

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 $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

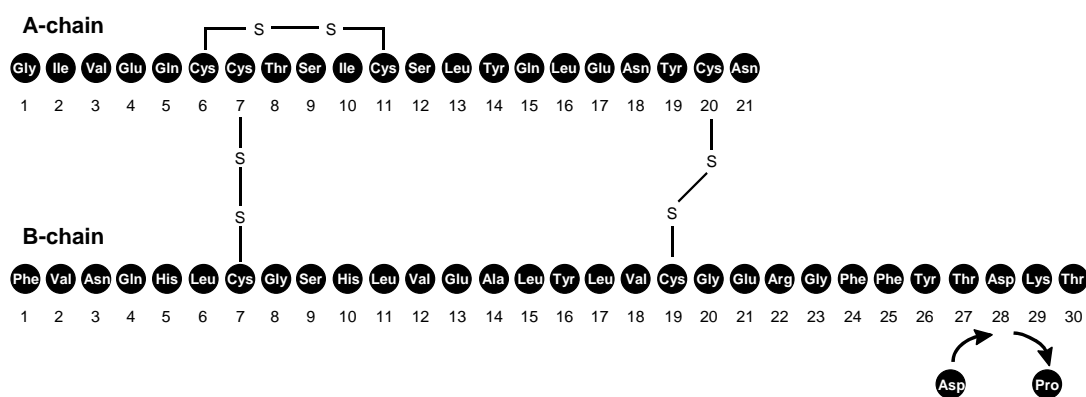


Figure 1. Structural formula of insulin aspart.

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 μ g/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.

In a randomized, double-blind, crossover study 17 healthy Caucasian male subjects between 18 and 40 years of age received an intravenous infusion of either NovoLog or regular human insulin at 1.5 mU/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.22 l/h/kg for the NovoLog group and 1.24 l/h/kg for the regular human insulin group.

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.

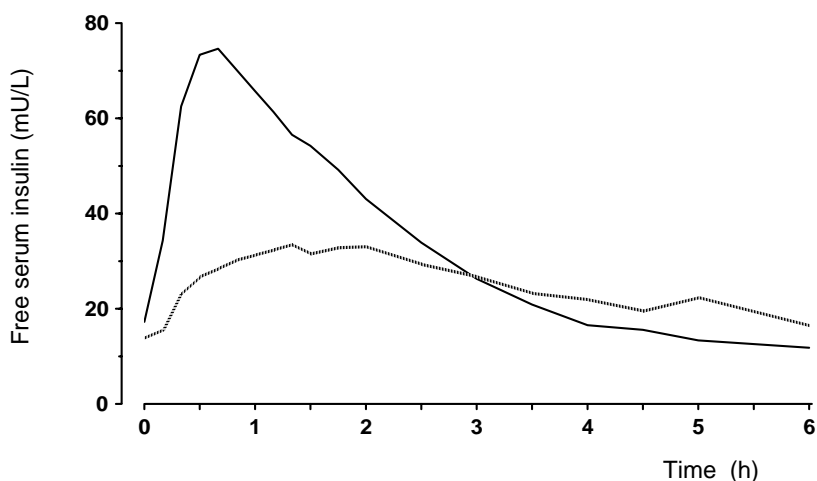


Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

In studies in healthy volunteers (total n=107) 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 subcutaneous administration of 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.

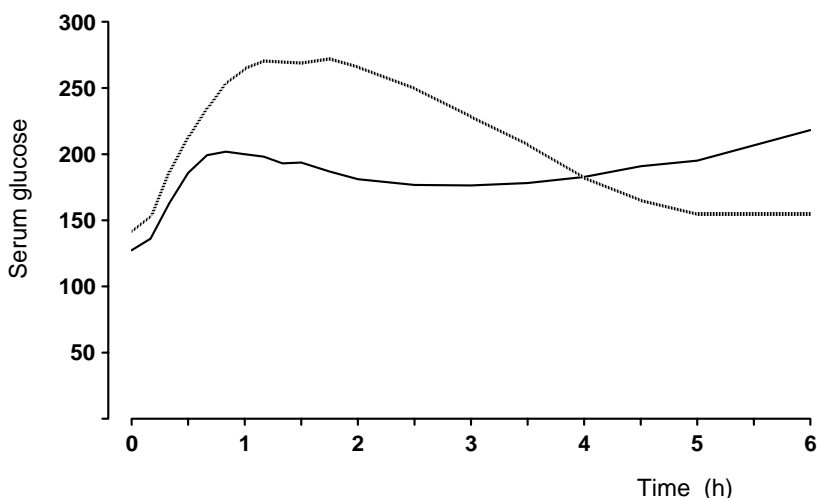
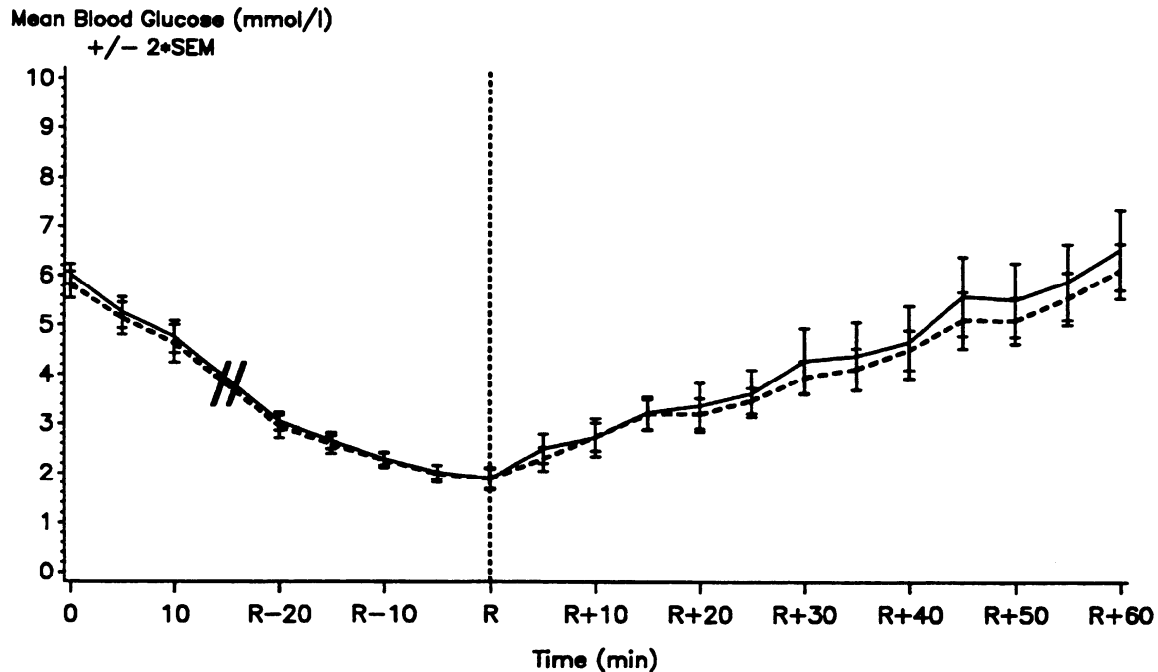


Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

A double-blind, randomized, two-way cross-over study with 16 patients with Type 1 diabetes demonstrated that intravenous infusion of NovoLog resulted in a blood glucose profile that was similar to that after intravenous infusion with regular human insulin (see Figure 4).



Note: The slashes on the mean profile indicate a jump on the time axis

Figure 4. Mean blood glucose profiles following intravenous infusion of NovoLog (hatched curve) and regular human insulin (solid curve) in 16 patients with Type 1 diabetes. R represents the time of autonomic reaction.

