HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NovoLog® safely and effectively. See full prescribing information for NovoLog.

NovoLog (insulin aspart [rDNA origin] injection) solution for subcutaneous use
Initial U.S. Approval: 2000

·····INDICATIONS AND USAGE·····

- NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1).

·····DOSAGE AND ADMINISTRATION·····

- The dosage of NovoLog must be individualized.
- *Subcutaneous injection:* NovoLog should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.2).
- *Use in pumps*: Change the NovoLog in the reservoir at least every 6 days, change the infusion set, and the infusion set insertion site at least every 3 days. NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump (2.3).
- *Intravenous use*: NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride (2.4).

·····DOSAGE FORMS AND STRENGTHS·····

Each presentation contains 100 Units of insulin aspart per mL (U-100)

- 10 mL vials (3)
- 3 mL PenFill® cartridges for the 3 mL PenFill cartridge device (3)
- 3 mL NovoLog FlexPen (3)

·····CONTRAINDICATIONS·····

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog or one of its excipients.

·····WARNINGS AND PRECAUTIONS·····

- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision (5.1, 5.2).
- Insulin, particularly when given intravenously or in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5).
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog (5.6).

·····ADVERSE REACTIONS·····

Adverse reactions observed with NovoLog include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

·····DRUG INTERACTIONS·····

- The following may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics (7).
- The following 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), atypical antipsychotics (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: [3/2008]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Diabetes Mellitus

NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog is an insulin analog with an earlier onset of action than regular human insulin. The dosage of NovoLog must be individualized. NovoLog given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. 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.

Do not use NovoLog that is viscous (thickened) or cloudy; use only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

2.2 Subcutaneous Injection

NovoLog should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, it should be injected immediately (within 5-10 minutes) before a meal. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action of NovoLog will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog may be diluted with Insulin Diluting Medium for NovoLog for subcutaneous injection. Diluting one part NovoLog to nine parts diluent will yield a concentration one-tenth that of NovoLog (equivalent to U-10). Diluting one part NovoLog to one part diluent will yield a concentration one-half that of NovoLog (equivalent to U-50).

2.3 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

NovoLog can also be infused subcutaneously by an external insulin pump [*see Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2)*]. Diluted insulin should not be used in external insulin pumps. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, pre-meal boluses of NovoLog should be infused immediately (within 5-10 minutes) before a meal. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is usually given as meal-related boluses of NovoLog and the remainder is given as a basal infusion. **Change the**

NovoLog in the reservoir at least every 6 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The following insulin pumps have been used in NovoLog clinical or in vitro studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- Disetronic® D-TRON® and H-TRON®

Before using a different insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

2.4 Intravenous Use

NovoLog can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. For intravenous use, NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride.

Inspect NovoLog for particulate matter and discoloration prior to parenteral administration.

3 DOSAGE FORMS AND STRENGTHS

NovoLog is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL PenFill cartridges for the 3 mL PenFill cartridge delivery device (with or without the addition of a NovoPen® 3 PenMate®) with NovoFine® disposable needles
- 3 mL NovoLog FlexPen

4 CONTRAINDICATIONS

NovoLog is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

NovoLog has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog should immediately be followed by a meal within 5-10 minutes. Because of NovoLog's short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. 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 many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations [*see Clinical Pharmacology (12)*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*see Drug Interactions (7)*]. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

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 longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [*see Drug Interactions (7)*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia.

5.3 Hypokalemia

All insulin products, including NovoLog, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin).

5.4 Renal Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.5 Hepatic Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hypersensitivity and Allergic Reactions

Local Reactions - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog injection. These 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. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog.

Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog. Anaphylactic reactions with NovoLog have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog-treated patients discontinued due to allergic reactions.

5.7 Antibody Production

Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. Increases in anti-insulin antibodies are observed more frequently with NovoLog than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human 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. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose.

5.8 Mixing of Insulins

- Mixing NovoLog with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog, without significantly affecting the time to peak concentration or total bioavailability of NovoLog. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first, and the mixture should be injected immediately after mixing.
- The efficacy and safety of mixing NovoLog with insulin preparations produced by other manufacturers have not been studied.
- Insulin mixtures should not be administered intravenously.

