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.

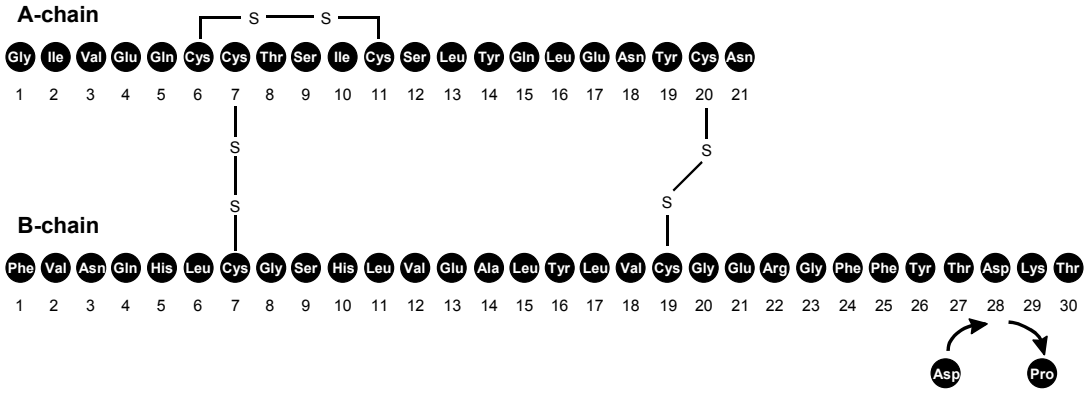

Figure 1. Structural formula of insulin aspart.

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 7.2-7.6. 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.

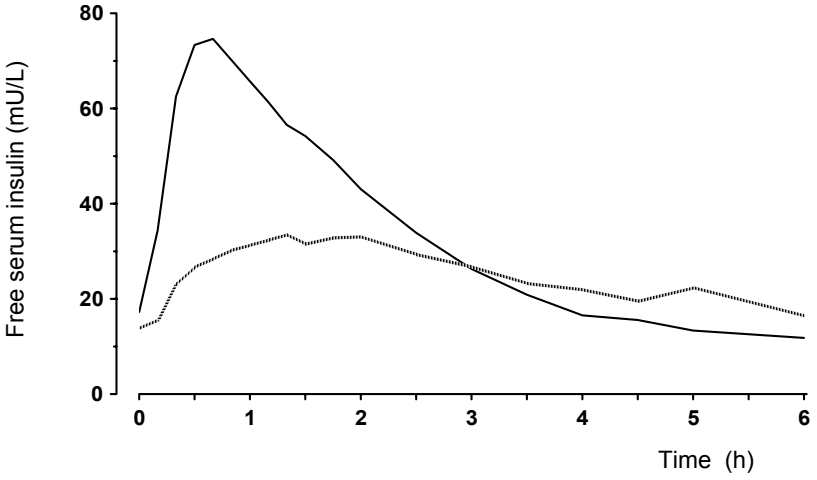

Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

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.

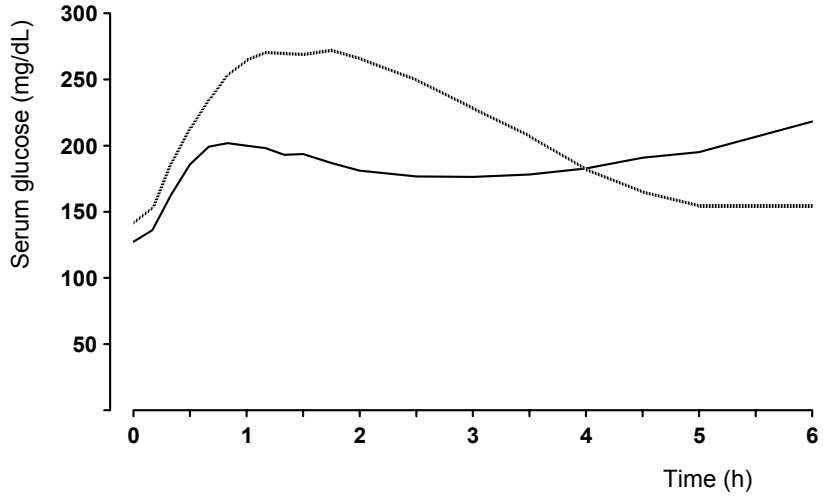

Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

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 glucodynamics 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 metacresol 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

Pumps:
NovoLog is recommended for use in Disetronic H-TRON series, MiniMed 500 series, and other equivalent pumps.