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 ≥ 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 HbA1c) 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/m²), the pharmacokinetic parameters, AUC and C_{max}, 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 C_{max} 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 HbA_{1c}, 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. 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 HbA1c 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.

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 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. NovoLog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (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). Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when NovoLog or any other insulin is administered intravenously. 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 lactation (see PREGNANCY-TERATOGENIC EFFECTS-PREGNANCY CATEGORY).

Usage in Pumps

NovoLog is recommended for use in pump systems suitable for insulin infusion as listed below.

Pumps:

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 cresol, 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 lactation (see PREGNANCY-TERATOGENIC EFFECTS-PREGNANCY CATEGORY).

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. When NovoLog is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

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 B

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. 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.

An open-label, randomized study compared the safety and efficacy of NovoLog versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies (NovoLog: 157, human insulin: 165)). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA1c of ~ 6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

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

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) age 6 to 18 years compared the following treatment regimens: NovoLog (n = 187) or Novolin R (n = 96). NPH insulin was administered as the basal insulin. NovoLog achieved glycemic control comparable to Novolin R, as measured by change in HbA_{1c}. The incidence of hypoglycemia was similar for both treatment groups. NovoLog and regular human insulin have also been compared in children with type 1 diabetes (n=26) age 2 to 6 years. As measured by end-of-treatment HbA_{1c} and fructosamine, glycemic control with NovoLog was comparable to that obtained with regular human insulin. As observed in the 6 to 18 year old pediatric population, the rates of hypoglycemia were similar in both treatment groups.

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 HbA_{1c} 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

Excess insulin may cause hypoglycemia and hypokalemia, particularly during IV administration. 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. Hypokalemia must be corrected appropriately.

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 insulin requirement may vary and 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. 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.

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. 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.

Intravenous administration of NovoLog is possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. For intravenous use, NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems with the infusion fluids 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags.

NovoLog may be diluted with Insulin Diluting Medium for NovoLog to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50).

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

*NovoLog PenFill cartridges are designed for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices, with or without the addition of a NovoPen® 3 PenMate®, and NovoFine® disposable needles.

RECOMMENDED STORAGE

NovoLog in unopened vials, cartridges, and NovoLog FlexPen 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)

Infusion bags prepared as indicated under DOSAGE AND ADMINISTRATION are stable at room temperature for 24 hours. A certain amount of insulin will be initially adsorbed to the material of the infusion bag.

NovoLog diluted with Insulin Diluting Medium for NovoLog may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Rx only

Date of Issue: January 12, 2007

Version 12

© Novo Nordisk A/S 2002-2006

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

www.novonordisk-us.com

NovoLog[®], NovoPen[®] 3, PenFill[®], Novolin[®], FlexPen[®], PenMate[®], and NovoFine[®] are trademarks of Novo Nordisk A/S.

H-TRON[®] is a trademark of Disetronic Medical Systems, Inc.

NovoLog[®] is covered by US Patent Nos 5,618,913, 5,866,538, and other patents pending.

Information For The Patient

NovoLog® FlexPen®

Insulin aspart (recombinant DNA origin) Injection in a 3 mL Prefilled Syringe

100 units/mL (U-100)

Read this leaflet carefully before using NovoLog®. Read the information you get when you refill your NovoLog prescription because there may be new information. This leaflet does not take the place of complete discussions with your health care provider. If you have questions about NovoLog or about diabetes, talk with your health care provider.

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

- 1. NovoLog® is different than human regular insulin because it starts to work faster (rapid onset of action) and will not work as long (shorter duration of action) in your body as human regular insulin. You should eat a meal within 5 to 10 minutes after your injection of NovoLog to reduce the risk of low blood sugar (hypoglycemia). The shorter duration of action of NovoLog means that if you have Type 1 diabetes, you may need to change your dose of total insulin or your dose of basal intermediate or long-acting insulin (e.g., NPH). You may also need to change the number of injections of basal insulin. You also may need to use a longer-acting insulin to give the best glucose control. Any change in dosage should be made under the supervision of your health care provider and carefully monitored.**
- 2. Any change of insulin should be made cautiously and only under medical supervision. Changes in strength, manufacturer, type (e.g., Regular, NPH, Lente®), species (beef, pork, beef-pork, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in the timing or dose of NovoLog or the longer-acting insulin, or both. Patients taking NovoLog may require a change in dose from that used with other insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.**

40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83

For your safety, read the section “What are the possible side effects of insulins?” for symptoms of low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia).

What is NovoLog?

NovoLog is a human insulin analogue that lowers your blood sugar faster than human regular insulin. NovoLog is a clear, colorless, sterile solution for injection under the skin (subcutaneously). The active ingredient in NovoLog is insulin aspart. Insulin aspart is identical to human insulin except for one amino acid, which has been changed in the insulin molecule. Insulin aspart is produced by recombinant DNA technology.

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.

The concentration of NovoLog is 100 units of insulin aspart per milliliter (U 100).

NovoLog FlexPen syringes are for single person use only.

What is diabetes, and how is insulin used to treat diabetes?

Insulin is normally produced by the pancreas, a gland that lies behind the stomach. Without insulin, glucose is trapped in the bloodstream and cannot enter the cells of the body. Glucose is a simple sugar made from the food you eat. Some people who do not make any, or enough, of their own insulin, or who cannot use the insulin they do make, must take insulin by injection to control the amount of glucose in their blood (their blood glucose levels). Treatment for diabetes may involve injections of insulin, injections of insulin combined with an oral (taken by mouth) antidiabetic medicine, or an oral antidiabetic medicine alone.

Each case of diabetes is different and requires direct and continued medical supervision. Your health care provider has told you the type, strength and amount of insulin you should use and the time(s) when you should inject it. Your health care provider has also discussed a diet and exercise schedule with you. Contact your health care provider if you have any problems or if you have questions.

84 **What types of insulin are available?**

85
86 There are 3 types of insulin: animal insulins, human insulins, and insulin
87 analogs. Animal insulins may vary in animal source and how pure they are.
88 Human insulin is identical in structure to the insulin produced by the human
89 pancreas, and thus differs from animal insulins. Insulin analogs differ slightly
90 from human insulin in their chemical structure and are synthetic. Insulin analogs
91 differ in time of action from human insulin because the rate of absorption after
92 injection under the skin (subcutaneous) is different. However, they work the
93 same way as human insulin once they are absorbed. The animal insulins differ
94 slightly from human insulin in their chemical structure. Your health care provider
95 has prescribed the insulin that is right for you; be sure you have purchased the
96 correct insulin and check it carefully before you use it.

97
98

99 **Who should not use NovoLog?**

100

101 **Do not take NovoLog if:**

102

- 102 • Your blood sugar (glucose) is too low (hypoglycemia).
- 103 • You are allergic to insulin aspart or any of the ingredients contained in
104 NovoLog (check with your health care provider or pharmacist if you are not
105 sure).
- 106 • You are not planning to eat immediately following your injection.

107

108 Tell your health care provider or diabetes educator if you plan to become pregnant or
109 breast feed, or if you become pregnant. NovoLog has not been tested for use in women
110 who are nursing.

111

112 Tell your health care provider or diabetes educator about all medicines and supplements
113 that you are using. Some medicines, including non-prescription medicines and dietary
114 supplements, may affect your diabetes.

115

116 **What should I know about insulin use?**

117

- 118 • A change in the type, strength or species of insulin could require a dosage
119 adjustment. Any change in insulin should be made under medical
120 supervision.
- 121 • Monitor your glucose levels as directed by your health care provider.
122 You may have learned how to test your blood or urine for glucose. It is
123 important to do these tests regularly and to record the results for review with
124 your health care provider or diabetes educator.
- 125 • Always carry a quick source of sugar such as candy, mints, or glucose
126 tablets.
- 127 • Always carry identification that states that you have diabetes.
- 128 • Always ask your health care provider or pharmacist before taking any drug.

