NovoLog®
Insulin aspart (rDNA origin) Injection

DESCRIPTION

NovoLog® (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. NovoLog is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8.

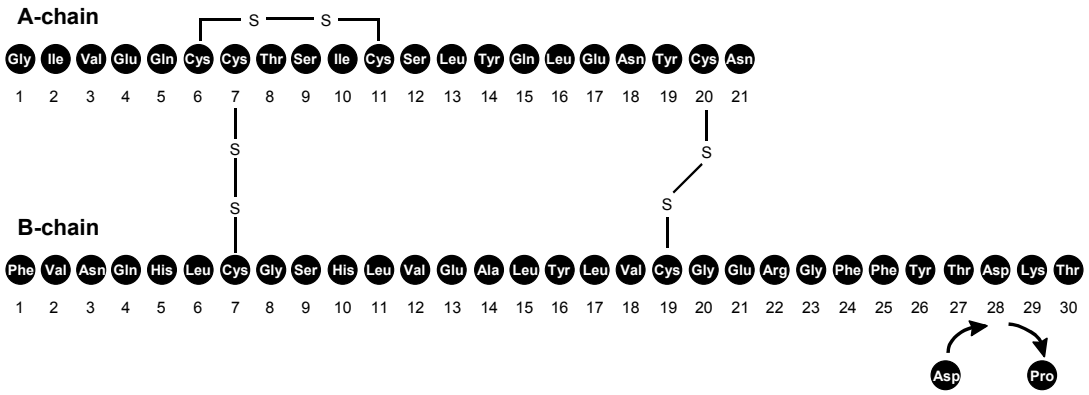

Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, and sodium chloride 0.58 mg/mL. NovoLog has a pH of 7.2-to 7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of Action

The primary activity of NovoLog is the regulation of glucose metabolism. Insulins, including NovoLog, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see Figure 2 and Figure 3).

Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog reduces the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

Bioavailability and Absorption - NovoLog has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after subcutaneous injection (see Figure 2 and Figure 3). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

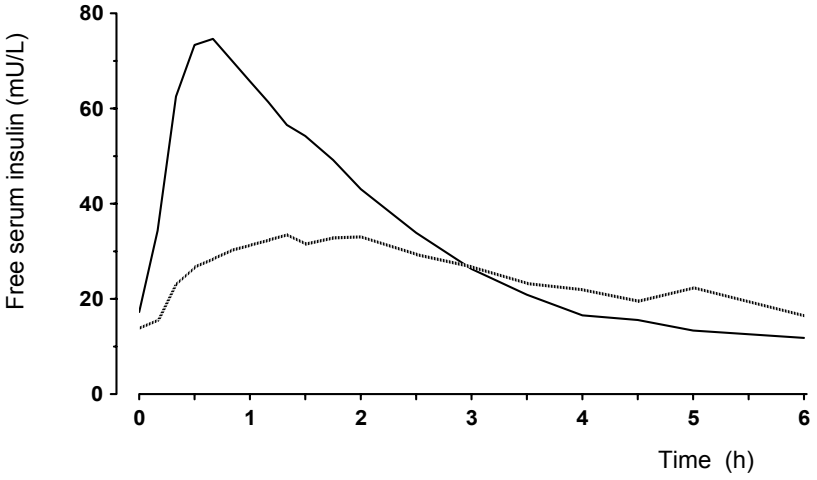

Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

In studies in healthy volunteers (total n=l07) and patients with Type 1 diabetes (total n=40), NovoLog consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40 to 50 minutes for NovoLog versus 80 to 120 minutes for regular human insulin. In a clinical trial in patients with Type 1 diabetes, NovoLog and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82.1 and 35.9 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with Type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog and regular human insulin described above, were observed independent of the injection site (abdomen, thigh, or upper arm). Differences in pharmacokinetics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

Distribution and Elimination - NovoLog has a low binding to plasma proteins, 0-9%, similar to regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that NovoLog has a more rapid onset of action than regular human insulin.

In a 6-hour study in patients with Type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog occurred between 1 and 3 hours after subcutaneous injection (see Figure 3). The duration of action for NovoLog is 3 to 5 hours compared to 5 to 8 hours for regular human insulin. The time course of action of insulin and insulin analogs such as NovoLog may vary considerably in different individuals or within the same individual. The parameters of NovoLog activity (time of onset, peak time and duration) as designated in Figure 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