5.9 Continuous Subcutaneous Insulin Infusion by External Pump

When used in an external subcutaneous insulin infusion pump, NovoLog should not be mixed with any other insulin or diluent. When using NovoLog in an external insulin pump, the NovoLog-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog-specific information may differ from general pump manual instructions.

Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis 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 a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)*].

NovoLog should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog that will be used in a pump should not be mixed with other insulin or with a diluent** [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9) and How Supplied/Storage and Handling (16.2), Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

- *Hypoglycemia*

  Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog [*see Warnings and Precautions (5)*].

- *Insulin initiation and glucose control intensification*

  Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

  Long-term use of insulin, including NovoLog, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy.

- *Weight gain*

  Weight gain can occur with some insulin therapies, including NovoLog, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- *Peripheral Edema*

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Frequencies of adverse drug reactions*

The frequencies of adverse drug reactions during NovoLog clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog compared to human regular insulin are listed)

	NovoLog + NPH N= 596		Human Regular Insulin + NPH N= 286	
Preferred Term	**N**	**(%)**	**N**	**(%)**
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog compared to human regular insulin are listed)

	NovoLog + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	**(%)**	**N**	**(%)**
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL,with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Postmarketing Data

The following additional adverse reactions have been identified during postapproval use of NovoLog. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog have been identified during postapproval use [*see Patient Counseling Information (17)*].

7 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, pramlintide, 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), atypical antipsychotics.
- 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.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 these patients. Therefore, female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking NovoLog.

An open-label, randomized study compared the safety and efficacy of NovoLog (n=157) versus regular human insulin (n=165) in 322 pregnant women with type 1 diabetes. Two-thirds of the enrolled patients were already pregnant when they entered the study. Because only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Both groups achieved a mean HbA_{1c} of ~ 6% 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 in 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.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Use of NovoLog is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NovoLog is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. NovoLog has not been studied in pediatric patients younger than 2 years of age. NovoLog has not been studied in pediatric patients with type 2 diabetes. Please see *Section 14* ***CLINICAL STUDIES*** for summaries of clinical studies.

8.5 Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog in 3 controlled clinical studies, 2.6% (n=36) were 65 years of age or over. One-half of these patients had type 1 diabetes (18/1285) and the other half had type 2 diabetes (18/90). 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.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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.

11 DESCRIPTION

NovoLog (insulin aspart [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. 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). Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8.

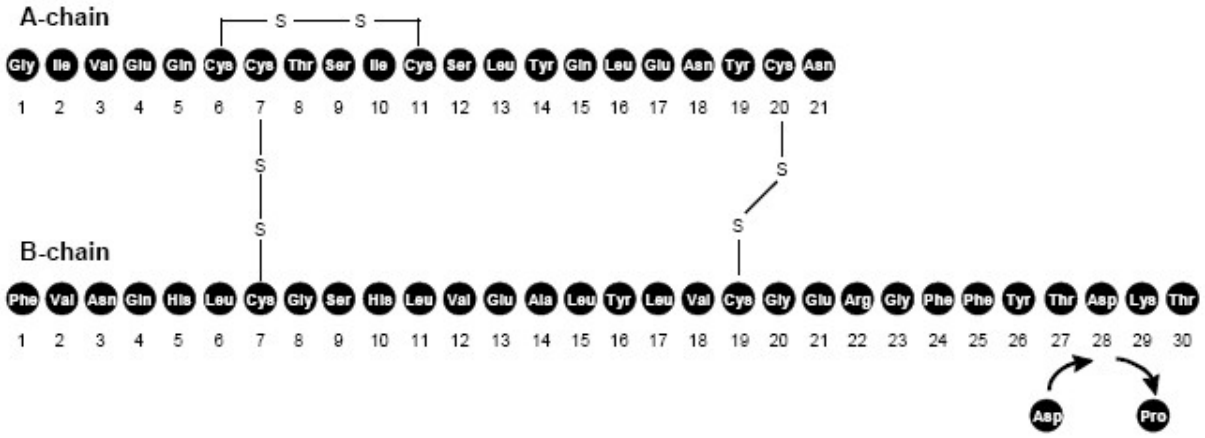

Figure 1. Structural formula of insulin aspart.

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

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 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 2). The duration of action for NovoLog is 3 to 5 hours. 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 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [*see Warnings and Precautions (5.1)*].

