NovoLog™
Insulin Aspart (rDNA origin) Injection

DESCRIPTION

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

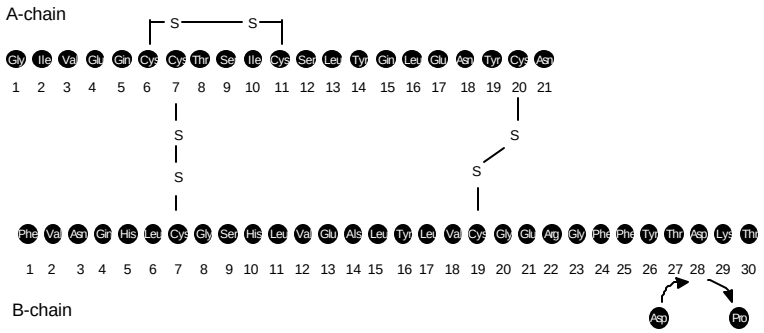

Figure 1. Structural formula of insulin aspart.

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

CLINICAL PHARMACOLOGY

Mechanism of action

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

In standard biological assays in mice and rabbits, one unit of NovoLog™ has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog™ is more

rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see Figure 2 and Figure 3).

Pharmacokinetics

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

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

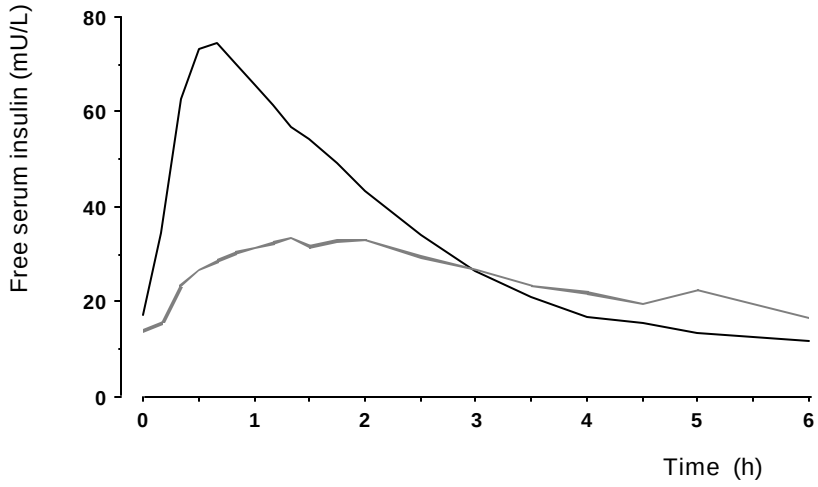

Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog™ (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

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

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

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog™ and regular human insulin described above, were observed independent of the injection site (abdomen, thigh, or upper arm).

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

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

In a 6-hour study in patients with Type 1 diabetes (n= 22), the maximum glucose-lowering effect of NovoLog™ occurred between 1 and 3 hours after subcutaneous injection (see Figure 3). The duration of action for NovoLog™ is 3 to 5 hours compared to 5 to 8 hours for regular human insulin. The time course of action of insulin and insulin analogs such as NovoLog™ may vary considerably in different individuals or within the same individual. The parameters of NovoLog™ activity (time of onset, peak time and duration) as designated in Figure 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General).

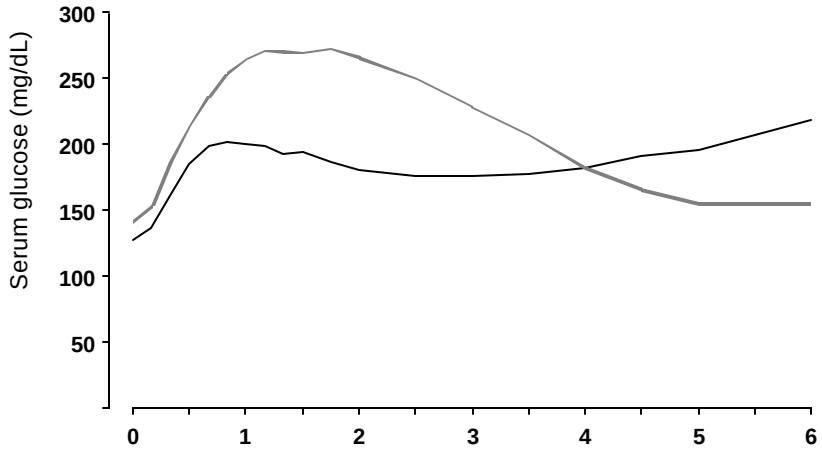

Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog™ (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

Special populations

Age and Gender

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.