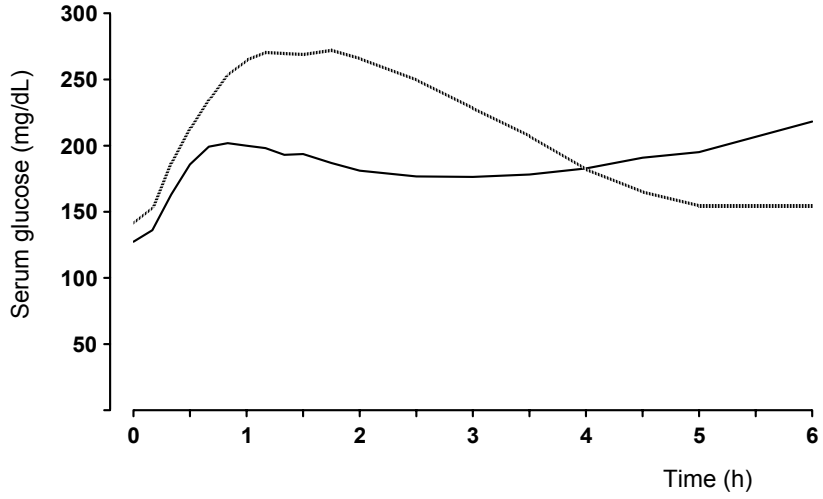

Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

Special Populations

Children and Adolescents - The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade $\geq$ 2], n=9) with Type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with Type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with Type 1 diabetes.

Geriatrics - The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

Gender - In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbAlc) between genders in a trial in patients with Type 1 diabetes.

Obesity - In a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m^2), the pharmacokinetic parameters, AUC and Cmax, of NovoLog were generally unaffected by BMI. Clearance of NovoLog was reduced by 28% in patients with BMI >32 compared to patients with BMI <23 when a single dose of 0.1 U/kg NovoLog was administered. However, only 3 patients with BMI <23 were studied.

Ethnic Origin - The effect of ethnic origin on the pharmacokinetics of NovoLog has not been studied.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of NovoLog was administered in a study of 18 patients with creatinine clearance values ranging from normal to <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and Cmax of NovoLog was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. In an open-label, single-dose study of 24 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment), no correlation was found between the degree of hepatic failure and any NovoLog pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy - The effect of pregnancy on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied (see PRECAUTIONS, Pregnancy).

Smoking - The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog has not been studied.

CLINICAL STUDIES

To evaluate the safety and efficacy of NovoLog in patients with Type 1 diabetes, two six-month, open-label, active-control (NovoLog vs. Novolin® R) studies were conducted (see Table 1). NovoLog was administered by subcutaneous injection immediately prior to meals

and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA1c, the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party), and the incidence of ketosis were clinically comparable for the two treatment regimens. The mean total daily doses of insulin were greater (1-3 U/day) in the NovoLog-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. To achieve improved glycemic control, some patients required more than three doses of meal-related insulin and/or more than one dose of basal insulin (see Table 1). No serum glucose measurements were obtained in these studies.

To evaluate the safety and efficacy of NovoLog in patients with Type 2 diabetes, one six-month, open-label, active-control (NovoLog vs. Novolin R) study was conducted (see Table 1). NovoLog was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbAlc and the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party) were clinically comparable for the two treatment regimens. The mean total daily dose of insulin was greater (2 U/day) in the NovoLog-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. To achieve improved glycemic control, some patients required more than three doses of meal-related insulin and/or more than one dose of basal insulin (see Table 1).

Table 1. Results of two six-month, active-control, open-label trials in patients with Type 1 diabetes (Studies A and B) and one six-month, active-control, open-label trial in patients with Type 2 diabetes (Study C).

Study	Treatment (n)	Mean HbA1c (%)		Hypoglycemia[1] (events / month / patient)	% of Patients Using Various Numbers of Insulin Injections / Day[2]				
		Baseline	Month 6		Rapid-acting			Basal	
					1 - 2	3	4 - 5	1	2
A	NovoLog (n=694)	8.0	7.9	0.06	3	75	22	54	46
	Novolin R (n=346)	8.0	8.0	0.06	6	75	19	63	37
B	NovoLog (n=573)	7.9	7.8	0.08	4	90	6	94	6
	Novolin R (n=272)	8.0	7.9	0.06	4	91	4	93	7
C	NovoLog (n=90)	8.1	7.7	0.02	4	93	4	97	4
	Novolin R (n=86)	7.8	7.8	0.01	2	93	5	93	7

[1] Events requiring intervention from a third party during the last three months of treatment
[2] Percentages are rounded to the nearest whole number

To evaluate the use of NovoLog by subcutaneous infusion with an external pump, two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog

versus Velosulin (buffered regular human insulin) in patients with Type 1 diabetes. Changes in HbA1c and rates of hypoglycemia were comparable. Patients with Type 2 diabetes were also studied in an open-label, parallel design trial (16 weeks [n=127]) using NovoLog by subcutaneous infusion compared to pre-prandial injection (in conjunction with basal NPH injections). Reductions in HbA1c and rates of hypoglycemia were comparable (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE).