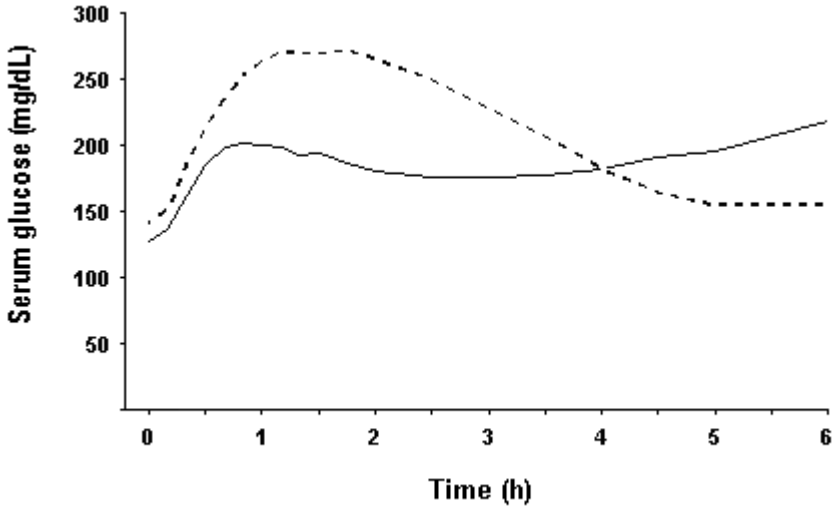

Figure 2. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

A double-blind, randomized, two-way cross-over study in 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. NovoLog or human insulin was infused until the patient's blood glucose decreased to 36 mg/dL, or until the patient demonstrated signs of hypoglycemia (rise in heart rate and onset of sweating), defined as the time of autonomic reaction (R) (see Figure 3).

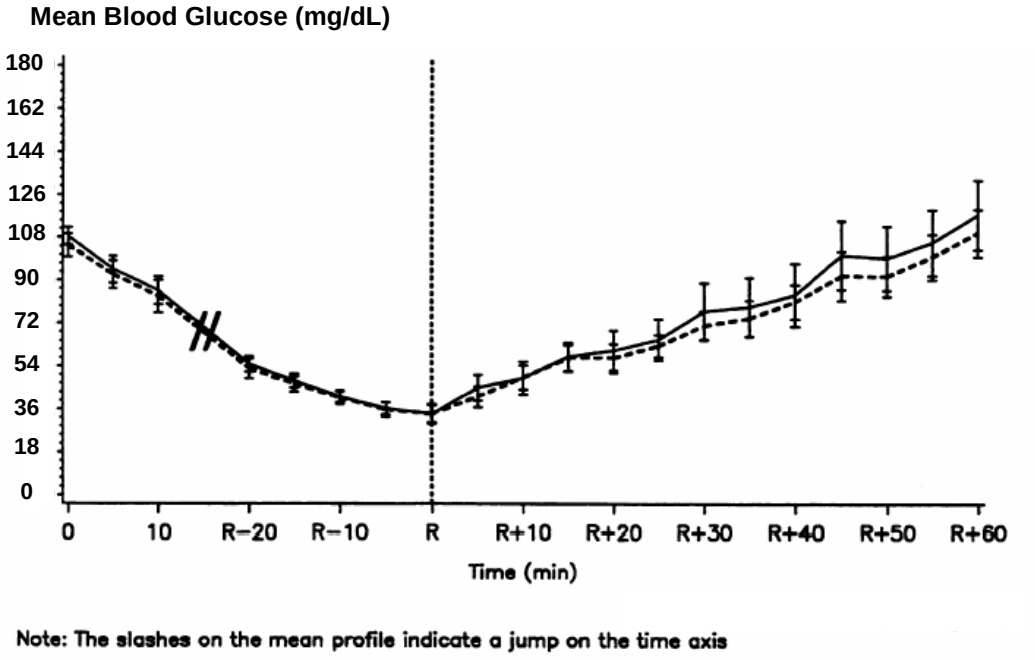

Figure 3. Mean blood glucose profiles following intravenous infusion of NovoLog (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

12.3 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 1.2 l/h/kg for the NovoLog group and 1.2 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 4). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

