Toronto, Novolin[®]ge NPH, or Novolin[®]ge Premixed Insulin Preparations, it may occur with the first dose or during the first several weeks or months.

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.

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. 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 insulin are mixed with short-acting soluble insulins, the short-acting insulin should be drawn into the syringe first.

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.

Routine Injection Procedure

Syringes

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

1. 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.
2. 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, 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.
3. 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).
4. 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.
5. 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.

Novolin[®]ge InnoLet[®], Novolin[®]ge FlexPen[®] and Novo Nordisk Insulin Delivery Devices

Penfill[®] cartridges are only for use in Novolin-Pen[®] Novo Nordisk insulin delivery devices

described in the *Dosage Forms, Composition and Packaging* section. If treatment involves two insulins in Penfill[®] cartridges, a separate Novolin-Pen[®] Novo Nordisk Insulin Delivery Device should be used for each type of insulin.

Novolin[®]ge Penfill[®], Novolin[®]ge InnoLet[®] and Novolin[®]ge FlexPen[®] must not be refilled.

Follow carefully the instructions for assembly and use of the, Novolin[®]ge InnoLet[®] and Novolin[®]ge FlexPen[®].

1. 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 (piston) is visible than equal to the width of the white bar code band.
2. 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.
3. Wipe the rubber membrane of the Penfill[®] cartridge, Novolin[®]ge InnoLet[®] or Novolin[®]ge FlexPen[®] and the site of injection with a suitable antiseptic, such as alcohol, and allow to dry.
4. Remove the protective disc from a NovoFine[®] needle and screw it firmly onto the Novo Nordisk Insulin Delivery Device. Pull off the outer and inner needle caps.
5. 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, Novolin[®]ge InnoLet[®] and Novolin[®]ge FlexPen[®] 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.
6. 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.
 7. NovoFine[®] 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.

Use only Novolin[®]ge Penfill[®] cartridges and NovoFine[®] needles with Novolin-Pen[®] systems.

Use only NovoFine[®] needles with Novo Nordisk Insulin Delivery Devices.

Novolin[®]ge Toronto is usually administered subcutaneously in the abdominal wall. The thigh, the buttocks or the deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

Novolin[®]ge NPH are usually administered subcutaneously in the thigh. If convenient, the abdominal wall, the buttocks or the deltoid region may also be used. 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 in the thigh or abdominal wall. If convenient, the buttocks or the deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

OVERDOSAGE

Hypoglycemia may occur if the diabetic administers too much insulin, misses a meal or exercises more than usual. The first symptoms can come on suddenly and may include cold sweat, rapid heart beat, nervousness or shakiness. If untreated, the situation may progress to unconsciousness. In rare cases, the nature and intensity of hypoglycemia warning symptoms may change. This has been observed in patients with long duration of diabetes (with diabetic neuropathy), after changes of regimen and in patients on strict metabolic control. However, if severe hypoglycemia is not treated it can cause temporary or permanent brain damage or death.

In the event of an overdose, glucose should be given orally if the patient is conscious. Where the patient is unconscious, an intramuscular, subcutaneous or intravenous injection of glucagon should be given and oral carbohydrate administered when the patient responds. Alternatively, intravenous glucose may be administered; it must be given if there is no response to glucagon within 10 to 15 minutes.

ACTION AND CLINICAL PHARMACOLOGY

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, including 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.

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.

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 are 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.

Excretion:

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.

STORAGE AND STABILITY

Temperature:

Novolin[®]ge that is not being used should be stored in a refrigerator between 2°C - 10°C 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/FlexPen[®]/InnoLet[®] and Novolin[®]ge Penfill[®] cartridge/FlexPen[®]/InnoLet[®] 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 25° C (vial) or 30° C (Penfill[®], FlexPen[®] and InnoLet[®]).

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

Novolin[®]ge FlexPen[®] and Novolin[®]ge InnoLet[®] can be in-use or carried as a spare for up to one month at room temperature (not above 30° C). When in use, the insulin delivery device are to be maintained at room temperature.

Light:

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

Others:

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Novolin[®]ge (Insulin, Human Biosynthetic) preparations are available in 10 ml vials, 3mL Penfill[®] cartridges, 3mL Novolin[®]ge FlexPen[®] disposable prefilled insulin delivery devices and 3mL Novolin[®]ge InnoLet[®] compact prefilled insulin delivery devices in a strength of 100 units/ml. Novolin[®]ge preparations are available in the following presentations:

10 ml vials	3.0 ml Penfill [®] cartridges	Novolin [®] ge InnoLet [®] 3.0 mL	Novolin [®] ge FlexPen [®] 3.0 mL
Novolin [®] ge Toronto	Novolin [®] ge Toronto	Novolin [®] ge Toronto	Novolin [®] ge Toronto
Novolin [®] ge NPH	Novolin [®] ge NPH	Novolin [®] ge NPH	Novolin [®] ge NPH
Novolin [®] ge 30/70	Novolin [®] ge 30/70	Novolin [®] ge 30/70	Novolin [®] ge 30/70
	Novolin [®] ge 40/60	Novolin [®] ge 40/60	
	Novolin [®] ge 50/50	Novolin [®] ge 50/50	

Novolin-Pen[®] systems are insulin delivery devices designed for use with Novolin[®]ge Penfill[®] insulin cartridges and NovoFine[®] needles.

Novolin[®]ge FlexPen[®] Insulin Delivery Devices and Novolin[®]ge InnoLet[®] Insulin Delivery Devices are designed for use with NovoFine[®] short cap needles of 8 mm or shorter in

length. The needle box is marked with an S.

Novolin[®]**ge** FlexPen[®] is a prefilled disposable dial-a-dose insulin delivery device containing a Novolin[®]**ge** preparation. The 3.0 ml device is capable of delivering 1-60 units in increments of 1 unit, with a single depression of a push button.

Novolin[®]**ge** InnoLet[®] is a simple, compact prefilled insulin delivery device containing a Novolin[®]**ge** preparation. The delivery device is capable of delivering 1-50 units of insulin in increments of 1 unit, with a single depression of a push button.