129

130 **Always consult your health care provider if you have any questions about**
131 **your condition or the use of insulin.**

132

133 **What should I know about NovoLog use?**

134

135 Inject NovoLog immediately before a meal.

- 136 • The effects of NovoLog will start within 10 to 20 minutes after the injection is
- 137 made.
- 138 • The maximum effect will be between 1 and 3 hours after the injection is
- 139 made.
- 140 • The effect will last for 3 to 5 hours after the injection.

141

142 Due to this shorter duration of action, NovoLog is usually taken in combination
143 with intermediate or longer-acting insulins. The effects of insulin may be different
144 for different people. Even in the same person, the effects may vary from day to
145 day. Because of this variation, the time periods listed here are general
146 guidelines only. **See the section “How should I give a NovoLog® FlexPen**
147 **Prefilled syringe injection” at the end of this Information For The Patient for**
148 **detailed instructions.**

149

150 **What can affect how much insulin I need?**

151

152 **Illness**

153 Even if you have an acute illness, especially with vomiting or fever, continue
154 taking your insulin. If possible, stay on your regular diet. If you have trouble
155 eating, drink fruit juices, regular soft drinks, or clear soups. If you can, eat small
156 amounts of bland foods. Test your urine for glucose and ketones and, if
157 possible, test your blood glucose. Note the results and contact your health care
158 provider for possible insulin dose adjustment. If you have severe and continued
159 vomiting, get emergency medical care.

160

161 **Travel**

162 If you are traveling across more than two time zones, consult your health care
163 provider about adjusting your insulin schedule.

164

165 **Exercise**

166 Exercise may lower your body's need for insulin during and for some time after
167 physical activity. Exercise may also speed up the effect of a NovoLog dose,
168 especially if the exercise involves the area of the injection site. Discuss with your
169 health care provider how you should adjust your treatment to account for
170 exercise.

171

172 **Usage in Pregnancy**

173 It is especially important to maintain good control of your diabetes during
174 pregnancy. Pay special attention to your diet, exercise, and insulin regimens. If
175 you are planning to have a baby, are pregnant, or are nursing a baby, consult
176 your health care provider or diabetes educator. NovoLog has not been tested for
177 use in women who are nursing.

178

179 **Use with other Medicines**

180 Insulin requirements may increase or decrease when taken in combination with
181 other medicines. Drugs such as birth control pills, niacin, corticosteroids, or
182 thyroid replacement therapy may increase insulin requirements. Drugs such as
183 antidiabetic medicines, salicylates (for example, aspirin), sulfa antibiotics, and
184 certain antidepressants may decrease insulin requirements. Your health care
185 provider is aware of other medicines that may affect your diabetes control.
186 Always discuss any medicines you are taking with your health care provider.

187

188 Beta blocking agents (used for the treatment of certain heart conditions and high
189 blood pressure) may mask the symptoms of hypoglycemia or may increase or
190 decrease the effects of NovoLog. ACE inhibitors (used for the treatment of
191 certain heart conditions and high blood pressure) may increase the effects of
192 NovoLog.

193

194 Drinking alcohol may lead to hypoglycemia.

195

196 **What are the possible side effects of insulins?**

197

198 **Hypoglycemia (Insulin Reaction)**

199 Insulin reaction (hypoglycemia) is the most common side effect of insulins.
200 Hypoglycemia occurs when the blood glucose falls very low. The first symptoms
201 of an insulin reaction usually begin suddenly. Hypoglycemia can be caused by:

- 202 1. missing or delaying meals
- 203 2. taking too much insulin
- 204 3. exercising or working more than usual
- 205 4. an infection or illness (especially with diarrhea, vomiting, or fever)
- 206 5. a change in the body's need for insulin
- 207 6. diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney
208 or liver disease
- 209 7. interactions with other drugs that lower blood glucose, such as oral
210 hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and
211 certain antidepressants
- 212 8. drinking alcoholic beverages

213

214 **Symptoms of mild to moderate hypoglycemia** may occur suddenly and can
215 include:

216

- sweating
- dizziness

217

- 218 • palpitation
- 219 • tremor
- 220 • restlessness
- 221 • tingling in the hands, feet, lips, or tongue
- 222 • lightheadedness
- 223 • trouble concentrating
- 224 • headache
- 225 • drowsiness
- 226 • sleep problems
- 227 • anxiety
- 228 • blurred vision
- 229 • slurred speech
- 230 • depression
- 231 • irritability
- 232 • abnormal behavior
- 233 • unsteady movement
- 234 • personality changes

235

236 If you drink or eat something right away (a glass of milk or orange juice, or
237 several sugar candies), you can often stop symptoms from getting worse. If
238 symptoms continue, call your health care provider right away-- hypoglycemia can
239 lead to unconsciousness. If hypoglycemia causes loss of consciousness, you
240 must have emergency medical care right away. If you have had repeated
241 hypoglycemic reactions or if hypoglycemia has led to a loss of consciousness,
242 contact your health care provider. Severe hypoglycemia can result in temporary
243 or permanent harm to your heart function, brain function, or death.

244

245 **In certain cases, the type and strength of the warning symptoms of**
246 **hypoglycemia may change. This may happen especially with very tight**
247 **glucose control or in patients with diabetic nerve problems (neuropathy).** If
248 you do not recognize early warning symptoms, you may not be able to take steps
249 to avoid more serious hypoglycemia. **Symptoms of severe hypoglycemia** can
250 include disorientation, unconsciousness, or seizures. Hypoglycemia can result in
251 death. Be alert for all of the various types of symptoms that can indicate
252 hypoglycemia. Patients who develop hypoglycemia without early warning
253 symptoms should monitor their blood glucose frequently, especially before
254 activities such as driving. If the blood glucose is below your normal fasting
255 glucose, you should eat or drink sugar-containing foods to treat your
256 hypoglycemia.

257

258 Patients should always carry a quick source of sugar, such as candy, mints, or
259 glucose tablets. More severe hypoglycemia may require the help of another
260 person. Patients who are unable to take sugar orally or who are unconscious
261 require an injection of glucagon or should be treated with intravenous glucose at
262 a medical facility.

263

264 Learn to recognize your own symptoms of hypoglycemia. If you are uncertain
265 about these symptoms, you should monitor your blood glucose frequently to help
266 you learn to recognize the symptoms that you experience with hypoglycemia. If
267 you have frequent episodes of hypoglycemia or have trouble recognizing the
268 symptoms, consult your health care provider to discuss possible changes in
269 therapy, meal plan, and exercise programs to help you avoid hypoglycemia.

270

271 **Hyperglycemia and Diabetic Acidosis**

272 Hyperglycemia (too much glucose in the blood) may develop if your body has too
273 little insulin. Hyperglycemia can be brought about by any of the following:

- 274 1. Not taking your insulin or taking less than the health care provider has
275 prescribed
- 276 2. Eating significantly more than your meal plan suggests
- 277 3. Developing a fever, infection, or other significant stressful situation

278

279 In patients with insulin-dependent diabetes (Type 1 diabetes), continued
280 hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic
281 acidosis usually come on slowly, over a period of hours or days. Symptoms
282 include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on
283 the breath. With acidosis, urine tests show large amounts of glucose and
284 acetone. More severe symptoms are heavy breathing and a rapid pulse. If
285 uncorrected, continued hyperglycemia or diabetic acidosis can lead to nausea,
286 vomiting, dehydration, loss of consciousness, or death. Therefore, it is important
287 that you obtain medical help right away.