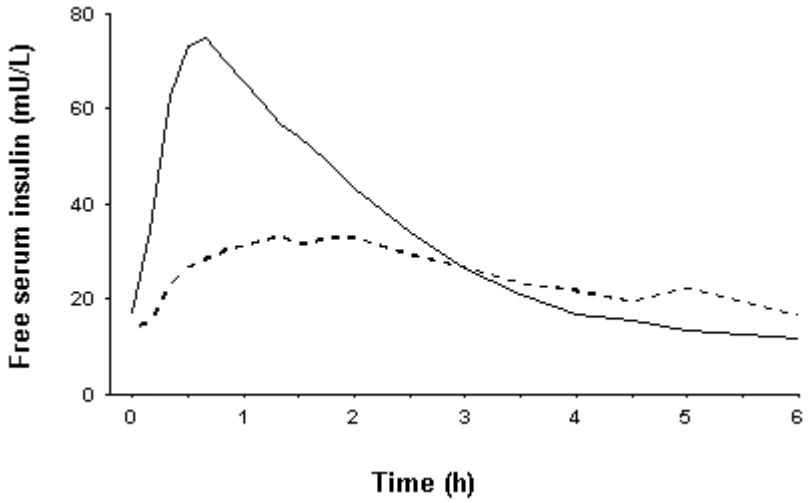

Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

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 and 36 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 site of injection (abdomen, thigh, or upper arm).

Distribution and Elimination - NovoLog has low binding to plasma proteins (<10%), similar to that seen with 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.

Specific Populations

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

type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with type 1 diabetes.

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 HbA_{1c}) between genders in a trial in patients with type 1 diabetes.

Obesity - A single subcutaneous dose of 0.1 U/kg NovoLog was administered in a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m^2). The pharmacokinetic parameters, AUC and C_{max}, of NovoLog were generally unaffected by BMI in the different groups – BMI 19-23 kg/m^2 (N=4); BMI 23-27 kg/m^2 (N=7); BMI 27-32 kg/m^2 (N=6) and BMI >32 kg/m^2 (N=6). Clearance of NovoLog was reduced by 28% in patients with BMI >32 kg/m^2 compared to patients with BMI <23 kg/m^2.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of 0.08 U/kg NovoLog was administered in a study to subjects with either normal (N=6) creatinine clearance (CLcr) (> 80 ml/min) or mild (N=7; CLcr = 50-80 ml/min), moderate (N=3; CLcr = 30-50 ml/min) or severe (but not requiring hemodialysis) (N=2; CLcr = <30 ml/min) renal impairment. In this small study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of NovoLog. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction [*see Warnings and Precautions (5.4)*].

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. A single subcutaneous dose of 0.06 U/kg NovoLog was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this small study, there was no correlation 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 Warnings and Precautions (5.5)*].

The effect of age, ethnic origin, pregnancy and smoking on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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.

13.2 Animal Toxicology and/or Pharmacology

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 *Section 12* CLINICAL PHARMACOLOGY Figure 2 and Figure 4).

14 CLINICAL STUDIES

14.1 Subcutaneous Daily Injections

Two six-month, open-label, active-controlled studies were conducted to compare the safety and efficacy of NovoLog to Novolin R in adult patients with type 1 diabetes. Because the two study designs and results were similar, data are shown for only one study (see Table 3). 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} and the incidence rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens in this study (Table 3) as well as in the other clinical studies that are cited in this section. Diabetic ketoacidosis was not reported in any of the adult studies in either treatment group.

Table 3. Subcutaneous NovoLog Administration in Type 1 Diabetes (24 weeks; n=882)

	NovoLog + NPH	Novolin R + NPH
N	596	286
Baseline HbA_{1c} (%)*	7.9 ±1.1	8.0 ± 1.2
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	0.0 ± 0.8
Treatment Difference in HbA_{1c} ,Mean (95% confidence interval)	-0.2 (-0.3, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	104 (17%)	54 (19%)
Baseline body weight (kg)*	75.3 ± 14.5	75.9 ± 13.1
Weight Change from baseline (kg)*	0.5 ± 3.3	0.9 ± 2.9

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) aged 6 to 18 years compared two subcutaneous multiple-dose 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} (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog and regular human insulin have also been compared in children with type 1 diabetes (n=26) aged 2 to 6 years with similar effects on HbA_{1c} and hypoglycemia.