The following non-medicinal ingredients are found in Novolin[®]**ge** Toronto: glycerol, hydrochloric acid and/or sodium hydroxide (for pH adjustment), metacresol, water for injections, zinc chloride.

The following non-medicinal ingredients are found in Novolin[®]**ge** NPH and Novolin[®]**ge** Premixed Insulin Preparations: disodium phosphate dihydrate, glycerol, hydrochloric acid and/or sodium hydroxide, metacresol, phenol, protamine sulphate, water for injections, zinc chloride.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

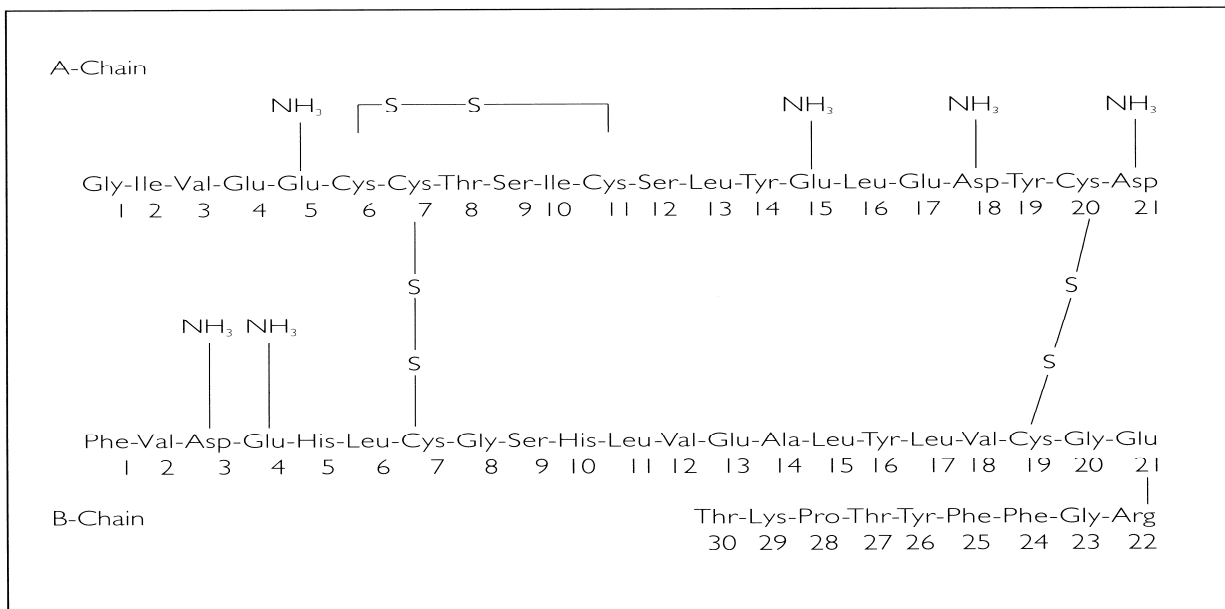
Proper name: Insulin, Human Biosynthetic

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 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.

CLINICAL TRIALS

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

Study demographics and trial design

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⁽¹⁴⁾. 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⁽¹³⁾ was uncontrolled and sequential. Twelve^(1, 3, 4, 7-11, 15-18) were open, randomized, parallel, asymmetrical comparisons of Novolin[®]**ge** with the corresponding Novolin[®] (ss) preparations employing a similar protocol. One study⁽²⁾ 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⁽²⁰⁾. 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.

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^(5,6) 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.

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 3 -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)
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			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	Bromsulphophthalein test	No	No
7. Blood Sugar	Rat	Effects on streptozocin induced diabetes	Yes	Yes
8. Isolated Smooth Muscle Preparations	Guinea-Pig	Ilium stimulated with acetylcholine, histamine, serotonin and nicotine	No	No
	Guinea-Pig	Vas deferens stimulated with noradrenaline (concentration of the insulins 50 U/I)	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⁽¹²⁾ 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 4 - 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 used)	No	No

TOXICOLOGY

Animal Toxicity

Table 5 - Details of Animal Toxicity Studies.

	Animal Species			
	Mice and Rats	Rats	Rabbits	Beagles

	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
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 intramuscular 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.

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Important: Please Read

Important: Please Read

PART III: CONSUMER INFORMATION

Novolin[®]ge Toronto
[Penfill[®]/ FlexPen[®]/ InnoLet[®]]

Insulin Injection
Human Biosynthetic 10 mL / 3 mL

This leaflet is Part III of a three-part 'Product Monograph' published when Novolin[®]ge Toronto insulin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Novolin[®]ge Toronto insulin. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine has been prescribed for you. Do 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 or your pharmacist.

ABOUT THIS MEDICATION

A direction leaflet containing information for the patient is included in each package.

What the medication is used for:

Novolin[®]ge Toronto [Penfill[®]/ FlexPen[®]/ InnoLet[®]] is human insulin used to treat diabetes. It comes in a [10 mL vial that you use to fill a syringe] [3 mL cartridge call Penfill[®] which fits into a Novo Nordisk Insulin Delivery Device] [Novolin[®]ge FlexPen[®] prefilled insulin delivery device] [Novolin[®]ge InnoLet[®] compact prefilled insulin delivery device].

Novolin[®]ge Toronto insulin is indicated for:

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

What it does:

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 half 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.

When it should not be used:

Do not use Novolin[®]ge Toronto:

- ▶ **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see 'What the important nonmedicinal ingredients are' listed below). Look out for the signs of allergy in 'Possible side effects'.
- ▶ **If you feel a hypo** coming on (a hypo is short for a hypoglycemic reaction and is a symptom of low blood sugar). See 'What to do in an emergency', for more about hypos.

What do you have to consider during pregnancy or while breastfeeding?

If you are pregnant or planning to become pregnant you should see your doctor immediately to discuss your need for and type of insulin in order to control your diabetes and avoid hyperglycaemia (too high blood sugar) and hypoglycaemia (too low blood sugar) as these conditions could harm your baby.

Breastfeeding while you are taking insulin does not put your baby at risk. Your insulin dosage and diet may, however, need to be adjusted.