INDICATIONS AND USAGE

NovoLog is indicated for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps (see WARNINGS, PRECAUTIONS [especially Usage in Pumps], Information for Patients [especially For Patients Using Pumps], Mixing of Insulins, DOSAGE AND ADMINISTRATION, RECOMMENDED STORAGE).

CONTRAINDICATIONS

NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog or one of its excipients.

WARNINGS

NovoLog differs from regular human insulin by a more rapid onset and a shorter duration of activity. Because of the fast onset of action, the injection of NovoLog should immediately be followed by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Any change of insulin dose should be made cautiously and only 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.

Insulin Pumps: When used in an external insulin pump for subcutaneous infusion, NovoLog should not be diluted or mixed with any other insulin. Physicians and patients should carefully evaluate information on pump use in the NovoLog physician and patient package inserts and in the pump manufacturer's manual (e.g. NovoLog-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to NovoLog usage, because NovoLog-specific information may

differ from general pump manual instructions). Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences may be particularly relevant when patients are switched from multiple injection therapy or infusion with buffered regular insulin. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required (see PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE).

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of NovoLog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Allergy - Local Allergy - As with other insulin therapy, 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, but in some occasions, may require discontinuation of NovoLog. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.
Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.
Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.
In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production - Increases in levels of anti-insulin antibodies that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. The number of patients treated with insulin aspart experiencing these increases is greater than the number among those treated with human regular insulin. Data from a 12-month controlled trial in patients with Type 1 diabetes suggest that the increase in these antibodies is transient. The differences in antibody levels between the human regular insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. They do not appear to cause deterioration in HbA1c or to necessitate increases in insulin dose.

Pregnancy and Lactation
Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation.

Usage in Pumps
NovoLog is recommended for use in Disetronic H-TRON® plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, or 507 with MiniMed 3 mL syringes and Polyfin® or Sof-set® infusion sets.

In-vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation, may occur with the use of NovoLog for more than two days at 37°C (98.6°F) in infusion sets and reservoirs. NovoLog in clinical use should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump** (see WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE).

Information for Patients

For all patients:
Patients should be informed about potential risks and advantages of NovoLog therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

For patients using pumps
Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories. NovoLog is recommended for use with Disetronic H-TRON plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, and 507 with MiniMed 3 mL syringes and Polyfin or Sof-set infusion sets. The use of NovoLog in quick-release infusion sets and cartridge adapters has not been assessed.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), the infusion sets (reservoir syringe, tubing, and catheter) and the NovoLog in the reservoir should be replaced, and a new infusion site selected every 48 hours or less. Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of NovoLog.

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences are particularly relevant when patients are switched from infused buffered regular insulin or multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their physician (see WARNINGS, PRECAUTIONS, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE).

Laboratory Tests

As with all insulin therapy, the therapeutic response to NovoLog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

Mixing of Insulins

- A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.
- The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).
- Mixtures should not be administered intravenously.
- When used in external subcutaneous infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in

females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

Pregnancy - Teratogenic Effects - Pregnancy Category C

There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant women. NovoLog should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Subcutaneous reproduction and teratology studies have been performed with NovoLog and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of NovoLog in children have not been studied.

Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog in 3 human insulin-controlled clinical studies, 2.6% (n=36) were 65 years of age or over. Half of these patients had Type 1 diabetes (18/1285) and half had Type 2 (18/90) diabetes. The HbA1c response to NovoLog, as compared to human insulin, did not differ by age, particularly in patients with Type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog action have not been performed.

ADVERSE REACTIONS

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as Whole - *Allergic reactions* (see PRECAUTIONS, Allergy).

Skin and Appendages - *Injection site reaction, lipodystrophy, pruritus, rash* (see PRECAUTIONS, Allergy; Information for Patients, Usage in Pumps).

Other – *Hypoglycemia, Hyperglycemia and ketosis* (see WARNINGS and PRECAUTIONS).

In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

NovoLog should generally be given immediately before a meal (start of meal within 5- to 10 minutes after injection) because of its fast onset of action. The dosage of NovoLog should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The total daily individual insulin requirement is usually between 0.5- to 1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 50- to 70% of total insulin requirements may be provided by NovoLog and the remainder provided by an intermediate-acting or long-acting insulin. When used in external insulin infusion pumps, the initial programming of the pump is based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is given as meal-related boluses of NovoLog and the remainder as basal infusion. Because of NovoLog's comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human regular insulin. Additional basal insulin injections, or higher basal rates in external

subcutaneous infusion pumps may be necessary. **Infusion sets and the insulin in the infusion sets must be changed every 48 hours or sooner to assure the activity of NovoLog and proper pump function** (see WARNINGS, PRECAUTIONS, Information for Patients).