Reservoirs and infusion sets:
NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies have shown that pump malfunction, loss of metacresol, and insulin degradation, may occur when NovoLog is maintained in a pump system for more than 48 hours. Reservoirs and infusion sets should be changed at least every 48 hours.

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.

Pumps:
NovoLog is recommended for use in Disetronic H-TRON series, MiniMed 500 series, and other equivalent pumps

Reservoirs and infusion sets:
NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), reservoirs, infusion sets, and injection site should be changed at least every 48 hours.

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 to1.0 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. **NovoLog in the reservoir and infusion sets, and the injection site must be changed at least every 48 hours.**

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 Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices: NovoPen®3, NovoPen Junior, Innovo®, and InDuo®.

NovoLog FlexPen Prefilled syringes are for use with NovoFine disposable needles.

RECOMMENDED STORAGE

NovoLog in unopened vials, cartridges, 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. The infusion set (tubing and needle) should be changed at least every 48 hours.

NovoLog in the reservoir should be discarded after at least every 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

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

Rx only

Date of Issue: XX xx, 2004
8-XXXX-XX-XXX-X

Manufactured For Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey 08540
Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

www.novonordisk-us.com

Information For The Patient
NovoLog® (Insulin aspart [rDNA origin] Injection)
3 mL PenFill® Disposable Cartridge (300 units per cartridge)
10 mL Vial (1000 units per vial)
100 units/mL (U-100)

- What is the most important information I should know about NovoLog?
  - For all NovoLog users
  - For pump users
- What is NovoLog?
- Who should not use NovoLog?
- What should I know about using insulin?
- What should I know about using NovoLog?
- What should I avoid when using NovoLog?
- What are the possible side effects of NovoLog?
- How should I store NovoLog?
- General advice
- Injection and pump infusion instructions
  - How should I inject NovoLog?
    - Using Vials
    - Using Cartridges
  - How should I infuse NovoLog with an external subcutaneous insulin infusion pump?
  - How should I mix insulins?

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?

For All NovoLog Users

- NovoLog (NO-voe-log) is different from regular human insulin and buffered regular human insulin (Velosulin). It works faster (rapid onset of action) and will not work as long (shorter duration of action) as regular human insulin or buffered regular human insulin (Velosulin).

- Because the onset of action is fast, you should eat a meal 5 to10 minutes after a NovoLog injection or NovoLog bolus infusion dose given by an external pump. (A bolus is a large dose.) Eating right after the dose will reduce the risk of low blood sugar (hypoglycemia).

- The shorter duration of NovoLog's action means that you may need to use an intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog insulin infusion in the pump. This will give the best glucose control and will help you avoid hyperglycemia (high blood sugar) and ketoacidosis (too much acid [low pH] in your body).

- Glucose monitoring is recommended for all patients who use insulin.

If you use NovoLog by injection, you may need to increase some or all of the following:
- your total dose of insulin
- your dose of intermediate or long-acting insulin (for example, NPH)
- the number of injections of basal insulin

If you infuse NovoLog into the skin (subcutaneous tissue) by pump, you may need to increase some or all of the following:
- your total insulin dose
- the basal infusion dose
- the proportion of total insulin given as a basal infusion

Age and exposure to heat affect the stability of NovoLog and its preservative. Also, NovoLog does not work well after it has been frozen. Therefore, do not use old insulin or insulin that has been exposed to temperature extremes. Hyperglycemia may be a sign that the insulin is no longer working and needs to be replaced.

Do not mix NovoLog:
- with any other insulins when used in a pump
- with Lantus® (insulin glargine [rDNA origin] injection) when used with injections by syringe

(You may, however, mix NovoLog with NPH when used with injections by syringe. See: How should I mix insulins?)

For Pump Users

- Glucose monitoring is very important for patients using external pump subcutaneous infusion therapy. You should be aware that pump or infusion set malfunctions that result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis. Accordingly, problems with the infusion pump, the flow of insulin, or the quality of the insulin should be identified and corrected as quickly as possible. There is only a small amount of insulin infused into the skin with a pump. The faster absorption through the skin of rapid-acting insulin analogs and shorter duration of action may give you less time to identify and correct the problem than with buffered regular insulin.