Alcohol use

Alcohol (including beer and wine) may lead to hypoglycaemia (too low blood sugar). Therefore, be careful when you drink alcohol and never drink alcohol on an empty stomach. Follow your physician's advice regarding diet and alcohol consumption.

What should be done during an illness?

Never stop taking insulin if you are ill. Your need for insulin may, however, be changed.

If you have an infection, fever or an operation you may need to have more insulin than usual.

If you suffer from diarrhoea, vomiting or eat less than usual you may also need less insulin than usual.

What the medicinal ingredient is:

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.

What the important nonmedicinal ingredients are:

Zinc chloride, glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injections.

What dosage forms it comes in:

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
(designed for use with Novo Nordisk Insulin Delivery Devices)
- Novolin[®]ge Toronto FlexPen[®] 3 mL
- Novolin[®]ge Toronto InnoLet[®] 3 mL

Novolin[®]ge Toronto Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles.

Novolin[®]ge Toronto [FlexPen[®]] [InnoLet[®]] is designed for use with NovoFine[®] needles.

Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Novolin[®]ge Toronto [Penfill[®] insulin cartridges] [FlexPen[®]] [InnoLet[®]] in combination with products that do not meet the same specifications or quality standards.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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.
- Insulin suspensions are never to be administered intravenously.
- Insulin suspensions are not to be used in insulin infusion pumps.

Before you use Novolin[®]ge Toronto [Penfill[®] / FlexPen[®] / InnoLet[®]] talk to your doctor or pharmacist:

- ▶ **If you have trouble** with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ **If you drink alcohol:** watch for signs of a hypo and never drink alcohol on an empty stomach.
- ▶ **If you exercise more than usual** or if you want to change your usual diet.
- ▶ **If you are ill:** continue taking your insulin.
- ▶ **If you go abroad:** travelling over time zones may affect your insulin needs and the timing of your injections. 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.

Pregnancy and breastfeeding

- ▶ **If you are pregnant, planning a pregnancy or are breastfeeding** please contact your doctor for advice.

Driving and using machines

- ▶ **If you drive or use tools or machines:** watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognize hypos.

INTERACTIONS WITH THIS MEDICATION

When you use other medicines

Many 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. Talk to your doctor or pharmacist if you take, or have recently taken any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors; (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid (aspirin); anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

PROPER USE OF THIS MEDICATION

How to use

Novolin[®]ge Toronto
[Penfill[®] / FlexPen[®] / InnoLet[®]]

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. 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.

It is recommended that you measure your blood glucose regularly.

Before using Novolin[®]ge Toronto:

- ▶ **Check the label** to make sure you have the right type of insulin.
- ▶ **Disinfect the rubber membrane** with an alcohol swab.
- ▶ **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.

Novolin[®]ge Toronto Penfill[®] /FlexPen[®] /InnoLet[®]:

- ▶ **Always use a new needle** for each injection to prevent contamination.

Do not use Novolin[®]ge Toronto:

- ▶ **In insulin infusion pumps.**
- ▶ **If the insulin has not been stored correctly** or if it has been frozen (see 'How to Store Novolin[®]ge Toronto').
- ▶ **If the insulin does not appear water-clear and colourless.**
- ▶ **If 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.
- ▶ **If the [Penfill[®] cartridge or Novolin-Pen[®] Insulin Delivery Device containing the cartridge] [FlexPen[®]] [InnoLet[®]] is dropped, damaged or crushed;** there is a risk of leakage of insulin.

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 and NovoFine[®] 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.

How to use this insulin

Novolin[®]ge Toronto is for injection under the skin (subcutaneously). To avoid lumps always vary the site you inject (see 'Possible side effects'). 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.

Injecting Novolin[®]ge Toronto on its own

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

8. Inject immediately.

Mixing Novolin[®]ge Toronto with intermediate-acting insulin

1. Roll the vial of intermediate-acting insulin between your hands. Do this until the liquid is uniformly white and cloudy.
2. 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.
3. 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.
4. 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.
5. Now push the needle into the vial of intermediate-acting insulin. Then turn the vial and syringe upside down.
6. Draw the right dose of intermediate-acting insulin into the syringe.
7. Pull the needle out of the vial.
8. Make sure there is no air left in the syringe, and check the dose.
9. 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.
- ▶ **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.

Usual dose:

Follow carefully the instructions given by your doctor concerning type of insulin, dose, and time of injection. Any change in insulin should be made cautiously and only under medical supervision. Your insulin requirements may change due to a number of factors (illness, stress, medications, changes in diet or exercise routines, etc.). Follow your doctor's instructions to allow for these changes. The following can be considered as general guidelines only and you should consult your doctor for information, which is specific to your diabetes.

What about travelling?

The time difference between countries may mean that you have to take your insulin and meals at different times than usual. You should therefore consult your doctor if you are planning to go abroad or travel across time zones.

Overdose:

What factors may result in hypoglycaemia (low blood sugar)?

If you take too much insulin, miss a meal or exercise more than usual your blood sugar may become too low (i.e. hypoglycaemia).

The first **symptoms of hypoglycaemia** may come on suddenly. They may include: cold sweat, cool pale skin, fatigue, drowsiness, nervousness or tremor, feelings of anxiety, unusual tiredness and weakness, confusion, difficulty concentrating, excessive hunger, changes in vision, headache and nausea and palpitation.

What to do in case of hypoglycaemia?

If you experience any of the symptoms mentioned above, you should immediately take sugar or a sugar-containing product. Therefore, always carry a few lumps of sugar, candies, biscuits or fruit juice with you.

Your relatives, friends and close work-mates should know that you have diabetes and how they can help you if you get a severe hypoglycaemic reaction. They must be aware that an unconscious person should not be given anything to eat or drink (as choking is possible), but should be turned on their side and medical assistance sought immediately.

You may recover from unconsciousness more quickly if you are given an injection of the hormone glucagon by a person who has been instructed in how to use it. If glucagon is injected, you should also be given sugar, a product containing sugar or glucose by mouth as soon as you are conscious again.