288

289 **Allergy**

290 *Generalized Allergy:* An uncommon, but potentially serious reaction to insulins,
291 is generalized allergy, which may cause a rash over the whole body, shortness of
292 breath, wheezing, reduced blood pressure, fast pulse, or sweating. Severe
293 cases of generalized allergy may be life threatening. **If you think you are**
294 **having a generalized allergic reaction, notify a health care provider right**
295 **away.**

296

297 *Local Allergy:* Patients sometimes develop redness, swelling, and itching at the
298 site of injection. This condition, called "local allergy," usually clears up in a few
299 days to a few weeks. Sometimes, this condition may be related to factors other
300 than insulin, such as irritants in skin cleansing agents or poor injection technique.
301 If you have a local reaction, contact your health care provider.

302

303 **Lipodystrophy**

304 Sometimes, getting insulin subcutaneously can result in lipoatrophy (depression
305 in the skin) or lipohypertrophy (enlargement or thickening of tissue at the injection
306 site). If you notice either of these conditions, consult your health care provider.
307 A change in your injection technique may help reduce the problem.

308

309 **Always consult your health care provider if you have any questions about**
310 **your condition or the use of insulin.**

311

312 **How should I store NovoLog?**

313

- 314 • Store insulin in a refrigerator, but not in the freezer. Do not use NovoLog
315 FlexPen Prefilled syringe if it has been frozen. Keep unused NovoLog
316 FlexPen Prefilled syringes in the carton so that they will stay clean and
317 protected from light.
- 318 • The NovoLog FlexPen Prefilled syringe that you are currently using can be
319 kept unrefrigerated for 28 days, as long as it is kept as cool as possible
320 (below 86°F [30°C]). Keep away from direct heat and light. Throw away
321 unrefrigerated NovoLog FlexPen Prefilled syringes after 28 days, even if they
322 still contain NovoLog.
- 323 • Do not use NovoLog if it appears cloudy, thickened, slightly colored, or if solid
324 particles are visible. Use it only if it is clear and colorless.
- 325 • Never use NovoLog after the expiration date printed on the label and carton.

326

327 **General advice about prescription medicines**

328

329 Do not share your medicine with other persons. It may harm them. If you have
330 any questions about diabetes or NovoLog, ask you health care provider. Your
331 pharmacist or health care provider can give you the written information about
332 NovoLog that is written for health care professionals.

333

334 **How should I give a NovoLog FlexPen Prefilled syringe** 335 **injection?**

336

337 **Never share your NovoLog® FlexPen Prefilled syringe and needles.**
338 **Sharing may cause infections. Disposable needles are for single use. Use**
339 **the disposable needle once and throw it away properly, to protect others**
340 **from harm.**

341

342 **Caution**

343 If you do not follow the instructions and advice in this leaflet about antiseptic
344 measures for avoiding germs, you may develop infections, most commonly, at
345 the injection site.

346

347 **How do I prepare the injection?**

348

349 **Do not use NovoLog after the expiration date printed on the label and**
350 **carton.**

351

- 352 • Never place a single-use needle on your insulin delivery device until you are
353 ready to give an injection. Remove the needle after you complete the
354 injection and throw it away properly, so it will not harm others.
- 355 • To use this syringe, follow the directions on the back of this leaflet for using
356 this syringe.
- 357 • NovoLog FlexPen Prefilled syringes may contain a small amount of air. To
358 prevent an injection of air and to inject a full dose of insulin, you must do an
359 air shot before each injection. Directions for performing an air shot are on the
360 back of this leaflet.

361

362 **How do I give the injection?**

363

364 **Use the injection technique recommended by your health care provider.**

365

- 366 1. Do not inject insulin into your muscle unless your health care provider has
367 advised it. Never inject insulin into a vein.
- 368 2. The following areas are suitable for subcutaneous (under the skin) insulin
369 injection: thighs, upper arms, buttocks, and abdomen. Do not change areas
370 without consulting your health care provider because the insulin absorption
371 and duration of action may vary. Absorption rate of the insulin affects the
372 insulin's onset and duration of action. The actual point of injection on your
373 body should be changed each time. Injection sites should be about an inch
374 apart, in the same area of your body.
- 375 3. Clean your hands with soap and water. Clean the injection site with soap and
376 water or with alcohol. The injection site on your body should be clean and
377 dry.
- 378 4. Pinch up the skin area to be injected and hold it firmly.
- 379 5. Hold your device like a pencil and push the needle quickly and firmly into the
380 pinched-up skin. If it goes straight in, it will probably sting less.
- 381 6. Release your skin and push the button on your device all the way in. This
382 injects the insulin beneath your skin. After the injection the needle should
383 remain under the skin for at least 6 seconds. Keep the push button fully
384 depressed until the needle is withdrawn from the skin. This will ensure that
385 the full dose has been delivered.
- 386 7. After injecting the insulin and ensuring all of the insulin is injected, pull the
387 needle out.
- 388 8. Press gently over the injection site for several seconds - **do not rub**. If slight
389 bleeding occurs, press lightly with a dry cotton swab for a few seconds - **do**
390 **not rub**.
- 391 9. Remove the needle from the NovoLog® FlexPen® Prefilled syringe. **Do not**
392 **reuse needles. Throw away used needles in a responsible manner so**
393 **they will not harm others. For example, you can use a hard-walled**
394 **container, such as a liquid laundry detergent bottle for this purpose.**

395

396 Date of Issue:

397

398 Novo Nordisk®, NovoLog®, Novolin®, FlexPen®, PenFill®, NovoPen®, and NovoFine® are
399 trademarks owned by Novo Nordisk A/S.

400

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

403

404 For information contact:

405 Novo Nordisk Inc.

406 100 College Road West

407 Princeton, New Jersey 08540

408 1-800-727-6500

409 www.novonordisk-us.com

410 Manufactured by

411 Novo Nordisk A/S

412 DK-2880 Bagsvaerd, Denmark

413

414 NovoLog® is covered by U.S. Patent Nos. 5,618,913, 5,866,538 and other patents pending.

415

416

417 Printed in Denmark

418

419 8-xxxx-xx-xxx-x

420

421

422 Second page of the insert:

423

424 **NovoLog® FlexPen® Prefilled syringe directions for use**

425

426 NovoLog FlexPen Prefilled syringe is a disposable dial-a-dose insulin delivery system able to
427 deliver from 1 to a maximum of 60 units. The dose can be adjusted in 1 unit increments.

428 NovoLog FlexPen Prefilled syringe is designed for use with NovoFine® single use needles or
429 other products specifically recommended by Novo Nordisk. NovoLog FlexPen Prefilled syringe is
430 not recommended for the blind or severely visually impaired without the assistance of a sighted
431 individual trained in the proper use of the product.