Time (h)

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

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

Obesity- The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of NovoLog™ has not been 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. The effect of renal impairment on the phamacokinetics of NovoLog™ has not been studied. 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. The effect of hepatic impairment on the pharmacokinetics of NovoLog™ has not been studied. Careful glucose monitoring and dose adjustments of insulin, including NovoLog™, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

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

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

Clinical Studies: To evaluate the safety and efficacy of NovoLog™ in patients with Type 1 diabetes, two six-month, open-label, active-control (NovoLog™ vs Novolin® R) studies were conducted (see Table 1). NovoLog™ was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Glycemic control (as measured by HbA1c), the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party), and the incidence of ketosis were clinically comparable for the two treatment regimens. The mean total daily doses of insulin were greater (1 - 3 U/day) in the NovoLog™-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. To achieve the stated levels of glycemic control, some patients required more than three doses of meal-related insulin and/or more than one dose of basal insulin (see Table 1). No serum glucose measurements were obtained in these studies.

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

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

Study	Treatment (n)	Mean HbA1c (%)		Hypoglycemia (events/month)	% of Patients Using Various Numbers of Insulin Injections/Day*				
		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

* Percentages are rounded to the nearest whole number

INDICATIONS AND USAGE

NovoLog™ is indicated for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog™ has a more rapid onset and a shorter duration of action than human regular insulin, NovoLog™ should normally be used in regimens together with an intermediate or long-acting insulin.

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 its rapid onset of action and a shorter duration of action. 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 Type 1 diabetes also require a longer-acting insulin to maintain adequate glucose control.

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.

Glucose monitoring is recommended for all patients with diabetes.

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.

PRECAUTIONS

General

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

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

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

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

Hypoglycemia- As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog™. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes

control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment- Although there are no specific data in patients with diabetes and renal impairment treated with NovoLog™, NovoLog™ dose requirements may be reduced in the presence of renal impairment, similar to observations with other insulins. (see CLINICAL PHARMACOLOGY, Pharmacokinetics)

Hepatic Impairment- Although there are no specific data in patients with diabetes and hepatic disease treated with NovoLog™, NovoLog™ dose requirements may be reduced in the presence of impaired hepatic function, similar to observations found withother insulins. (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, 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 trials and their extensions, two of 2136 patients treated with NovoLog™ were discontinued due to allergic reactions.

Antibody production- Insulin antibodies may develop during treatment with insulin. In large clinical trials, levels of antibodies that cross react with human insulin and insulin aspart were higher in patients treated with NovoLog™ compared to regular human insulin. The clinical significance of these antibodies is uncertain.

Information for 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 for use of injection devices, and proper storage of insulin.

The need for patient-performed regular blood glucose measurements should be considered when using NovoLog™ in order to obtain optimal glycemic control. Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog™ during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

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

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

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY)

Mixing of insulins- A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog™ with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog™, but that the time to peak and the total bioavailability of NovoLog™ were not significantly affected. If NovoLog™ is mixed with NPH human insulin,

NovoLog™ should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog™ and crystalline zinc insulin preparations, NovoLog™ should not be mixed with these preparations.

The effects of mixing NovoLog™ with insulins of animal source or insulin preparations produced by other manufacturers have not been studied *(see* WARNINGS).

Mixtures should not be administered intravenously.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog™**.** In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog™ at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog™ increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog™ was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog™ was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed**.**

Pregnancy: Teratogenic effects: Pregnancy Category C

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.

There are no well-controlled clinical studies of the use of NovoLog™ in pregnant women. 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. Because animal reproduction studies are not always predictive of human response, NovoLog™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use- Safety and effectiveness of NovoLog™ in children have not been studied.

Geriatric Use- In the large controlled clinical trials, 36 patients $\geq$ 65 years of age were treated with NovoLog™. No conclusions regarding the safety and efficacy of NovoLog™ in the elderly patients compared to younger adults can be reached from this limited data set.

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).
Other: **Hypoglycemia (see WARNINGS and PRECAUTIONS).**

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

NovoLog™ should generally be given immediately before a meal. The dosage of NovoLog™ should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The total daily individual insulin requirement is usually between 0.5 - 1.0 units/kg/day. In a meal-related treatment regimen, 50 - 70% of this requirement may be provided by NovoLog™ and the remainder provided by an intermediate-acting or long-acting insulin. Patients may require more basal insulin in relation to bolus insulin and more total insulin when using NovoLog™ compared to regular human insulin to prevent pre-meal hyperglycemia. Additional basal insulin injections may be necessary.

Because of the fast onset of action of NovoLog™, it should generally be given close to a meal (start of meal within 5-10 minutes after injection). The dose of NovoLog™ should be regularly adjusted according to blood glucose measurements.

NovoLog™ should be administered by subcutaneous injection in the abdominal wall, the thigh, or the upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use any NovoLog™ if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog™ should not be used after its 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

* NovoLog™ PenFill® cartridges are for use with NovoPen®3 Insulin Delivery Devices and NovoFine® disposable needles.

RECOMMENDED STORAGE

NovoLog™ should be stored between 2° and 8°C (36° to 46°F). *Do not freeze*. **Do not**

use NovoLog™ if it has been frozen. Cartridges or vials in use may be kept at ambient temperature below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight.

Rx only