If you do not respond to glucagon treatment, you will have to be treated in a hospital. See your doctor if you have had repeated hypoglycaemic reactions, or one leading to unconsciousness, as your insulin dose may need to be adjusted.

If severe hypoglycaemia is not treated, it can cause temporary or permanent brain damage or death.

What factors may result in hyperglycaemia (high blood sugar)?

If you are ill with fever or if you eat much more than usual and repeatedly take less insulin than you need, your blood sugar may become unusually high (i.e. result in hyperglycaemia).

The **symptoms of unusually high blood sugar levels** will appear gradually. They include: increased urination, thirst, loss of appetite, nausea, vomiting, drowsiness (fatigue), flushed dry skin, dry mouth, and acetone breath.

What to do in case of hyperglycaemia?

If you recognize any of the symptoms mentioned above, you should test your blood sugar level and your urine for ketones as soon as possible as the symptoms may indicate that you have a condition called ketoacidosis. If hyperglycaemia is not treated it can cause diabetic coma or death. You should therefore seek medical advice immediately and possibly take some extra insulin.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What to do in an emergency

If you get a hypo

A hypo means your blood sugar level is too low.

The warning signs of a hypo 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 hypo 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.

- ▶ **If severe hypoglycemia is not treated**, it can cause brain damage (temporary or permanent) and even death.
- ▶ **If you have a hypo that makes you pass out**, or if you get a lot of hypos, 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.

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. Seek medical advice after an injection of glucagon; you need to find the reason for your hypo in order to avoid getting more.

Causes of a hypo

You get a hypo 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.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycemia).

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.

If you get any of these signs, test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

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.

Causes of hyperglycemia

- Forgetting to take your insulin.
- Repeatedly taking less insulin than you need.
- An infection or fever.
- Eating more than usual.
- Exercising less than usual.

Possible side effects

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 'What to do in an emergency'.

Less commonly reported side effects

(less than 1 in 100)

Vision problems When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

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 prevent 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.

Signs of allergy Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These reactions usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:

- If signs of allergy spread to other parts of the body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy; feel like fainting.

You may have a very rare serious allergic reaction to Novolin[®] **ge** Toronto or one of its ingredients (called a systemic allergic reaction). See also the warning in 'Before you use Novolin[®] **ge** Toronto'.

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.

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)

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.

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.

HOW TO STORE IT

How to store

Novolin[®] **ge Toronto**

[Penfill[®] / FlexPen[®] / InnoLet[®]]

Keep out of the reach and sight of children.

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

Novolin[®] **ge Toronto:**

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[®] /FlexPen[®] /InnoLet[®]:**

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] [FlexPen[®]] [InnoLet[®]] in the outer carton when you are not using it, in order to protect it from light.

Novolin[®] **ge** Toronto [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] must be protected from excessive heat and sunlight.

Do not use Novolin[®] **ge** Toronto [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] after the expiry date which is printed on the label and the carton. The expiry date refers to the last day of that month.

Novolin[®] **ge** Toronto [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] 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.

REPORTING SUSPECTED SIDE EFFECTS

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

By toll-free telephone: 866-234-2345
By toll -free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

What Novolin[®]ge Toronto looks like and package content

The solution for injection comes as a clear, colourless, aqueous solution in packs of:

- 1 x 10 mL vial
- 1 x 5 x 3 mL Penfill[®] cartridges
- 1 x 3 mL FlexPen[®] insulin delivery device
- 1 x 3 mL InnoLet[®] insulin delivery device

1 mL contains 100 IU (International Units) of insulin human.

1 vial contains 10 mL equivalent to 1000 IU.

1 [Penfill[®]] [FlexPen[®]] [InnoLet[®]] contains 3 mL equivalent to 300 IU.

For further information, please refer to the '*Information for Health Care Professionals*'.

This summary does not contain all the known information about Novolin®ge Toronto. Talk to your doctor if you have any questions

This document plus the full product monograph, prepared for health professionals can be found at:
www.novonordisk.ca
or by contacting the sponsor, **Novo Nordisk Canada Inc.**, at
1-800-465-4334

The leaflet was prepared by **Novo Nordisk Canada Inc.**

Last revised: February 11, 2008

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Novolin[®]ge NPH
[Penfill[®]/ FlexPen[®]/ InnoLet[®]]

Insulin Isophane
Human Biosynthetic

10 mL / 3 mL

This leaflet is Part III of a three-part 'Product Monograph' published when Novolin[®]ge NPH insulin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Novolin[®]ge NPH insulin. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine has been prescribed for you. Do 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 or your pharmacist.

ABOUT THIS MEDICATION

A direction leaflet containing information for the patient is included in each package.

What the medication is used for:

Novolin[®]ge NPH [Penfill[®]/ FlexPen[®]/ InnoLet[®]] is human insulin used to treat diabetes. It comes in a [10 mL vial that you use to fill a syringe] [3 mL cartridge call Penfill[®], which fits into a Novo Nordisk Insulin Delivery Device] [Novolin[®]ge FlexPen[®] prefilled insulin delivery device] [Novolin[®]ge InnoLet[®] prefilled compact insulin delivery device].

Novolin[®]ge NPH insulin is indicated for:

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

What it does:

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.

When it should not be used:

Do not use Novolin[®]ge NPH:

- ▶ **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see 'What the important nonmedicinal ingredients are' listed below). Look out for the signs of allergy in 'Possible side effects'.
- ▶ **If you feel a hypo** coming on (a hypo is short for a hypoglycemic reaction and is a symptom of low blood sugar). See 'What to do in an emergency', for more about hypos.

What do you have to consider during pregnancy or while breastfeeding?

If you are pregnant or planning to become pregnant you should see your doctor immediately to discuss your need for and type of insulin in order to control your diabetes and avoid hyperglycaemia (too high blood sugar) and hypoglycaemia (too low blood sugar) as these conditions could harm your baby.

Breastfeeding while you are taking insulin does not put your baby at risk. Your insulin dosage and diet may, however, need to be adjusted.

Alcohol use

Alcohol (including beer and wine) may lead to hypoglycaemia (too low blood sugar). Therefore, be careful when you drink alcohol and never drink alcohol on an empty stomach. Follow your physician's advice regarding diet and alcohol consumption.