NovoLog should be administered by subcutaneous injection in the abdominal wall, the thigh, or the upper arm, or by continuous subcutaneous infusion in the abdominal wall. Injection sites and infusion sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use any NovoLog if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

HOW SUPPLIED
NovoLog is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).
10 mL vials NDC 0169-7501-11
3 mL PenFill® cartridges* NDC 0169-3303-12
3 mL NovoLog FlexPen® Prefilled syringe NDC 0169-6339-10
3 mL NovoLog InnoLet® Prefilled syringe NDC 0169-xxxx-xx

* NovoLog PenFill cartridges are for use with NovoFine® disposable needles and the following 3 mL PenFill cartridge compatible delivery devices: NovoPen 3, NovoPen Junior, Innovo® and InDuo®.
NovoLog FlexPen and NovoLog InnoLet Prefilled syringes are for use with NovoFine disposable needles.

RECOMMENDED STORAGE
NovoLog in unopened vials, cartridges, and NovoLog FlexPen and NovoLog InnoLet Prefilled syringes should be stored between 2° and 8°C (36° to 46°F). *Do not freeze.* **Do not use NovoLog if it has been frozen or exposed to temperatures that exceed 37°C (98.6°F).**
After a vial, cartridge, or Prefilled syringe has been punctured, it may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated. Cartridges should not be refrigerated after insertion into the Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices.

	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days **(Do not refrigerate)**

3 mL NovoLog Flex Pen	28 days	Until expiration date	28 days **(Do not refrigerate)**
3 mL NovoLog InnoLet	28 days	Until expiration date	28 days **(Do not refrigerate)**

Infusion sets (reservoirs, tubing, and catheters) and the NovoLog in the reservoir should be discarded after no more than 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

Rx only

Date of Issue: [insert date]
8-XXXX-XX-XXX-X

Manufactured For Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey 08540
www.novonordisk-us.com
Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

Information For The Patient
NovoLog® InnoLet® (Insulin aspart [rDNA origin] Injection) 3 mL Prefilled Syringe
100 units/mL (U-100)

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about NovoLog® (NO-voe-log), ask your doctor. Only your doctor can determine if NovoLog® is right for you.

What is the most important information I should know about NovoLog?

- Because NovoLog starts lowering blood glucose more quickly and will not work as long as human regular insulin, you should give NovoLog injection 5 to 10 minutes before you eat.
- Because NovoLog does not work as long as human regular insulin, you may need to add an intermediate-acting or longer-acting insulin (basal insulin) to give the best glucose control.
- Glucose monitoring is recommended for all patients who use insulin.

Age and exposure to heat affect the stability of NovoLog and its preservative. Also, NovoLog does not work after it has been frozen. Therefore, do not use old insulin or insulin that has been exposed to high temperature (greater than 37°C [98.6°F]) or frozen. Hyperglycemia may be a sign that the insulin is no longer working and needs to be replaced.

For your safety, read the section "What are the possible side effects of NovoLog?" to review the symptoms of low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia).

What is NovoLog?

NovoLog is a clear, colorless, sterile solution for injection under the skin (subcutaneously). Because NovoLog is made by recombinant DNA (rDNA) technology and is chemically different from the insulin made by the human body, it is called an insulin analog. The active ingredient in NovoLog is insulin aspart. The concentration of insulin aspart is 100 units per milliliter, or U100. NovoLog also contains: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, and sodium chloride. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. These ingredients help to preserve or stabilize NovoLog. The pH (balance between acid and alkaline conditions) is important to the stability of NovoLog.

Who should not use NovoLog?

Do not use NovoLog if:

- your blood sugar (glucose) is too low (hypoglycemia).
- you do not plan to eat right after your injection.
- you are allergic to insulin aspart or any of the ingredients mentioned above in "What is NovoLog?". Check with your doctor if you are not sure.

The effects of NovoLog on an unborn child or on a nursing baby are unknown. Therefore, tell your doctor if you plan to become pregnant or breast feed, or if you become pregnant.
Tell your doctor about all medicines and supplements that you are using. Some medicines, including non-prescription medicines and dietary supplements, may affect your diabetes.

What should I know about using insulin?

- Any change of insulin should be made cautiously and only under medical supervision. Changes in the strength, manufacturer, type (for example: Regular, NPH, Lente®), species (beef, pork, beef-pork, human) or method of manufacture (recombinant [rDNA] or animal source insulin) may result in the need for a change in the timing or dosage of the new insulin.
- Glucose monitoring will help you and your health care provider adjust the dosages.
- Always carry a quick source of sugar, such as candy or glucose tablets, to treat low blood sugars (hypoglycemia).
- Always carry identification that states that you have diabetes.

What should I know about using NovoLog?

See the end of this Information For The Patient for instructions about preparing and giving the injection.

- NovoLog starts working 10- to 20 minutes after injection. The greatest blood sugar lowering effect is between 1 and 3 hours after injection. This blood sugar lowering lasts for 3 to 5 hours. (The time periods are only general guidelines.)