432

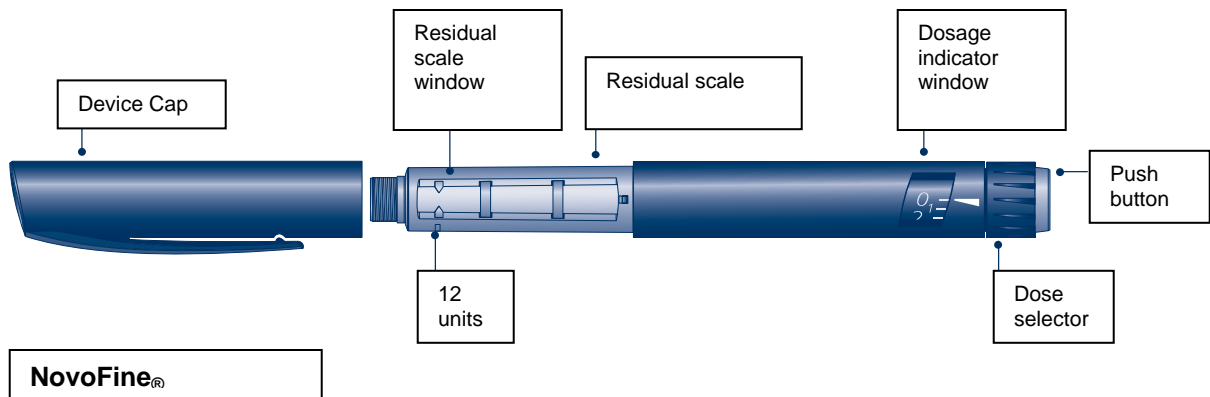
433 **Please read these instructions completely before using this device.**

434

435

436

437



438

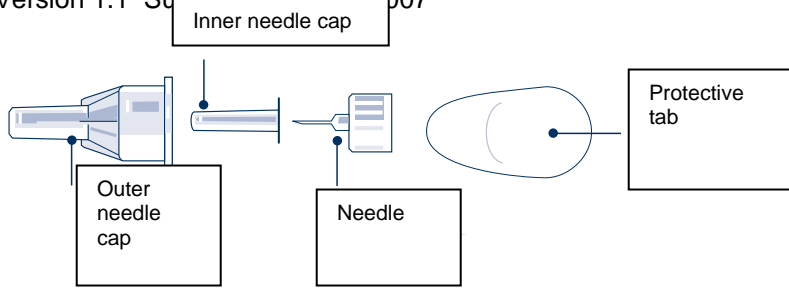
439

440

441

442

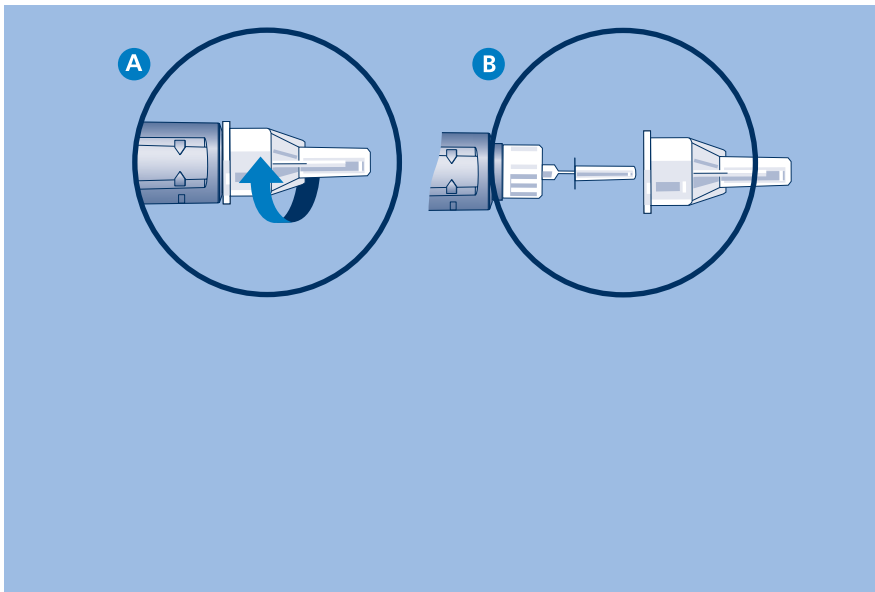
443



444
445
446
447
448
449
450

1. PREPARING THE SYRINGE

Pull off the cap.
Wipe the rubber stopper with an alcohol swab.



451
452
453
454
455
456
457
458
459
460
461
462
463
464

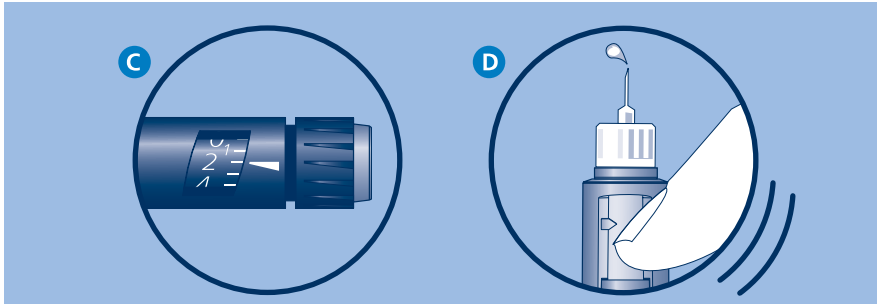
A. Remove the protective tab from the disposable needle and screw the needle onto the FlexPen. Never place a disposable needle on your FlexPen until you are ready to give an injection. Remove the needle right after use. If the needle is not removed, some liquid may leak from the FlexPen.

B. Pull off the outer and inner needle caps.

Giving the airshot 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, hold the syringe with the needle pointing up and tap the syringe gently with your finger so any air bubbles collect in the top of the reservoir. Remove both the plastic outer cap and the needle cap.

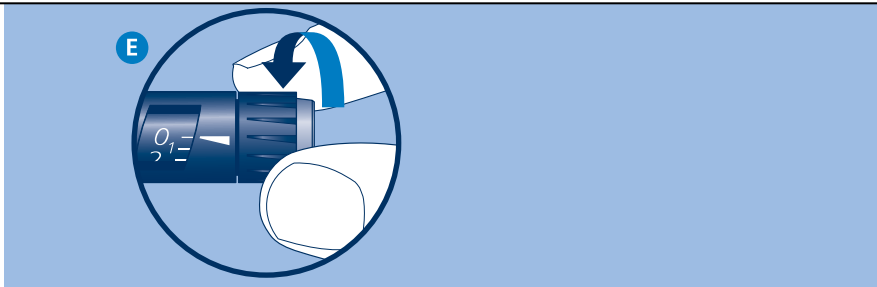
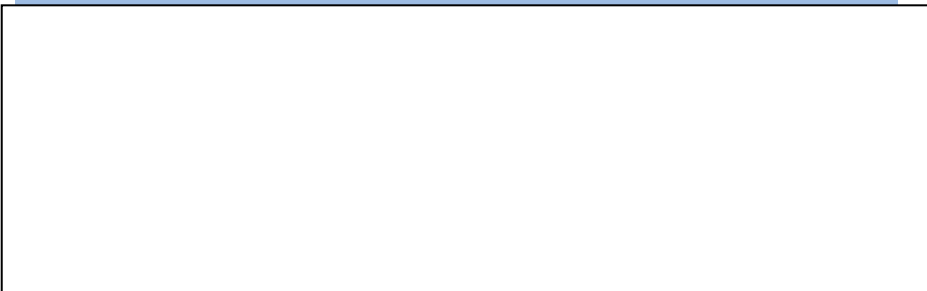


465
466
467
468
469
470
471
472
473
474
475

C. Dial 2 units.

D. Holding the syringe with the needle pointing up, tap the reservoir gently with your finger a few times. Still with the needle pointing up, press the push button as far as it will go and see if a drop of insulin appears at the needle tip. If not, repeat the procedure until insulin appears. Before the first use of each NovoLog FlexPen you may need to perform up to 6 airshots to get a droplet of insulin at the needle tip. If you need to make more than 6 airshots, do not use the syringe, and contact Novo Nordisk. 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