- Therefore, you should dose with insulin from a new vial of NovoLog if unexplained hyperglycemia or pump alarms do not respond to all of the following:
  - a repeat dose (injection or bolus) of NovoLog

- a change in the infusion set, including the NovoLog in the reservoir
- a change in the infusion site

If these measures do not work, you may need to resume skin (subcutaneous) injections with syringes or insulin pens. Continue to monitor your glucose and ketones. If problems continue, you must contact your doctor.

- When NovoLog is used in an external subcutaneous insulin infusion pump, you should use only recommended pumps. Reservoirs, infusion sets, and injection site should be changed at least every 48 hours. In addition, the reservoir, the infusion set, and infusion site should be changed:
  - with unexpected hyperglycemia or ketosis
  - when the alarm sounds, as specified by your pump manual
  - if the insulin or pump has been exposed to temperatures over 98.6^{o}F (37^{o}C), such as in a sauna, with long showers, or on a hot day
  - if the insulin or pump could have absorbed radiant heat, for example from sunlight, that would heat the insulin to over 98.6^{o}F (37^{o}C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may also affect the temperature

Patients who develop "pump bumps" (skin reactions at the infusion site) may need to change infusion sites more often than every 48 hours.

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 or infusion under the skin (subcutaneously). NovoLog is a human-made form of insulin to lower your blood sugar faster than human regular insulin. Because the insulin is human-made by recombinant DNA technology (rDNA) 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 insulin. The pH (balance between acid and alkaline conditions) is important to the stability of NovoLog. Increases in temperature can affect the stability of NovoLog, so it may not work well.

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 or infusion

- you are allergic to insulin aspart or any of the ingredients contained in 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. You may need to use another medicine.

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?

- Make any change of insulin 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 cause a need for a change in the timing or dose of the new insulin.
- Glucose monitoring will help you and your health care provider adjust 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 Patient Information for instructions for using NovoLog in injections and pumps.

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

- Because the onset of action is rapid, you should eat a meal within 5to10 minutes after a NovoLog injection or a NovoLog bolus dose from an external pump to avoid low blood sugar (hypoglycemia).

- The shorter duration of NovoLog's action means that you may need to use an intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog insulin infusion in the pump. This will help you avoid hyperglycemia and ketoacidosis.

- Do not inject or infuse in skin that has become reddened or bumpy or thickened after infusion or 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 or bolus infusions of NovoLog.

What are the possible side effects of NovoLog?

Insulins can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar). This is the most common side effect. It occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hypoglycemia can occur with**:

- **The wrong insulin dose.** This can happen with any of the following:
    - too much insulin is injected
    - the bolus dose of insulin infusion is set too high
    - the basal infusion dose is set too high
    - the pump does not work right, delivering too much insulin
- **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 can be 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. It also occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hyperglycemia can occur with:**

- **The wrong insulin dose.** This can happen from any of the following:
  - too little or no insulin is injected
  - the bolus dose of insulin infusion is set too low
  - the basal infusion dose is set too low
  - the pump or catheter system does not work right, delivering too little insulin
  - 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 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 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. It can **progress to diabetic ketoacidosis (DKA) or very high glucose levels (hyperosmolar coma) and result in unconsciousness and death.** Although DKA 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.

Glucose monitoring is very important for patients using external pump infusion therapy. You should be aware that pump or infusion set malfunctions that result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis. Accordingly, problems with the infusion pump, the flow of insulin, or the quality of the insulin should be identified and corrected as quickly as possible. The faster absorption of rapid-acting insulin analogs through the skin and shorter duration of action may give you less time to identify and correct the problem.

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 can be treated by extra doses of insulin and drinking fluids (rehydration). Patients using pumps should check pump function and replace the insulin in the reservoir-syringe, as well as change the tubing and catheter and the infusion site. **Patients using pumps may need to resume insulin injections with syringes or injection pens.** 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. Pump patients with site reactions may need to change their infusion sites more often than every 48 hours. Patients should avoid injection or infusion 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). Pump patients with lipodystrophy may need to change their infusion sites more often than every 48 hours. Patients should 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 air temperatures, heat from the sun, saunas, long showers, and other heat sources. This is especially important if you use a pump or an insulin pen, because you carry these devices with you and they may be exposed to different temperatures as you go about your daily activities. **Throw NovoLog away if it has been in temperatures greater than 98.6°F (37°C).**

- **Unopened NovoLog** should be stored in a refrigerator but not in the freezer and protected from light. Even if it has been refrigerated and protected from sunlight and unopened, it should not be used after the expiration date on the label and the carton. Unopened vials and cartridges can be stored unrefrigerated at temperatures below 86^{o}F (30^{o}C) and protected from light for up to 28 days.