- If you switch to NovoLog from a different insulin product, you may require a change in dosage from that used with other insulin products. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

- Do not inject in skin that has become reddened or bumpy or thickened after injection. Insulin absorption in these areas may not be the same as that in normal skin, and may change the onset and duration of insulin action.

- Use NovoLog only if it appears clear and colorless. Do not use NovoLog if it appears cloudy, thickened, or colored, or if it contains solid particles.

What should I avoid while using NovoLog?

- Drinking alcohol may lead to hypoglycemia.
- Do not miss meals after injections of NovoLog.

What are the possible side effects of NovoLog?

NovoLog, like other insulin products, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar) is the most common side effect. Hypoglycemia occurs when there is too much insulin, or not enough food in your body, or the amount and timing of insulin dosing is incorrect. Therefore, **hypoglycemia can occur with**:

- **Excessive (too much) insulin.** This can happen if too much insulin is injected.
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (for blood pressure and heart failure), salicylates, including aspirin and NSAIDS (for pain), some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake**. This can happen if:
  - a meal or snack is missed or delayed
  - you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body
  - alcohol interferes with carbohydrate metabolism
- **Too much glucose use by the body.** This can happen from:
  - too much exercise
  - higher than normal metabolism rates due to fever or an overactive thyroid

Hypoglycemia can be mild or severe. Its onset may be rapid. Patients with very good (tight) glucose control, patients with diabetic neuropathy (nerve problems), or patients using some Beta-blockers (used for high blood pressure and heart conditions) may have

few warning symptoms before severe hypoglycemia develops. Hypoglycemia may reduce your ability to drive a car or use mechanical equipment without risk of injury to yourself or others. Severe hypoglycemia can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death. Symptoms of hypoglycemia include:**

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision or slurred speech
- palpitations (rapid heart beat)
- sweating
- tremor (shaking) or unsteady gait (walking)

Mild to moderate hypoglycemia is treated by eating or drinking carbohydrates (milk, orange juice, sugar candies, or glucose tablets). More severe or continuing hypoglycemia may require the help of another person or emergency medical personnel. Patients who are unable to take sugar by mouth or who are unconscious may need treatment with a glucagon injection or glucose given intravenously (in the vein).

Talk with your doctor about severe, continuing, or frequent hypoglycemia, and hypoglycemia for which you had few warning symptoms.

Hyperglycemia (high blood sugar) is another common side effect. Hyperglycemia also occurs when there is too little insulin, or too much food in your body, or the amount and timing of insulin dosing is incorrect. Therefore, **hyperglycemia can occur with:**

- **Insufficient (too little) insulin.** This can happen from any of the following:
  - too little or no insulin is injected.
  - the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date.
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazide diuretics (water pills used for blood pressure), corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin**. These medical conditions include surgery, fevers, infections, heart attacks, and stress.
- **Too much carbohydrate intake**. This can happen if you
  - eat larger meals
  - eat more often
  - increase the proportion of carbohydrate in your meals

Hyperglycemia can be mild or severe. Hyperglycemia can **progress to diabetic ketoacidosis (DKA) or very high glucose levels (hyperosmolar coma) and result in unconsciousness and death.** Although diabetic acidosis occurs most often in patients with Type 1 diabetes, it can occur in patients with Type 2 diabetes who become severely ill. Urine or blood tests will show acetone, ketones, and high levels of glucose. Hyperosmolar coma occurs most often in patients with Type 2 diabetes. Urine and blood tests will show very high levels of glucose.
Because some patients experience few symptoms of hyperglycemia and ketosis, it is important to monitor your glucose several times a day. **Symptoms of hyperglycemia include:**

- confusion or drowsiness
- fruity smelling breath
- rapid, deep breathing
- increased thirst
- decreased appetite, nausea, or vomiting
- abdominal (stomach area) pain
- rapid heart rate
- increased urination and dehydration (too little fluid in your body)

Mild hyperglycemia is treated by drinking fluids (rehydration) and taking extra doses of insulin. Glucose and acetone-ketone levels should be monitored more often until they return to normal. **More severe or continuing hyperglycemia requires prompt evaluation and treatment by your health care provider.**

Allergy can be serious. Generalized allergy is an uncommon, but possibly life-threatening, reaction to insulin products. **Symptoms include:**

- itchy rash over the entire body
- shortness of breath or wheezing
- confusion
- low blood pressure
- rapid heart beat
- sweating

If you think you are having a generalized allergic reaction, get emergency medical help right away.

Allergic reactions at the injection site (itching, redness, hardness, or swelling) are more common than generalized allergy. They may need several days or weeks to clear up. Avoid injection of insulin into skin areas that have reactions. Tell your doctor about such reactions, because they can become more severe, or they may change the absorption of insulin.