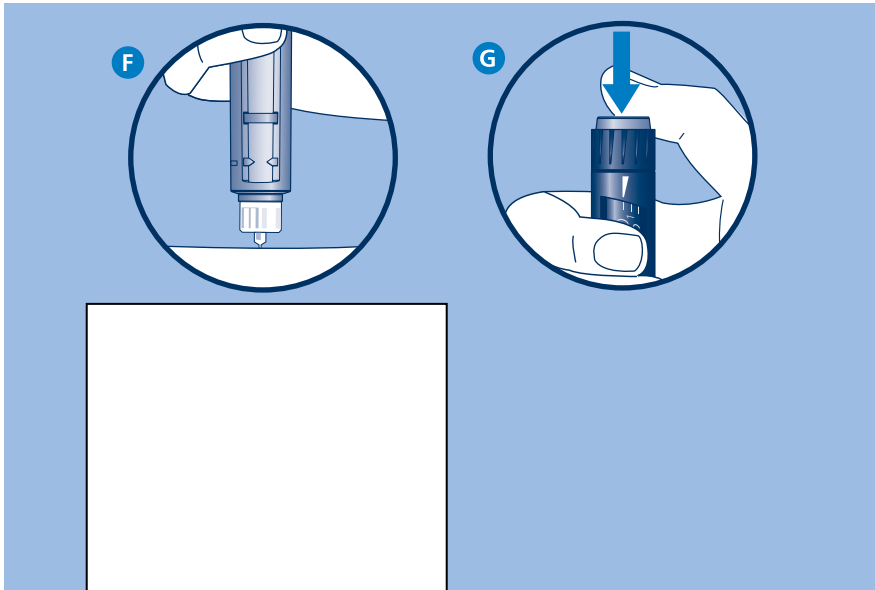


476
477
478
479
480
481
482

E. Check that the dose selector is set at **0**. Dial the number of units you need to inject. The dose can be corrected either up or down by turning the dose selector in either direction. When dialing back be careful not to push the push button as insulin will come out. You cannot set a dose larger than the number of units left in the reservoir.

3. GIVING THE INJECTION

483



484

485

486 Use the injection technique recommended by your doctor.

487

488 **F.** Deliver the dose by pressing the push button all the way in. Be careful only to push the push
489 button when injecting.

490 **G.** After the injection the needle should remain under the skin for at least 6 seconds. Keep the
491 push button fully depressed until the needle is withdrawn from the skin. This will ensure that the
492 full dose has been delivered.

493

494 To avoid needlesticks, **do not** recap the needle. Throw away the needle safely after each
495 injection.

496

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

500

501

502 For more information see

503 **How do I give the injection** on the reverse side of this insert.

504

505 **4. SUBSEQUENT INJECTIONS**

506 **It is important that you use a new needle for each injection.** Follow the directions in steps 1
507 – 3.

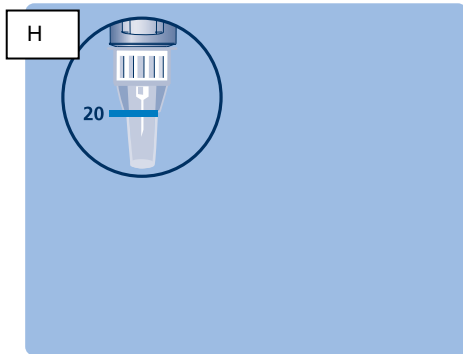
508

509 The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the
510 syringe. Do not use these numbers to measure the insulin dose.

511 You cannot set a dose greater than the number of units remaining in the reservoir.

512

513 **5. FUNCTION CHECK**



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

- Screw on a new NovoFine needle
- Give an airshot as described in sections C to D
- Put the outer needle cap onto the needle
- Dispense 20 units into the outer needle cap, holding the pen with the needle pointing downwards.

The insulin should fill the lower part of the cap (as shown in figure H). If NovoLog FlexPen has released too much or too little insulin, repeat the test. If it happens again, contact Novo Nordisk and do not use your NovoLog FlexPen.

Dispose of the used NovoLog FlexPen carefully without the needle attached.

6. IMPORTANT NOTES

- If you need to perform more than 6 airshots before the first use of NovoLog FlexPen syringe to get a droplet of insulin at the needle tip, do not use the FlexPen.
- Remember to perform an air shot before each injection. See figures C and D.
- Take care not to drop the FlexPen.
- Remember to keep the NovoLog FlexPen syringe with you; don't leave it in a car or other location where extremes of temperature can occur.
- NovoLog FlexPen syringe is designed for use with NovoFine disposable needles or other products specifically recommended by Novo Nordisk.
- Never place a disposable needle on this syringe until you are ready to use it. Remove the needle immediately after use.
- **Throw away used needles in a responsible manner, so others will not be harmed.**
- Throw away the used syringe, without the needle attached.
- Always carry a spare NovoLog FlexPen syringe with you in case your FlexPen is damaged or lost.
- Novo Nordisk cannot be held responsible for adverse reactions occurring as a consequence of using this insulin delivery system with products that are not recommended by Novo Nordisk.
- Keep this syringe out of the reach of children.

1
2
3 **Information For The Patient**
4 **NovoLog® (Insulin aspart [rDNA origin] Injection)**
5 **3 mL PenFill® Disposable Cartridge (300 units per cartridge)**
6 **10 mL Vial (1000 units per vial)**
7 **100 units/mL (U-100)**

- 8 • What is the most important information I should know about NovoLog?
9 • For all NovoLog users
10 • For pump users
11 • What is NovoLog?
12 • Who should not use NovoLog?
13 • What should I know about using insulin?
14 • What should I know about using NovoLog?
15 • What should I avoid when using NovoLog?
16 • What are the possible side effects of NovoLog?
17 • How should I store NovoLog?
18 • General advice
19 • Injection and pump infusion instructions
20 • How should I inject NovoLog?
21 • Using Vials
22 • Using Cartridges
23 • How should I infuse NovoLog with an external subcutaneous insulin infusion
24 pump?
25 • How should I mix insulins?
26

27 Read this information carefully before you begin treatment. Read the information you
28 get whenever you get more medicine. There may be new information. This information
29 does not take the place of talking with your doctor about your medical condition or your
30 treatment. If you have any questions about NovoLog (NO-voe-log), ask your doctor.
31 Only your doctor can determine if NovoLog is right for you.
32

33 **What is the most important information I should know about NovoLog?**
34

35 *For All NovoLog Users*

- 36 • NovoLog (NO-voe-log) is different from regular human insulin and buffered regular
37 human insulin (Velosulin). It works faster (rapid onset of action) and will not work as
38 long (shorter duration of action) as regular human insulin or buffered regular human
39 insulin (Velosulin).
40
41 • Because the onset of action is fast, you should eat a meal 5 to 10 minutes after a
42 NovoLog injection or NovoLog bolus infusion dose given by an external pump. (A
43 bolus is a large dose.) Eating right after the dose will reduce the risk of low blood
44 sugar (hypoglycemia).
45

- 46 • The shorter duration of NovoLog's action means that you may need to use an
47 intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog
48 insulin infusion in the pump. This will give the best glucose control and will help you
49 avoid hyperglycemia (high blood sugar) and ketoacidosis (too much acid [low pH] in
50 your body).
- 51
- 52 • Glucose monitoring is recommended for all patients who use insulin.
- 53

54 If you use NovoLog by injection, you may need to increase some or all of the following:

- 55 • your total dose of insulin
- 56 • your dose of intermediate or long-acting insulin (for example, NPH)
- 57 • the number of injections of basal insulin
- 58

59 If you infuse NovoLog into the skin (subcutaneous tissue) by pump, you may need to
60 increase some or all of the following:

- 61 • your total insulin dose
- 62 • the basal infusion dose
- 63 • the proportion of total insulin given as a basal infusion
- 64

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

69

70 **Do not mix NovoLog:**

- 71 • with any other insulins when used in a pump
- 72 • with Lantus[®] (insulin glargine [rDNA origin] injection) when used with injections
73 by syringe
- 74 (You may, however, mix NovoLog with NPH when used with injections by syringe.
75 See: How should I mix insulins?)
- 76