What should be done during an illness?

Never stop taking insulin if you are ill. Your need for insulin may, however, be changed.

If you have an infection, fever or an operation you may need to have more insulin than usual.

If you suffer from diarrhoea, vomiting or eat less than usual you may also need less insulin than usual.

What the medicinal ingredient is:

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.

What the important nonmedicinal ingredients are:

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

What dosage forms it comes in:

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

- Novolin[®] NPH 10 mL vial
- Novolin[®] NPH Penfill[®] 3 mL cartridge
(designed for use with Novo Nordisk Insulin Delivery Devices)
- Novolin[®]ge NPH FlexPen[®] 3 mL
- Novolin[®]ge NPH InnoLet[®] 3 mL

Novolin[®]ge NPH Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles.

Novolin[®]ge NPH [FlexPen[®]] [InnoLet[®]] is designed for use with NovoFine[®] needles.

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Insulin suspensions are never to be administered intravenously.
- Insulin suspensions are not to be used in insulin infusion pumps.

Before you use Novolin[®]ge NPH [Penfill[®]/ FlexPen[®]/ InnoLet[®]] talk to your doctor or pharmacist:

- ▶ **If you have trouble** with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ **If you drink alcohol:** watch for signs of a hypo and never drink alcohol on an empty stomach.
- ▶ **If you exercise more than usual** or if you want to change your usual diet.
- ▶ **If you are ill:** continue taking your insulin.
- ▶ **If you go abroad:** travelling over time zones may affect your insulin needs and the timing of your injections.

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.

Pregnancy and breastfeeding

- ▶ **If you are pregnant, planning a pregnancy or are breastfeeding** please contact your doctor for advice.

Driving and using machines

- ▶ **If you drive or use tools or machines:** watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognize hypos.

INTERACTIONS WITH THIS MEDICATION

When you use other medicines

Many 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. Talk to your doctor or pharmacist if you take, or have recently taken any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors; (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid (aspirin); anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

PROPER USE OF THIS MEDICATION

How to use

**Novolin[®]ge NPH
[Penfill[®]/ FlexPen[®]/ InnoLet[®]]**

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. 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.

It is recommended that you measure your blood glucose regularly.

Before using Novolin[®]ge NPH Penfill[®]:

- ▶ **Check the label** to make sure you have the right type of insulin.
- ▶ **Disinfect the rubber membrane** with an alcohol swab.
- ▶ **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.

Novolin[®]ge NPH Penfill[®] /FlexPen[®] /InnoLet[®]:

▶ **Always use a new needle** for each injection to prevent contamination.

Do not use Novolin[®]ge NPH:

▶ **In insulin infusion pumps.**

▶ **If the insulin has not been stored correctly** or if it has been frozen (see '*How to Store Novolin[®]ge NPH*').

▶ **If the insulin does not appear uniformly white and cloudy** when it is resuspended.

▶ **If 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.

▶ **If the [Penfill[®] cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge] [FlexPen[®]] [InnoLet[®]] is dropped, damaged or crushed;** there is a risk of leakage of insulin.

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 and NovoFine[®] 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.

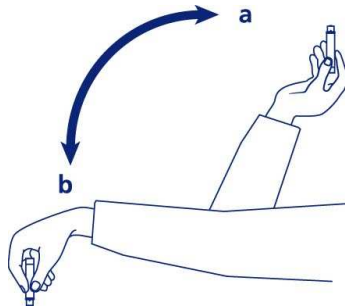
Resuspending the insulin

Resuspending is easier when the insulin has reached room temperature.

Before you put the Penfill[®] cartridge into the insulin delivery device, move it up and down between positions **a** and **b** and back (see diagram) so that the glass ball moves from one end of the cartridge to the other at least 20 times. Repeat this movement at least 10 times before each injection.

The movement must always be repeated until the liquid appears uniformly white and cloudy.

Complete the other stages of injection without delay.



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[®].

How to use this insulin

Novolin[®]ge NPH is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle. To avoid lumps always vary the site you inject (see '*Possible side effects*'). 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.

Injecting Novolin[®]ge NPH on its own

1. 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.
2. Draw air into the syringe, in the same amount as the dose of insulin you need.
3. Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
4. Turn the vial and syringe upside down.
5. Draw the right dose of insulin into the syringe.
6. Pull the needle out of the vial.
7. Make sure there is no air left in the syringe: point the needle upwards and push the air out.
8. Check you have the right dose.
9. Inject immediately.

Mixing Novolin[®]ge NPH with fast-acting insulin

1. 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.
2. 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.
3. 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.
4. 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.
5. Now push the needle into the vial of Novolin[®]ge NPH. Then turn the vial and syringe upside down.
6. Draw the right dose of Novolin[®]ge NPH into the syringe.
7. Pull the needle out of the vial.
8. Make sure there is no air left in the syringe, and check the dose.
9. 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.
- ▶ **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.

Usual dose:

Follow carefully the instructions given by your doctor concerning type of insulin, dose, and time of injection. Any change in insulin should be made cautiously and only under medical supervision. Your insulin requirements may change due to a number of factors (illness, stress, medications, changes in diet or exercise routines, etc.). Follow your doctor's instructions to allow for these changes. The following can be considered as general guidelines only and you should consult your doctor for information, which is specific to your diabetes.

What about travelling?

The time difference between countries may mean that you have to take your insulin and meals at different times than usual. You should therefore consult your doctor if you are planning to go abroad or travel across time zones.

Overdose:

What factors may result in hypoglycaemia (low blood sugar)?

If you take too much insulin, miss a meal or exercise more than usual your blood sugar may become too

low (i.e. hypoglycaemia).

The first **symptoms of hypoglycaemia** may come on suddenly. They may include: cold sweat, cool pale skin, fatigue, drowsiness, nervousness or tremor, feelings of anxiety, unusual tiredness and weakness, confusion, difficulty concentrating, excessive hunger, changes in vision, headache and nausea and palpitation.

What to do in case of hypoglycaemia?