Lipodystrophy is a common change in the fat below the injection site. These changes include loss of fat (depressions in the skin called lipoatrophy) or thickening of the tissue under the skin (lipohypertrophy). Avoid injection or infusion of insulin into skin areas

that have these reactions. Tell your doctor about such reactions because they can become more severe, or they may change the absorption of insulin.

How should I store NovoLog?

- **NovoLog can be damaged by high temperatures.** Therefore, be sure to protect it from high temperatures, heat from the sun, saunas, long showers, and other heat sources. This is especially important if you use NovoLog InnoLet because you carry this device with you and it may be exposed to different temperatures as you go about your daily activities. **Throw away NovoLog InnoLet if it has been exposed to temperatures greater than 37°C (98.6°F).**

- **Unopened NovoLog** should be stored in a refrigerator but not in the freezer. Do not use NovoLog if it has been frozen. Keep unused NovoLog InnoLet in the carton so that they will stay clean and protected from light. If unopened NovoLog InnoLet is stored at room temperature below 30°C (86°F) and protected from direct heat and sunlight, you can use it for up to 28 days.

- **After starting to use insulin,** do not refrigerate NovoLog InnoLet in use (the rubber stopper has been punctured). However, keep it ~~as cool as possible~~ at room temperature (below 30°C [86°F]) and away from direct heat and sunlight for up to 28 days**.**

- Never use NovoLog InnoLet if it has been stored improperly.

- Never use NovoLog InnoLet after the expiration date printed on the label or carton.

- **Throw away unrefrigerated NovoLog InnoLet after 28 days, even if they still contain insulin.**

	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days **(Do not refrigerate)**
3 mL NovoLog Flex Pen	28 days	Until expiration date	28 days **(Do not refrigerate)**
3 mL NovoLog InnoLet	28 days	Until expiration date	28 days **(Do not refrigerate)**

General advice

- NovoLog is available in:

i. 10 mL vials
ii. 3 mL PenFill cartridges for use with insulin Pen
iii. 3 mL NovoLog FlexPen Prefilled syringes
iv. 3 mL NovoLog InnoLet Prefilled syringes
v. For use with external insulin infusion pump

- This leaflet summarizes the most important information about NovoLog. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for additional information about NovoLog.

How do I prepare NovoLog InnoLet before I give an injection?

- Never attach a disposable needle on your **NovoLog InnoLet** Prefilled syringe until you are ready to give an injection. Remove it immediately after each injection. Follow the directions for use of this syringe on the reverse side of this insert.
- **NovoLog InnoLet** Prefilled syringes may contain a small amount of air. To prevent an injection of air and to make sure correct dose of insulin is given, an air shot must be done before each injection. See **Using the disposable NovoLog InnoLet Prefilled Syringe** for the instructions on how to do an air shot.

How do I give an injection using NovoLog InnoLet?

1. Thighs, upper arms, buttocks, abdomen are acceptable areas for an insulin injection. Do not change the injection areas without consulting your physician. Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.
2. The actual point of injection should be changed each time. Injection sites should be about an inch apart. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the device upright and push the needle quickly and firmly into the pinched-up area. Release the skin and push the push-button all the way in to inject insulin beneath the skin. To ensure that all the insulin is injected, keep the needle in the skin for at least 6 seconds after injection with your thumb on the push-button. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds – **DO NOT RUB**.
4. After the injection, remove the needle without replacing the cap. Hold the NovoLog InnoLet firmly while you unscrew the NovoFine disposable needle. **The NovoFine disposable needle must be removed immediately after each injection without replacing the cap.** If the NovoFine disposable needle is not removed, some liquid may leak out of the NovoLog InnoLet.
5. Used NovoFine disposable needles should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal

containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

Helpful information is published by The American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314, for people with diabetes.

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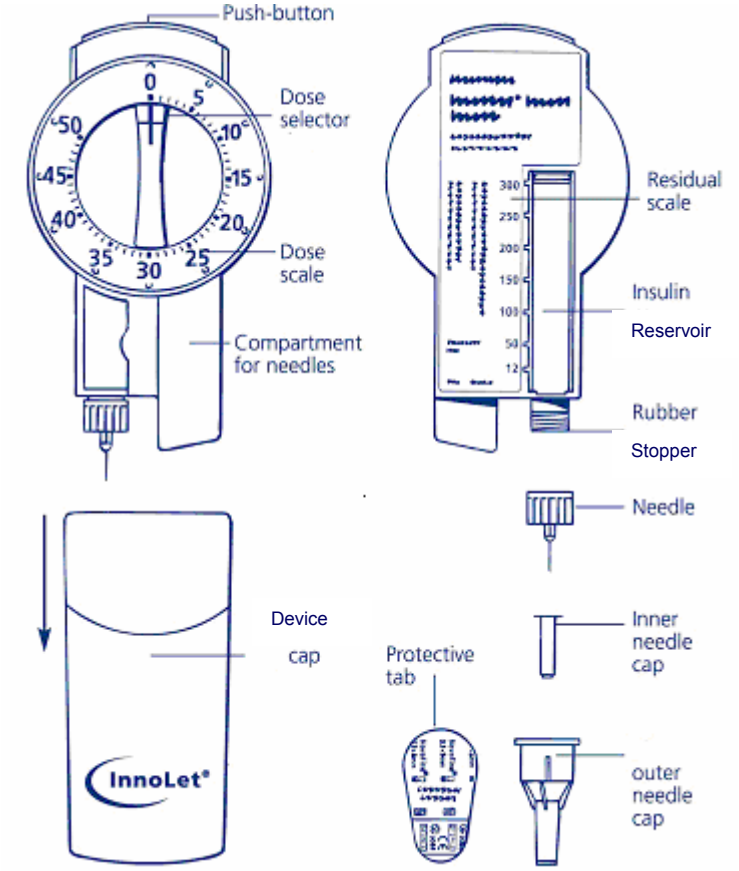
Using the disposable NovoLog InnoLet Prefilled Syringe