76

77 *For Pump Users*

- 78 • Glucose monitoring is very important for patients using external pump subcutaneous
79 infusion therapy. You should be aware that pump or infusion set malfunctions that
80 result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis.
81 Accordingly, problems with the infusion pump, the flow of insulin, or the quality of
82 the insulin should be identified and corrected as quickly as possible. There is only a
83 small amount of insulin infused into the skin with a pump. The faster absorption
84 through the skin of rapid-acting insulin analogs and shorter duration of action may
85 give you less time to identify and correct the problem than with buffered regular
86 insulin.
- 87
- 88 • Therefore, you should dose with insulin from a new vial of NovoLog if unexplained
89 hyperglycemia or pump alarms do not respond to all of the following:
 - 90 • a repeat dose (injection or bolus) of NovoLog

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

93

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

97

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

110

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

113

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

117

118 **What is NovoLog?**

119 NovoLog is a clear, colorless, sterile solution for injection or infusion under the skin
120 (subcutaneously). NovoLog is a human-made form of insulin to lower your blood sugar
121 faster than human regular insulin. Because the insulin is human-made by recombinant
122 DNA technology (rDNA) and is chemically different from the insulin made by the human
123 body, it is called an insulin analog. The active ingredient in NovoLog is insulin aspart.
124 The concentration of insulin aspart is 100 units per milliliter, or U100. NovoLog also
125 contains: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate,
126 and sodium chloride. Hydrochloric acid and/or sodium hydroxide may be added to adjust
127 the pH. These ingredients help to preserve or stabilize NovoLog insulin. The pH
128 (balance between acid and alkaline conditions) is important to the stability of NovoLog.
129 Increases in temperature can affect the stability of NovoLog, so it may not work well.

130

131 **Who should not use NovoLog?**

132 Do not use NovoLog if:

- 133 • your blood sugar (glucose) is too low (hypoglycemia)
- 134 • you do not plan to eat right after your injection or infusion

- 135 • you are allergic to insulin aspart or any of the ingredients contained in NovoLog
136 (check with your doctor if you are not sure)

137
138 Tell your health care provider or diabetes educator if you plan to become pregnant or
139 breast feed, or if you become pregnant. NovoLog has not been tested for use in women
140 who are nursing.

141
142 Tell your health care provider or diabetes educator about all medicines and supplements
143 that you are using. Some medicines, including non-prescription medicines and dietary
144 supplements, may affect your diabetes.

145
146 **What should I know about using insulin?**

- 147 • Make any change of insulin cautiously and only under medical supervision. Changes
148 in the strength, manufacturer, type (for example: Regular, NPH, Lente[®]), species
149 (beef, pork, beef-pork, human) or method of manufacture (recombinant [rDNA] or
150 animal source insulin) may cause a need for a change in the timing or dose of the new
151 insulin.
- 152 • Glucose monitoring will help you and your health care provider adjust dosages.
- 153 • Always carry a quick source of sugar, such as candy or glucose tablets, to treat low
154 blood sugars (hypoglycemia).
- 155 • Always carry identification that states that you have diabetes.

156
157 **What should I know about using NovoLog?**

158 *See the end of this Patient Information for instructions for using NovoLog in*
159 *injections and pumps.*

- 160
161 • NovoLog starts working 10 to 20 minutes after injection or infusion. The greatest
162 blood sugar lowering effect is between 1 and 3 hours after injection or infusion. This
163 blood sugar lowering lasts for 3 to 5 hours. (The time periods are only general
164 guidelines.)
- 165
166 • Because the onset of action is rapid, you should eat a meal within 5 to 10 minutes after
167 a NovoLog injection or a NovoLog bolus dose from an external pump to avoid low
168 blood sugar (hypoglycemia).
- 169
170 • The shorter duration of NovoLog's action means that you may need to use an
171 intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog
172 insulin infusion in the pump. This will help you avoid hyperglycemia and
173 ketoacidosis.
- 174
175 • Do not inject or infuse in skin that has become reddened or bumpy or thickened after
176 infusion or injection. Insulin absorption in these areas may not be the same as that in
177 normal skin, and may change the onset and duration of insulin action.

178

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

181

182 **What should I avoid while using NovoLog?**

- 183 • Drinking alcohol may lead to hypoglycemia.
184 • Do not miss meals after injections of NovoLog or bolus infusions of NovoLog.

185

186 **What are the possible side effects of NovoLog?**

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

189

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

- 194 • **The wrong insulin dose.** This can happen with any of the following:
195 • too much insulin is injected
196 • the bolus dose of insulin infusion is set too high
197 • the basal infusion dose is set too high
198 • the pump does not work right, delivering too much insulin
199 • **Medicines that directly lower glucose or increase sensitivity to insulin.** This can
200 happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for
201 infections), ACE inhibitors (for blood pressure and heart failure), salicylates,
202 including aspirin and NSAIDS (for pain), some antidepressants, and with other
203 medicines.
204 • **Medical conditions that limit the body's glucose reserve, lengthen the time**
205 **insulin stays in the body, or that increase sensitivity to insulin.** These conditions
206 include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and
207 the kidney.
208 • **Not enough carbohydrate (sugar or starch) intake.** This can happen if:
209 • a meal or snack is missed or delayed
210 • you have vomiting or diarrhea that decreases the amount of glucose absorbed by
211 your body
212 • alcohol interferes with carbohydrate metabolism
213 • **Too much glucose use by the body.** This can happen from:
214 • too much exercise
215 • higher than normal metabolism rates due to fever or an overactive thyroid

216

217 Hypoglycemia can be mild or severe. Its onset may be rapid. Patients with very good
218 (tight) glucose control, patients with diabetic neuropathy (nerve problems), or patients
219 using some Beta-blockers (used for high blood pressure and heart conditions) may have
220 few warning symptoms before severe hypoglycemia develops. Hypoglycemia may reduce
221 your ability to drive a car or use mechanical equipment without risk of injury to yourself
222 or others. Severe hypoglycemia can cause temporary or permanent harm to your heart or

223 brain. **It may cause unconsciousness, seizures, or death.** Symptoms of hypoglycemia
224 include:

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

235

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

241

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

244

245 **Hyperglycemia** (high blood sugar) is another common side effect. It also occurs when
246 there is a conflict between the amount of carbohydrates (source of glucose) from your
247 food, the amount of glucose used by your body, and the amount and timing of insulin
248 dosing. Therefore, **hyperglycemia can occur with:**

- 249 • **The wrong insulin dose.** This can happen from any of the following:
 - 250 • too little or no insulin is injected
 - 251 • the bolus dose of insulin infusion is set too low
 - 252 • the basal infusion dose is set too low
 - 253 • the pump or catheter system does not work right, delivering too little insulin
 - 254 • the insulin's ability to lower glucose is changed by incorrect storage (freezing,
255 excessive heat), or usage after the expiration date
- 256 • **Medicines that directly increase glucose or decrease sensitivity to insulin.** This
257 can happen, for example, with thiazide water pills (used for blood pressure),
258 corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- 259 • **Medical conditions that increase the body's production of glucose or decrease
260 sensitivity to insulin.** These medical conditions include fevers, infections, heart
261 attacks, and stress.
- 262 • **Too much carbohydrate intake.** This can happen if you
 - 263 • eat larger meals
 - 264 • eat more often
 - 265 • increase the proportion of carbohydrate in your meals

266

267 Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA)**
268 **or very high glucose levels (hyperosmolar coma) and result in unconsciousness and**
269 **death.** Although DKA occurs most often in patients with Type 1 diabetes, it can occur in
270 patients with Type 2 diabetes who become severely ill. Urine or blood tests will show
271 acetone, ketones, and high levels of glucose. Hyperosmolar coma occurs most often in
272 patients with Type 2 diabetes. Urine and blood tests will show very high levels of
273 glucose.