If you experience any of the symptoms mentioned above, you should immediately take sugar or a sugar-containing product. Therefore, always carry a few lumps of sugar, candies, biscuits or fruit juice with you.

Your relatives, friends and close work-mates should know that you have diabetes and how they can help you if you get a severe hypoglycaemic reaction. They must be aware that an unconscious person should not be given anything to eat or drink (as choking is possible), but should be turned on their side and medical assistance sought immediately.

You may recover from unconsciousness more quickly if you are given an injection of the hormone glucagon by a person who has been instructed in how to use it. If glucagon is injected, you should also be given sugar, a product containing sugar or glucose by mouth as soon as you are conscious again.

If you do not respond to glucagon treatment, you will have to be treated in a hospital. See your doctor if you have had repeated hypoglycaemic reactions, or one leading to unconsciousness, as your insulin dose may need to be adjusted.

If severe hypoglycaemia is not treated, it can cause temporary or permanent brain damage or death.

What factors may result in hyperglycaemia (high blood sugar)?

If you are ill with fever or if you eat much more than usual and repeatedly take less insulin than you need, your blood sugar may become unusually high (i.e. result in hyperglycaemia).

The **symptoms of unusually high blood sugar levels** will appear gradually. They include: increased urination, thirst, loss of appetite, nausea, vomiting, drowsiness (fatigue), flushed dry skin, dry mouth, and acetone breath.

What to do in case of hyperglycaemia?

If you recognize any of the symptoms mentioned above, you should test your blood sugar level and your urine for ketones as soon as possible as the symptoms may indicate that you have a condition called ketoacidosis. If hyperglycaemia is not treated it can cause diabetic coma or death. You should therefore seek medical advice immediately and possibly take some extra insulin.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What to do in an emergency

If you get a hypo

A hypo means your blood sugar level is too low.

The warning signs of a hypo 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 hypo 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.

- ▶ **If severe hypoglycemia is not treated**, it can cause brain damage (temporary or permanent) and even death.
- ▶ **If you have a hypo that makes you pass out**, or if you get a lot of hypos, 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.

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. Seek medical advice after an injection of glucagon; you need to find the reason for your hypo in order to avoid getting more.

Causes of a hypo

You get a hypo 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.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycemia).

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.

If you get any of these signs, test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

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.

Causes of hyperglycemia

- Forgetting to take your insulin.
- Repeatedly taking less insulin than you need.
- An infection or fever.
- Eating more than usual.
- Exercising less than usual.

Possible side effects

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 '*What to do in an emergency*'.

Less commonly reported side effects

(less than 1 in 100)

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 prevent 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.

Signs of allergy Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These reactions usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:

- If signs of allergy spread to other parts of the body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy; feel like fainting.

You may have a very rare serious allergic reaction to Novolin[®]ge NPH or one of its ingredients (called a systemic allergic reaction). See also the warning in '*Before you use Novolin[®]ge NPH*'.

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 reaction usually 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.

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.

HOW TO STORE IT

How to store

Novolin[®]ge NPH

[Penfill[®]/ FlexPen[®]/ InnoLet[®]]

Keep out of the reach and sight of children.

Novolin[®]ge NPH [vial] [Penfill[®]] [FlexPen[®]] [InnoLet[®]] 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 NPH [vial] [Penfill[®]] [FlexPen[®]] [InnoLet[®]] 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[®]] [FlexPen[®]] [InnoLet[®]] 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 use Novolin[®]ge NPH*'

Novolin[®]ge NPH:

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[®] /FlexPen[®] /InnoLet[®]:

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] [FlexPen[®]] [InnoLet[®]] in the outer carton when you are not using it, in order to protect it from light.

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

Do not use Novolin[®]ge NPH [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] after the expiry date which is printed on the label and the carton. The expiry date refers to the last day of that month.

Novolin[®]ge NPH [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] 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.

REPORTING SUSPECTED SIDE EFFECTS

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

By toll-free telephone: 866-234-2345
By toll -free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

What Novolin[®]ge NPH [Penfill[®]] [FlexPen[®]] [InnoLet[®]] 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 x 3 mL FlexPen[®] insulin delivery device
- 1 x 3 mL InnoLet[®] insulin delivery device

1 mL contains 100 IU (International Units) of insulin human.

1 vial contains 10 mL equivalent to 1000 IU.

1 [Penfill[®]] [FlexPen[®]] [InnoLet[®]] contains 3 mL equivalent to 300 IU.

For further information, please refer to the 'Information for Health Care Professionals'.

This summary does not contain all the known information about Novolin[®]ge NPH. Talk to your doctor if you have any questions

This document plus the full product monograph, prepared for health professionals can be found at:
www.novonordisk.ca
or by contacting the sponsor, **Novo Nordisk Canada Inc.**, at
1-800-465-4334

The leaflet was prepared by **Novo Nordisk Canada Inc.**

Last revised: February 1, 2008

Novo Nordisk[®], **Novolin**[®], [**Penfill**[®]] [**FlexPen**[®]] [**InnoLet**[®]], **NovoFine**[®], **The All-In-One System**[®], **Devices Matter**[®], and **Novolin-Pen**[®], are trademarks owned by Novo Nordisk A/S and used by Novo Nordisk Canada Inc. under licence.

Novolin[®]ge [Penfill[®]/ FlexPen[®]/ InnoLet[®]]

Premixed insulin preparations

Insulin Injection 30% and Insulin Isophane 70%

Insulin Injection 40% and Insulin Isophane 60%

Insulin Injection 50% and Insulin Isophane 50%

Human Biosynthetic

10 mL / 3 mL

This leaflet is Part III of a three-part 'Product Monograph' published when Novolin[®]ge premixed insulin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Novolin[®]ge premixed insulin. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine has been prescribed for you. Do 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 or your pharmacist.

ABOUT THIS MEDICATION

A direction leaflet containing information for the patient is included in each package.

What the medication is used for:

Novolin[®]ge [Penfill[®]/ FlexPen[®]/ InnoLet[®]] premixed is human insulin used to treat diabetes. It comes in a [10 mL vial that you use to fill a syringe] [3 mL cartridge call Penfill[®] which fits into a Novo Nordisk Insulin Delivery Device] [Novolin[®]ge FlexPen[®] prefilled insulin delivery device] [Novolin[®]ge InnoLet[®] compact prefilled insulin delivery device].