NovoLog InnoLet is a disposable dial-a-dose insulin delivery system able to deliver 1 to a maximum of 50 units. The dose can be adjusted in increments of 1 unit. NovoLog InnoLet is designed for use with NovoFine® single-use needles. NovoLog InnoLet is not recommended for the blind or visually impaired patients without the assistance of a sighted individual trained in the proper use of the product.

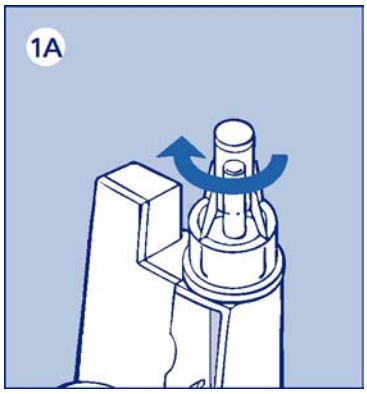
Please read these instructions completely before using this device.



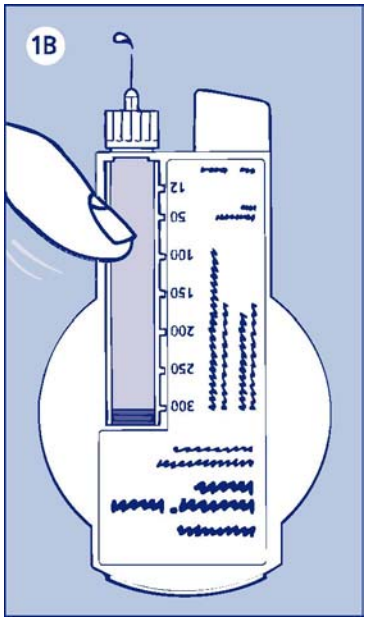
PREPARING THE NOVOLOG INNOLET:

a. Pull off the cap.

b. Wipe the rubber stopper with an alcohol swab.



1A. Remove the protective tab from the disposable needle and screw the needle onto the NovoLog InnoLet (see diagram **1A**). Never place a disposable needle on your NovoLog InnoLet until you are ready to give an injection. Remove the needle immediately after use. If the needle is not removed, some liquid may leak from the NovoLog InnoLet.

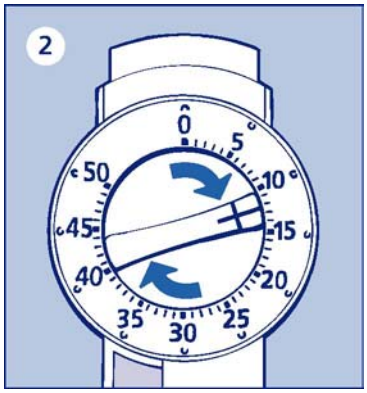


1B. Giving the air shot before each injection:
Small amounts of air may collect in the needle and insulin reservoir during normal use. **To avoid injecting air and to ensure proper dosing, dial 2 units by turning the dose selector clockwise.** Hold the NovoLog InnoLet with the needle pointing up and tap the insulin reservoir gently with your finger so any air bubbles collect in the top of the reservoir. Remove both the plastic outer and inner needle cap.

With the needle pointing up, press the push button as far as it will go and the dose selector returns to zero. See if a drop of insulin appears at the needle tip (see diagram 1**B**). If not, repeat the procedure until insulin appears. Before the first use of NovoLog InnoLet, you may need to perform up to 6 air shots to get a droplet of insulin at the

needle tip. If you need to make more than 6 air shots, do not use the syringe, and contact Novo Nordisk at 1-800-727-6500. A small air bubble may remain but it will not be injected because the operating mechanism prevents the reservoir from being completely emptied.