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

281 Because some patients experience few symptoms of hyperglycemia and ketosis, it is
282 important to monitor your glucose several times a day. Symptoms of hyperglycemia
283 include:

- 284 • confusion or drowsiness
- 285 • fruity smelling breath
- 286 • rapid, deep breathing
- 287 • increased thirst
- 288 • decreased appetite, nausea, or vomiting
- 289 • abdominal (stomach area) pain
- 290 • rapid heart rate
- 291 • increased urination and dehydration (too little fluid in your body)

292
293 Mild hyperglycemia can be treated by extra doses of insulin and drinking fluids
294 (rehydration). Patients using pumps should check pump function and replace the insulin
295 in the reservoir-syringe, as well as change the tubing and catheter and the infusion site.
296 **Patients using pumps may need to resume insulin injections with syringes or**
297 **injection pens.** Glucose and acetone-ketone levels should be monitored more often until
298 they return to normal. **More severe or continuing hyperglycemia requires prompt**
299 **evaluation and treatment by your health care provider.**

300
301 **Allergy can be serious.** Generalized allergy is an uncommon, but possibly life-
302 threatening, reaction to insulin products. Symptoms include:

- 303 • itchy rash over the entire body
- 304 • shortness of breath or wheezing
- 305 • confusion
- 306 • low blood pressure
- 307 • rapid heart beat
- 308 • sweating

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

311

312 Allergic reactions at the injection site (itching, redness, hardness, or swelling) are more
313 common than generalized allergy. They may need several days or weeks to clear up.
314 Pump patients with site reactions may need to change their infusion sites more often than
315 every 48 hours. Patients should avoid injection or infusion of insulin into skin areas that
316 have reactions. Tell your doctor about such reactions, because they can become more
317 severe, or they may change the absorption of insulin.

318

319 **Lipodystrophy** is a common change in the fat below the injection site. These changes
320 include loss of fat (depressions in the skin called lipoatrophy) or thickening of the tissue
321 under the skin (lipohypertrophy). Pump patients with lipodystrophy may need to change
322 their infusion sites more often than every 48 hours. Patients should avoid injection or
323 infusion of insulin into skin areas that have these reactions. Tell your doctor about such
324 reactions because they can become more severe, or they may change the absorption of
325 insulin.

326

327 **How should I store NovoLog?**

- 328 • **NovoLog can be damaged by high temperatures.** Therefore, be sure to protect it
329 from high air temperatures, heat from the sun, saunas, long showers, and other heat
330 sources. This is especially important if you use a pump or an insulin pen, because
331 you carry these devices with you and they may be exposed to different temperatures
332 as you go about your daily activities. **Throw NovoLog away if it has been in**
333 **temperatures greater than 98.6°F (37°C).**
- 334
- 335 • **Unopened NovoLog** should be stored in a refrigerator but not in the freezer and
336 protected from light. Even if it has been refrigerated and protected from sunlight and
337 unopened, it should not be used after the expiration date on the label and the carton.
338 Unopened vials and cartridges can be stored unrefrigerated at temperatures below
339 86°F (30°C) and protected from light for up to 28 days.
- 340
- 341 • **Punctured vials and cartridges** can be stored unrefrigerated at temperatures below
342 86°F (30°C) and protected from light for up to 28 days. Punctured vials may be
343 stored in the refrigerator. Cartridges inserted into their NovoPen[®] 3 device should not
344 be stored in the refrigerator.
- 345
- 346 • **The NovoLog in the pump reservoir and the complete infusion set** (reservoir,
347 tubing, catheter-needle) should be replaced **at least every 48 hours.** Replacement
348 should be more often than every 48 hours if you have hyperglycemia, the pump alarm
349 sounds, or the insulin flow is blocked (occlusion).
- 350
- 351 • Never use NovoLog if it has been stored improperly.

352

353 **General advice**

354 This leaflet summarizes the most important information about NovoLog. If you would
355 like more information, talk with your doctor. You can ask your pharmacist or doctor for
356 information about NovoLog that is written for health professionals.

357

358 **Injection and pump infusion instructions**

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

371

372 *How should I inject NovoLog?*

373

374 *Using Vials*

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

401

402 *Using Cartridges*

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

429

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

431

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

434

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

- 446 4. Remove air bubbles from the reservoir according to the pump manufacturers'
447 instructions.
- 448 5. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the
449 infusion set until you see a drop of insulin coming out of the infusion needle-catheter.
450 Flick the tubing to remove air bubbles. Follow the pump manufacturers' instructions
451 for additional priming.
- 452 6. Prime the needle-catheter and insert the infusion set into the skin according to the
453 pump manufacturer.
- 454 7. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin
455 infusion according to instructions from your doctor and the manufacturer of your
456 pump equipment.
- 457 8. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the
458 insulin every 48 hours or less, even if you have not used all of the insulin. This will
459 help ensure that NovoLog and the pump works well. (See "What is the most
460 important information I should know about NovoLog?")
- 461 9. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the
462 insulin if you experience a pump alarm, catheter blockage, hyperglycemia, or if your
463 pump insulin has been exposed to heat greater than 98.6°F (37°C). (See "What is the
464 most important information I should know about NovoLog?") Hyperglycemia
465 identified with glucose monitoring may be the first indication of a problem with the
466 pump, infusion set, or NovoLog. Hyperglycemia in the absence of an alarm still
467 requires you to investigate because pump alarms are designed to detect back-pressure
468 and occlusion. The alarms may not detect all the changes to NovoLog that could
469 result in hyperglycemia. You may need to resume subcutaneous insulin injections if
470 the cause of the problem cannot be promptly identified or fixed. (See
471 "Hyperglycemia" under "What are the possible side effects of NovoLog?")
472 Remember that long stretches of tubing increase the risk for kinking and expose the
473 insulin in the tubing to more variations in temperature.
474

475 **These instructions give you specific information for use of NovoLog in external**
476 **subcutaneous infusion pumps, but are not a substitute for pump education.**
477

478 *How should I mix insulins?*
479

480 **NovoLog should be mixed only when syringe injections are used.** NovoLog can be
481 mixed with NPH human insulin immediately before use. The NovoLog should be drawn
482 into the syringe before the NPH. Mixing with other insulins has not been studied.

483 **NovoLog should not be mixed with Lantus (insulin glargine [rDNA origin]**
484 **injection). Mixed insulins should NEVER be used in a pump or for intravenous**
485 **infusion.**
486

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

- 492 NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog
493 vial and may change how quickly it works.)
494 4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into
495 the NovoLog vial. With the needle in place, turn the vial upside-down and withdraw
496 the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the
497 full dose and not an air dose.
498 5. Insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe-
499 needle still in it. Withdraw the correct dose of NPH.
500 6. Inject immediately to reduce changes in how quickly the insulin works.

501
502

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

505

506 For information contact:
507 Novo Nordisk Inc.,
508 100 College Road West
509 Princeton, New Jersey 08540
510 1-800-727-6500
511 www.novonordisk-us.com

512

513 Manufactured by
514 Novo Nordisk A/S
515 2880 Bagsvaerd, Denmark

516

517 NovoLog® is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents
518 pending.

519

520 NovoLog®, PenFill®, NovoPen®, Innovo®, NovoFine®, and Lente® are trademarks of
521 Novo Nordisk A/S.

522 Lantus® is a trademark of Aventis Pharmaceuticals Inc.

523 H-TRON® is a trademark of Disetronic Medical Systems, Inc.

524 InDuo® is a trademark of LifeScan, Inc., a Johnson & Johnson company.

525

526

527 Date of Issue

528

529 8-XXXX-XX-XXX-X

530

531 Printed in Denmark

532

533