Novolin[®]ge premixed insulin is indicated for:

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

What it does:

Novolin[®]ge premix 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 half an hour after you take it, and the effect will last for approximately 24 hours.

When it should not be used:

Do not use Novolin[®]ge premixed insulin:

- ▶ **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see 'What the important nonmedicinal ingredients are' listed below). Look out for the signs of allergy in 'Possible side effects'.
- ▶ **If you feel a hypo** coming on (a hypo is short for a hypoglycemic reaction and is a symptom of low blood sugar). See 'What to do in an emergency', for more about hypos.

What do you have to consider during pregnancy or while breastfeeding?

If you are pregnant or planning to become pregnant you should see your doctor immediately to discuss your need for and type of insulin in order to control your diabetes and avoid hyperglycaemia (too high blood sugar) and hypoglycaemia (too low blood sugar) as these conditions could harm your baby.

Breastfeeding while you are taking insulin does not put your baby at risk. Your insulin dosage and diet may, however, need to be adjusted.

Alcohol use

Alcohol (including beer and wine) may lead to hypoglycaemia (too low blood sugar). Therefore, be careful when you drink alcohol and never drink alcohol on an empty stomach. Follow your physician's advice regarding diet and alcohol consumption.

What should be done during an illness?

Never stop taking insulin if you are ill. Your need for insulin may, however, be changed.

If you have an infection, fever or an operation you may need to have more insulin than usual.

If you suffer from diarrhoea, vomiting or eat less than usual you may also need less insulin than usual.

What the medicinal ingredient is:

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.

What the important nonmedicinal ingredients are:

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

What dosage forms it comes in:

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
- (designed for use with Novo Nordisk Insulin Delivery Devices)
- Novolin[®]ge 30/70 FlexPen[®] 3 mL
- Novolin[®]ge 40/60 FlexPen[®] 3 mL
- Novolin[®]ge 50/50 FlexPen[®] 3 mL
- Novolin[®]ge 30/70 InnoLet[®] 3 mL
- Novolin[®]ge 40/60 InnoLet[®] 3 mL
- Novolin[®]ge 50/50 InnoLet[®] 3 mL

Novolin[®]ge premixed insulin cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles.

Novolin[®]ge premixed [FlexPen[®]] [InnoLet[®]] is designed for use with NovoFine[®] needles.

Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Novolin[®]ge premixed [Penfill[®] insulin cartridges] [FlexPen[®]] [InnoLet[®]] in combination with products that do not meet the same specifications or quality standards.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Insulin suspensions are never to be administered intravenously.
- Insulin suspensions are not to be used in insulin infusion pumps.

Before you use Novolin[®]ge [Penfill[®]/ FlexPen[®]/ InnoLet[®]] premixed talk to your doctor or pharmacist:

- ▶ **If you have trouble** with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ **If you drink alcohol:** watch for signs of a hypo and never drink alcohol on an empty stomach.
- ▶ **If you exercise more than usual** or if you want to change your usual diet.
- ▶ **If you are ill:** continue taking your insulin.
- ▶ **If you go abroad:** travelling over time zones may affect your insulin needs and the timing of your injections.

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.

Pregnancy and breastfeeding

- ▶ **If you are pregnant, planning a pregnancy or are breastfeeding** please contact your doctor for advice.

Driving and using machines

- ▶ **If you drive or use tools or machines:** watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognize hypos.

INTERACTIONS WITH THIS MEDICATION

When you use other medicines

Many 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. Talk to your doctor or pharmacist if you take, or have recently taken any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors; (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid (aspirin); anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

PROPER USE OF THIS MEDICATION

How to use

Novolin[®]ge [Penfill[®]/ FlexPen[®]/ InnoLet[®]] premixed

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. 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.

It is recommended that you measure your blood glucose regularly.

Before using Novolin[®]ge premixed:

- ▶ **Check the label** to make sure you have the right type of insulin.
- ▶ **Disinfect the rubber membrane** with an alcohol swab.
- ▶ **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.

Novolin[®]ge 30/70, Novolin[®]ge 40/60, Novolin[®]ge 50/50 Penfill[®] /FlexPen[®] /InnoLet[®]:

- ▶ **Always use a new needle** for each injection to prevent contamination

Do not use Novolin[®]ge premixed:

- ▶ **In insulin infusion pumps.**
- ▶ **If the insulin has not been stored correctly** or if it has been frozen (see 'How to Store Novolin[®]ge premixed').
- ▶ **If the insulin does not appear uniformly white and cloudy** when it is resuspended.
- ▶ **If 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.
- ▶ **If the [Penfill[®] cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge] [FlexPen[®]] [InnoLet[®]] is dropped, damaged or crushed;** there is a risk of leakage of insulin.

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

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

If you are treated with Novolin[®]ge Penfill[®] premixed 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.

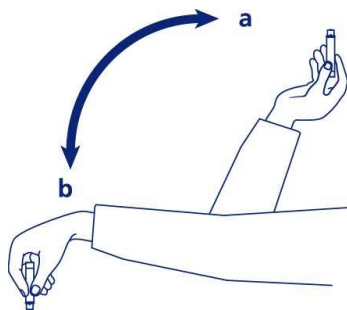
Resuspending the insulin

Resuspending is easier when the insulin has reached room temperature.

Before you put the Penfill[®] cartridge into the insulin delivery device, move it up and down between positions **a** and **b** and back (see diagram) so that the glass ball moves from one end of the cartridge to the other at least 20 times. Repeat this movement at least 10 times before each injection.

The movement must always be repeated until the liquid appears uniformly white and cloudy.

Complete the other stages of injection without delay.



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®.

How to use this insulin

Novolin®**ge** premixed insulin is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle. To avoid lumps always vary the site you inject (see '*Possible side effects*'). 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.