- **Punctured vials and cartridges** can be stored unrefrigerated at temperatures below 86^{o}F (30^{o}C) and protected from light for up to 28 days. Punctured vials may be stored in the refrigerator. Cartridges inserted into their NovoPen® 3 device should not be stored in the refrigerator.

- **The NovoLog in the pump reservoir and the complete infusion set** (reservoir, tubing, catheter-needle) should be replaced **at least every 48 hours.** Replacement should be more often than every 48 hours if you have hyperglycemia, the pump alarm sounds, or the insulin flow is blocked (occlusion).

- Never use NovoLog if it has been stored improperly.

General advice

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 information about NovoLog that is written for health professionals.

Injection and pump infusion instructions

- NovoLog comes in 10 mL (milliliter) vials or in 3 mL cartridges. NovoLog can be withdrawn from vials with syringes for injection or for insertion into the reservoirs of external subcutaneous infusion pumps (Disetronic H-TRON® series, MiniMed 500 series, or other pumps recommended by your doctor.)
- Doses of insulin are measured in units. NovoLog is available as a U-100 insulin. One milliliter (mL) of U-100 contains 100 units of insulin aspart (1 mL=1 cc). Only U-100 type syringes should be used for injection to ensure proper dosing.
- Disposable syringes and needles are sterile if the package is sealed. They should be used only once and thrown away properly, to protect others from harm.
- NovoLog PenFill® cartridges are for use with NovoFine® disposable needles and the following Novo Nordisk 3 mL PenFill® compatible insulin delivery devices: NovoPen® 3, NovoPen® Junior, Innovo®, and InDuo®. Never share needles.

How should I inject NovoLog?

Using Vials

1. The vial and the insulin should be inspected. The insulin should be clear and colorless. The tamper-resistant cap should be in place to be removed by you. If the cap had been removed before your first use of the vial, or if the insulin is cloudy or colored, you should return the vial to the pharmacy. Do not use it.
2. Both the injection site and your hands should be cleaned with soap and water or with alcohol. The injection site should be dry before you inject.
3. The rubber stopper should be wiped with an alcohol wipe.
4. The plunger of the syringe should be pulled back until the black tip is at the level for the number of units to be injected.
5. Insert the needle of the syringe through the rubber stopper of the vial. Push in the syringe plunger completely to put air into the vial.
6. Turn the vial upside-down with the needle-syringe still attached, and pull the plunger back a few units past the correct dose.
7. Remove any air bubbles by flicking the syringe and squirting air bubbles out the needle. Continue pushing the plunger until you have the correct dose.
8. Lift the vial off the syringe.
9. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold between your fingers and push the needle straight into the pinched skin. Because insulin absorption and activity can be affected by the site you choose, you should discuss the injection site with your doctor.
10. Release the pinched skin and push the plunger in completely. Keep the needle in the skin for a few seconds before withdrawing the syringe.
11. Press the injection site for a few seconds to reduce bleeding. **Do not rub.**
12. To avoid needle sticks, throw away the syringe and needle without recapping. Discuss sterile technique and proper disposal of your used insulin supplies with your doctor.

Using Cartridges

1. The cartridge and the insulin should be inspected. The insulin should be clear and colorless. The tamper-resistant foil should be in place to be removed by you. If the foil had been punctured or removed before your first use of the cartridge or if the insulin is cloudy or colored, you should return the cartridge to the pharmacy. Do not use it.
2. Both the injection site and your hands should be cleaned with soap and water or with alcohol. The injection site should be dry before you inject. Do not use skin that is reddened, itchy, or thickened as an infusion site.
3. Insert a 3 mL cartridge in the pen-device barrel. Attach a new needle to the end of the cartridge and turn the pen device upside-down so that any air bubbles can be eliminated by flicking the pen device and squirting air bubbles out the needle. (This should eliminate extra air for all future doses from that cartridge. However, the needle will need to be changed for each dose.)
4. Set the dose to be delivered by twisting the top of the pen-device until the correct number appears in the window.
5. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold between your fingers and push the needle straight into the pinched skin. Because insulin absorption and activity can be affected by the site you choose, you should discuss the injection site with your doctor.
6. Release the pinched skin. Inject the dose by pressing the flat plunger button on the top of the pen-device. Keep the needle in the skin for a few seconds before withdrawing the pen-device.
7. Press the injection site for a few seconds to reduce bleeding. **Do not rub.**
8. Throw away the disposable needle without recapping to avoid needle sticks. Discuss sterile technique and proper disposal of your used insulin supplies with your doctor.