Table 4. Pediatric Subcutaneous Administration of NovoLog in Type 1 Diabetes (24 weeks; n=283)

	NovoLog + NPH	Novolin R + NPH
N	187	96
Baseline HbA_{1c} (%)*	8.3 ± 1.2	8.3 ± 1.3
Change from Baseline HbA_{1c} (%)	0.1± 1.0	0.1± 1.1
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.1 (-0.5, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	11 (6%)	9 (9%)
Diabetic ketoacidosis (n, %)	10 (5%)	2 (2%)
Baseline body weight (kg)*	50.6 ± 19.6	48.7 ± 15.8
Weight Change from baseline (kg)*	2.7 ± 3.5	2.4 ± 2.6

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

One six-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NovoLog to Novolin R in patients with type 2 diabetes (Table 5). 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_{lc} and the rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens.

Table 5. Subcutaneous NovoLog Administration in Type 2 Diabetes (6 months; n=176)

	NovoLog + NPH	Novolin R + NPH
N	90	86
Baseline HbA_{1c} (%)*	8.1 ± 1.2	7.8 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.3 ± 1.0	-0.1 ± 0.8
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	- 0.1 (-0.4, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.6 ± 0.3	0.6 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.7 ± 0.3
Patients with severe hypoglycemia (n, %)**	9 (10%)	5 (8%)
Baseline body weight (kg)*	88.4 ± 13.3	85.8 ± 14.8
Weight Change from baseline (kg)*	1.2 ± 3.0	0.4 ± 3.1

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

14.2 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

Two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog to buffered regular human insulin (Velosulin) in adults with type 1 diabetes receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA_{1c} and rates of severe hypoglycemia.

Table 6. Adult Insulin Pump Study in Type 1 Diabetes (16 weeks; n=118)

	NovoLog	Buffered human insulin
N	59	59
Baseline HbA_{1c} (%)*	7.3 ± 0.7	7.5 ± 0.8
Change from Baseline HbA_{1c} (%)	0.0 ± 0.5	0.2 ± 0.6
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.3 (-0.1, 0.4)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.8	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.7	0.6 ± 0.2
Patients with severe hypoglycemia (n, %)**	1 (2%)	2 (3%)
Baseline body weight (kg)*	77.4 ± 16.1	74.8 ± 13.8
Weight Change from baseline (kg)*	0.1 ± 3.5	-0.0 ± 1.7

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes (n=298) aged 4-18 years compared two subcutaneous infusion regimens administered via an external insulin pump: NovoLog (n=198) or insulin lispro (n=100). These two treatments resulted in comparable changes from baseline in HbA_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 7).

Table 7. Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

	NovoLog	Lispro
N	198	100
Baseline HbA_{1c} (%)*	8.0 ± 0.9	8.2 ± 0.8
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	-0.1 ± 0.7
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	-0.1 (-0.3, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.9 ± 0.3	0.9 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.2	0.9 ± 0.2
Patients with severe hypoglycemia (n, %)**	19 (10%)	8 (8%)
Diabetic ketoacidosis (n, %)	1 (0.5%)	0 (0)
Baseline body weight (kg)*	54.1 ± 19.7	55.5 ± 19.0
Weight Change from baseline (kg)*	1.8 ± 2.1	1.6 ± 2.1

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

An open-label, 16-week parallel design trial compared pre-prandial NovoLog injection in conjunction with NPH injections to NovoLog administered by continuous subcutaneous infusion in 127 adults with type 2 diabetes. The two treatment groups had similar reductions in HbA_{1c} and rates of severe hypoglycemia (Table 8) [*see Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

Table 8. Pump Therapy in Type 2 Diabetes (16 weeks; n=127)

	NovoLog pump	NovoLog + NPH
N	66	61
Baseline HbA_{1c} (%)*	8.2 ± 1.4	8.0 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.6 ± 1.1	-0.5 ± 0.9
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.1 (0.4, 0.3)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.8 ± 0.5
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.4	0.9 ± 0.5
Baseline body weight (kg)*	96.4 ± 17.0	96.9 ± 17.9
Weight Change from baseline (kg)*	1.7 ± 3.7	0.7 ± 4.1

*Values are Mean ± SD

14.3 Intravenous Administration of NovoLog

See *Section 12.2* CLINICAL PHARMACOLOGY/Pharmacodynamics.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 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	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) with NovoFine disposable needles.