Before injecting Novolin®ge 30/70

1. 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.
2. Draw air into the syringe, in the same amount as the dose of insulin you need.
3. Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
4. Turn the vial and syringe upside down.
5. Draw the right dose of insulin into the syringe.
6. Pull the needle out of the vial.
7. Make sure there is no air left in the syringe: point the needle upwards and push the air out.
8. Check you have the right dose.
9. 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.
- ▶ **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.

Usual dose:

Follow carefully the instructions given by your doctor concerning type of insulin, dose, and time of injection. Any change in insulin should be made cautiously and only under medical supervision. Your insulin requirements may change due to a number of factors (illness, stress, medications, changes in diet or exercise routines, etc.). Follow your doctor's instructions to allow for these changes. The following can be considered as general guidelines only and you should consult your doctor for information, which is specific to your diabetes.

What about travelling?

The time difference between countries may mean that you have to take your insulin and meals at different times than usual. You should therefore consult your doctor if you are planning to go abroad or travel across time zones.

Overdose:

What factors may result in hypoglycaemia (low blood sugar)?

If you take too much insulin, miss a meal or exercise more than usual your blood sugar may become too low (i.e. hypoglycaemia).

The first **symptoms of hypoglycaemia** may come on suddenly. They may include: cold sweat, cool pale skin, fatigue, drowsiness, nervousness or tremor, feelings of anxiety, unusual tiredness and weakness, confusion, difficulty concentrating, excessive hunger, changes in vision, headache and nausea and palpitation.

What to do in case of hypoglycaemia?

If you experience any of the symptoms mentioned above, you should immediately take sugar or a sugar-containing product. Therefore, always carry a few lumps of sugar, candies, biscuits or fruit juice with you.

Your relatives, friends and close work-mates should know that you have diabetes and how they can help you if you get a severe hypoglycaemic reaction. They must be aware that an unconscious person should not be given anything to eat or drink (as choking is possible), but should be turned on their side and medical assistance sought immediately.

You may recover from unconsciousness more quickly if you are given an injection of the hormone glucagon by a person who has been instructed in how to use it. If glucagon is injected, you should also be given sugar, a product containing sugar or glucose by mouth as soon as you are conscious again.

If you do not respond to glucagon treatment, you will have to be treated in a hospital. See your doctor if you have had repeated hypoglycaemic reactions, or one leading to unconsciousness, as your insulin dose may need to be adjusted.

If severe hypoglycaemia is not treated, it can cause temporary or permanent brain damage or death.

What factors may result in hyperglycaemia (high blood sugar)?

If you are ill with fever or if you eat much more than usual and repeatedly take less insulin than you need, your blood sugar may become unusually high (i.e. result in hyperglycaemia).

The **symptoms of unusually high blood sugar levels** will appear gradually. They include: increased urination, thirst, loss of appetite, nausea, vomiting, drowsiness (fatigue), flushed dry skin, dry mouth, and acetone breath.

What to do in case of hyperglycaemia?

If you recognize any of the symptoms mentioned above, you should test your blood sugar level and your urine for ketones as soon as possible as the symptoms may indicate that you have a condition called ketoacidosis. If hyperglycaemia is not treated it can cause diabetic coma or death. You should therefore seek medical advice immediately and possibly take some extra insulin.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What to do in an emergency

If you get a hypo

A hypo means your blood sugar level is too low.

The warning signs of a hypo 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 hypo 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.

► **If severe hypoglycemia is not treated**, it can cause brain damage (temporary or permanent) and

even death.

- ▶ **If you have a hypo that makes you pass out**, or if you get a lot of hypos, 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.

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. Seek medical advice after an injection of glucagon; you need to find the reason for your hypo in order to avoid getting more.

Causes of a hypo

You get a hypo 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.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycemia).

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.

If you get any of these signs, test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

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.

Causes of hyperglycemia

- Forgetting to take your insulin.
- Repeatedly taking less insulin than you need.
- An infection or fever.
- Eating more than usual.
- Exercising less than usual.

Possible

side effects

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 '*What to do in an emergency*'.

Less commonly reported side effects

(less than 1 in 100)

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 prevent 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.

Signs of allergy Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These reactions usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:

- If signs of allergy spread to other parts of the body, or

- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy; feel like fainting.

You may have a very rare serious allergic reaction to Novolin[®] **ge** premixed insulin or one of its ingredients (called a systemic allergic reaction). See also the warning in '*Before you use Novolin[®] ge premixed*'.

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 reaction usually disappears.

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.

HOW TO STORE IT

How to store

Novolin[®] ge [Penfill[®] / FlexPen[®] / InnoLet[®]] premixed

Keep out of the reach and sight of children.

Novolin[®] ge premixed insulin [vial] [in Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] 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] [in Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] that is being used or is about to be used is not to be kept in a refrigerator. After removing Novolin[®] ge premixed [vial] [in Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] 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 use Novolin[®] ge premixed*'.

Novolin[®] ge 30/70:

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[®] /FlexPen[®] /InnoLet[®]:

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] [FlexPen[®]] [InnoLet[®]] in the outer carton when you are not using it, in order to protect it from light.

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

Do not use Novolin[®] ge premixed insulin [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] after the expiry date which is printed on the label and the carton. The expiry date refers to the last day of that month.

Novolin[®] ge premixed insulin [vial] [Penfill[®] cartridge] [FlexPen[®]] [InnoLet[®]] 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.

REPORTING SUSPECTED SIDE EFFECTS

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

By toll-free telephone: 866-234-2345
By toll -free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

What Novolin[®]ge premixed insulin 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 x 3 mL FlexPen[®] insulin delivery device
- 1 x 3 mL InnoLet[®] insulin delivery device

1 mL contains 100 IU (International Units) of insulin human.

1 vial contains 10 mL equivalent to 1000 IU.

1 [Penfill[®]] [FlexPen[®]] [InnoLet[®]] contains 3 mL equivalent to 300 IU.

For further information, please refer to the '*Information for Health Care Professionals*'.

This summary does not contain all the known information about Novolin[®]ge premixed insulin. Talk to your doctor if you have any questions

This document plus the full product monograph, prepared for health professionals can be found at:
www.novonordisk.ca
or by contacting the sponsor, **Novo Nordisk Canada Inc.**, at
1-800-465-4334

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