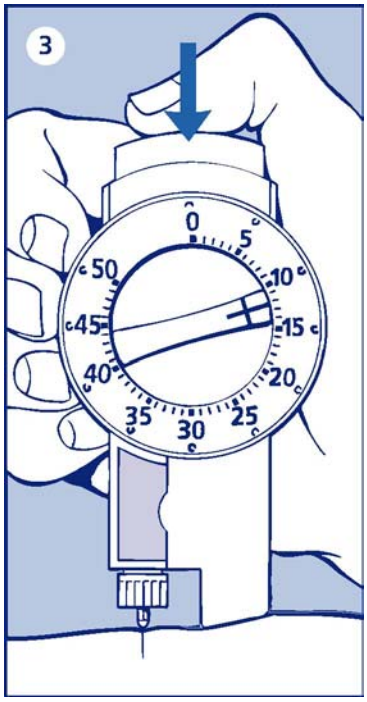
2. SETTING THE DOSE



Always check that the push button is fully depressed and the dose selector is set at 0. Hold the NovoLog InnoLet in front of you and dial the dose selector clockwise to set the required dose. Do not put your hand over the push button when dialing the dose. If the button is not allowed to rise freely, insulin will be pushed out of the needle. You will hear a click for every single unit dialed. Do not rely on this click for setting your dose. If you have set a wrong dose, simply dial the dose selector forward or backwards until the right number of units has been set. You cannot set a dose larger than the number of units left in the reservoir. **50 units is the maximum dose.**

3. GIVING THE INJECTION

Use the injection technique recommended by your doctor or health care professionals.



Check that you have set the proper dose and depress the push button as far as it will go. Make sure not to block the dose selector while injecting, as the dose selector must be allowed to return to zero when you press the push button. When depressing the push button you may hear a clicking sound. Do not rely on this clicking sound as a means of confirming your dose.

After the injection, the needle should remain under the skin for at least 6 seconds. Keep the push button fully depressed until the needle is withdrawn from the skin. This will ensure that the full dose has been delivered. If blood appears after you pull the needle from your skin, press the injection site lightly with a finger. **Do not rub the area.**

Do not recap the needle. Remove the used needle and dispose of it in a puncture-resistant container. Used syringes, needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

It is important that you use a new needle for each injection. Health care professionals, relatives, and other caregivers, should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.

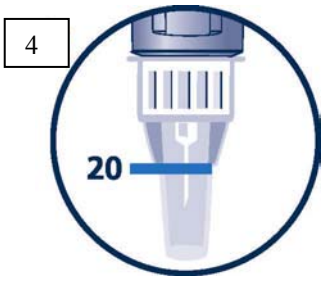
LATER (SUBSEQUENT) INJECTIONS

It is important that you use a new needle for each injection.

Always check that the push button is fully depressed and the dose selector is at zero before using the NovoLog InnoLet again. If not, turn the dose selector until the push button is completely down. Then proceed as stated in steps 1-3.

The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the NovoLog InnoLet. Do not use these numbers to measure the insulin dose. You cannot set a dose greater than the number of units remaining in the reservoir.

4. FUNCTION CHECK



If your disposable NovoLog InnoLet is not working properly, follow this procedure:

- Screw on a new NovoFine needle
- Give an air shot as described in section 1B
- Put the outer needle cap onto the needle
- Dispense 20 units into the outer needle cap, holding the NovoLog InnoLet with the needle pointing down.

The insulin should fill the lower part of the cap (as shown in diagram 4). If the disposable NovoLog InnoLet has released too much, or too little insulin, repeat the test. If it happens again, do not use your disposable NovoLog InnoLet and contact Novo Nordisk® at 1-800-727-6500.
Dispose of the used NovoLog InnoLet carefully without the needle attached.

5. IMPORTANT NOTES

- If you need to perform more than 6 air shots before the first use of the NovoLog InnoLet to get a droplet of insulin at the needle tip, do not use it.
- Remember to perform an air shot before each injection. See diagram **1B.**
- Care should be taken not to drop your NovoLog InnoLet or subject it to impact.
- Remember to keep the NovoLog InnoLet with you. Don't leave it in a car or other location where it can get too hot or too cold.
- NovoLog InnoLet is designed for use with NovoFine disposable needles.
- **Do NOT** attach a disposable needle on the NovoLog InnoLet until you are ready to use it. Remove the needle right after use without recapping.
- **Throw away used needles properly, so other people will not be harmed.** Used NovoFine disposable needles should be placed in sharps containers (such as red

biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

- Throw away the used NovoLog InnoLet carefully, without the needle attached.
- Always carry a spare NovoLog InnoLet with you in case your NovoLog InnoLet is damaged or lost.
- To avoid possible transmission of disease, do not let anyone else use your NovoLog InnoLet, even if they attach a new needle.
- Novo Nordisk is not responsible for harm due to using this insulin delivery system with products not recommended by Novo Nordisk.
- Keep this NovoLog InnoLet out of the reach of children.