16.2 Recommended Storage

Unused NovoLog should be stored in a refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze NovoLog and do not use NovoLog if it has been frozen.** NovoLog should not be drawn into a syringe and stored for later use.

Vials: After initial use a vial 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.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill cartridges or NovoLog FlexPen Prefilled Syringes:

Once a cartridge or a NovoLog FlexPen is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog FlexPen or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog FlexPen and all PenFill cartridges away from direct heat and sunlight. Unpunctured NovoLog FlexPen and PenFill cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog FlexPen and PenFill cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill cartridge delivery device or NovoLog FlexPen without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Pump:

NovoLog in the pump reservoir should be discarded after at least every 6 days of use or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and the infusion set insertion site should be changed at least every 3 days.

Summary of Storage Conditions:

The storage conditions are summarized in the following table:

Table 9. Storage conditions for vial, PenFill cartridges and NovoLog FlexPen Prefilled syringe

NovoLog presentation	**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)

Storage of Diluted NovoLog

NovoLog diluted with Insulin Diluting Medium for NovoLog to a concentration equivalent to U-10 or equivalent to U-50 may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NovoLog in Infusion Fluids

Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion bag.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling *(17.3)*]

17.1 Physician Instructions

Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and benefits of NovoLog therapy including the possible adverse reactions. 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.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental substitutions between NovoLog and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between NovoLog and any other insulin. **The written prescription for NovoLog should be written clearly, to avoid confusion with other insulin products, for example, NovoLog Mix 70/30.**

17.2 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.

The following insulin pumps have been used in NovoLog clinical or in vitro studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- Disetronic® D-TRON® and H-TRON®

Before using another insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

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), insulin in the reservoir should be replaced at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.

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 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 Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

17.3 FDA Approved Patient Labeling

Rx only

Date of Issue:

Version

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

NovoLog® is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents pending.
FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, and other patents pending.
PenFill® is covered by US Patent Nos. 6,126,646, 5,693,027, DES 347894, and other patents pending.

Manufactured By Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Manufactured For Novo Nordisk Inc., Princeton, New Jersey 08540

www.novonordisk-us.com

Patient Information

NovoLog® (NŌ-vō-log)

(insulin aspart [rDNA origin] Injection)

Important:
Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with NovoLog before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog?

NovoLog is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use NovoLog?

Do not take NovoLog if:

- Your blood sugar is too low (hypoglycemia)
- You are allergic to anything in NovoLog. See the end of this leaflet for a complete list of ingredients in NovoLog. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

- **about all of your medical conditions.** Medical conditions can affect your insulin needs and your dose of NovoLog.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog has not been studied in nursing women.
- **about all medicines you take,** including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your NovoLog dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take NovoLog?
Only use NovoLog if it appears clear and colorless. There may be air bubbles. This is normal. If it looks cloudy, thickened, or colored, or if it contains solid particles do not use it and call Novo Nordisk at 1-800-727-6500.

NovoLog comes in:

- 10 mL vials (small bottles) for use with syringe
- 3 mL PenFill® cartridges for use with the Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices and NovoFine® disposable needles. The cartridge delivery device can be used with a NovoPen® 3 PenMate®
- 3 mL NovoLog FlexPen®

Read the instructions for use that come with your NovoLog product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog before you start taking it.

- **Take NovoLog exactly as prescribed.** You should eat a meal within 5 to 10 minutes after using NovoLog to avoid low blood sugar.
- **NovoLog is a fast-acting insulin.** The effects of NovoLog start working 10 to 20 minutes after injection or bolus pump infusion.
- **Do not inject NovoLog if you do not plan to eat right after your injection or bolus pump infusion.**
- The greatest blood sugar lowering effect is between 1 and 3 hours after the injection or infusion. This blood sugar lowering lasts for 3 to 5 hours.
- **While using NovoLog you may have to change** your total dose of insulin, your dose of longer-acting insulin, or the number of injections of longer-acting insulin you use. Pump users given NovoLog may need to change the amount of total insulin given as a basal infusion.
- **Do not mix NovoLog:**
    - with any other insulins when used in a pump
    - with any insulins other than NPH when used with injections by syringe