How should I infuse NovoLog with an external subcutaneous insulin infusion pump?

NovoLog is recommended for use with the Disetronic H-TRON®series, MiniMed 500 series, or other pumps recommended by your doctor.

1. Inspect your insulin as you would for an injection. The insulin should be clear and colorless and without particles. The tamper-resistant cap should be in place to be removed by you. If the cap had been removed before your first use of the vial or if the insulin is cloudy or colored, you should return the vial to the pharmacy. Do not use it.
2. Both the infusion site and your hands should be cleaned with soap and water or with alcohol. The infusion site should be dry before you insert the catheter-needle and tubing. Do not use skin that is reddened, itchy, bumpy or thickened as an infusion site because the onset and duration of NovoLog action may not be the same as that in normal skin.
3. Fill the reservoir-syringe with 2 days worth of NovoLog plus about 25 extra units to prime the pump and fill up the dead space of the infusion tubing.

4. Remove air bubbles from the reservoir according to the pump manufacturers' instructions.
5. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the infusion set until you see a drop of insulin coming out of the infusion needle-catheter. Flick the tubing to remove air bubbles. Follow the pump manufacturers' instructions for additional priming.
6. Prime the needle-catheter and insert the infusion set into the skin according to the pump manufacturer.
7. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin infusion according to instructions from your doctor and the manufacturer of your pump equipment.
8. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin every 48 hours or less, even if you have not used all of the insulin. This will help ensure that NovoLog and the pump works well. (See "What is the most important information I should know about NovoLog?")
9. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin if you experience a pump alarm, catheter blockage, hyperglycemia, or if your pump insulin has been exposed to heat greater than 98.6^{o}F (37^{o}C). (See "What is the most important information I should know about NovoLog?") Hyperglycemia identified with glucose monitoring may be the first indication of a problem with the pump, infusion set, or NovoLog. Hyperglycemia in the absence of an alarm still requires you to investigate because pump alarms are designed to detect back-pressure and occlusion. The alarms may not detect all the changes to NovoLog that could result in hyperglycemia. You may need to resume subcutaneous insulin injections if the cause of the problem cannot be promptly identified or fixed. (See "Hyperglycemia" under "What are the possible side effects of NovoLog?") Remember that long stretches of tubing increase the risk for kinking and expose the insulin in the tubing to more variations in temperature.

These instructions give you specific information for use of NovoLog in external subcutaneous infusion pumps, but are not a substitute for pump education.

How should I mix insulins?

NovoLog should be mixed only when syringe injections are used. NovoLog can be mixed with NPH human insulin immediately before use. The NovoLog should be drawn into the syringe before the NPH. Mixing with other insulins has not been studied. **NovoLog should not be mixed with Lantus® (insulin glargine [rDNA origin] injection). Mixed insulins should NEVER be used in a pump or for intravenous infusion.**

1. Add together the doses of NPH and NovoLog. The total dose will determine the final volume in the syringe after drawing up both insulins into the syringe.
2. Roll the NPH vial between your hands until the liquid is equally cloudy throughout.
3. Draw into the syringe the same amount of air as the NPH dose. Inject this air into the NPH vial and then remove the needle without withdrawing or touching any of the

NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog vial and may change how quickly it works.)

4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into the NovoLog vial. With the needle in place, turn the vial upside-down and withdraw the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the full dose and not an air dose.
5. Insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe-needle still in it. Withdraw the correct dose of NPH.
6. Inject immediately to reduce changes in how quickly the insulin works.

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

For information contact:
Novo Nordisk Pharmaceuticals Inc.,
100 College Road West
Princeton, New Jersey 08540
1-800-727-6500
www.novonordisk-us.com

Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

License under U.S. Patent No. 5,618,913 and Des. 347,894

NovoLog®, PenFill®, NovoPen®, Innovo®, NovoFine®, and Lente® are trademarks of Novo Nordisk A/S.
Lantus® is a trademark of Aventis Pharmaceuticals Inc.
H-TRON™ is a trademark of Disetronic Medical Systems, Inc.
InDuo™ is a trademark of LifeScan, Inc., a Johnson & Johnson company.

Date of Issue: XX xx, 2004

8-XXXX-XX-XXX-X

Printed in Denmark