If your doctor recommends diluting NovoLog, follow your doctor's instructions exactly so that you know:

- How to make NovoLog more dilute (that is, a smaller number of units of NovoLog for a given amount of liquid) and
- How to use this more dilute form of NovoLog. **Do not use dilute insulin in a pump.**

- **Inject NovoLog into the skin of your stomach area, upper arms, buttocks or upper legs.** NovoLog may affect your blood sugar levels sooner if you inject it into the skin of your stomach area. **Never inject NovoLog into a vein or into a muscle.**
- **Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection.**
- **If you take too much NovoLog**, **your blood sugar may fall low (hypoglycemia).** You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See "What are the possible side effects of NovoLog?" for more information on low blood sugar (hypoglycemia).
- **If you forget to take your dose of NovoLog, your blood sugar may go too high (hyperglycemia).** If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:
  - increased thirst
  - frequent urination
  - drowsiness
  - loss of appetite
  - a hard time breathing
  - fruity smell on the breath
  - high amounts of sugar and ketones in your urine
  - nausea, vomiting (throwing up) or stomach pain
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise

What should I avoid while using NovoLog?

- **Alcohol.** Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog.

- **Driving and operating machinery.** You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:
    - low blood sugar
    - decreased or no warning signs of low blood sugar

What are the possible side effects of NovoLog?

- **low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:

    - sweating
    - dizziness or lightheadedness
    - shakiness
    - hunger
    - fast heart beat
    - tingling of lips and tongue
    - trouble concentrating or confusion
    - blurred vision
    - slurred speech
    - anxiety, irritability or mood changes
    - headache

    Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

- **Serious allergic reaction (whole body reaction). Get medical help right away, if you develop** a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **Reactions at the injection site (local allergic reaction)**. You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider. You may need to stop using NovoLog and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.
- **Skin thickens or pits at the injection site (lipodystrophy).** Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.
- **Swelling of your hands and feet.**
- **Vision changes**
- **Low potassium in your blood (hypokalemia)**

- **Weight gain**

These are not all of the possible side effects from NovoLog. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NovoLog?

All Unopened NovoLog:

- **Keep all unopened NovoLog in the refrigerator between 36° to 46°F (2° to 8°C).**
- Do not freeze. Do not use NovoLog if it has been frozen.
- Keep unopened NovoLog in the carton to protect from light.

NovoLog in use:

- **Vials.**
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
  - Do not draw up NovoLog into a syringe and store for later use
  - Unopened vials can be used until the expiration date on the NovoLog label, if the medicine has been stored in a refrigerator.

- **PenFill Cartridges or NovoLog FlexPen Prefilled syringe.**
  - Keep at room temperature below 86°F (30°C) for up to 28 days.
  - Do not store a PenFill cartridge or NovoLog FlexPen Prefilled syringe that you are using in the refrigerator.
  - Keep PenFill cartridges and NovoLog FlexPen Prefilled syringe away from direct heat or light.
  - Throw away a used PenFill cartridge or NovoLog FlexPen Prefilled syringes after 28 days, even if there is insulin left in the cartridge or syringe.

- **NovoLog in the pump reservoir and the complete external pump infusion set**

- The infusion set and the infusion site should be changed **at least every 3 days.** The insulin in the reservoir should be changed **at least every 6 days** even if you have not used all of the insulin. Change the infusion set and the infusion site more often than every 3 days if you have high blood sugar (hyperglycemia), the pump alarm sounds, or the insulin flow is blocked (occlusion).

General advice about NovoLog
Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog for a condition for which it was not prescribed. Do not give NovoLog to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog. If you would like more information about NovoLog or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street Alexandria, VA 22311 and on www.diabetes.org.

NovoLog ingredients include:

- insulin aspart
- glycerin
- phenol
- metacresol
- zinc
- disodium hydrogen phosphate dihydrate
- sodium chloride
- water for injection

All NovoLog vials, PenFill cartridges and NovoLog FlexPen Prefilled syringes are latex free.

Date of Issue:
Version: 7

PenFill® is covered by US Patent Nos. 6,126,646, 5,693,027, DES 347894, and other patents pending.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about NovoLog® contact:
Novo Nordisk Inc.
100 College Road West,
Princeton, New Jersey 08540

Patient Instructions for Use
NovoLog® 10 mL vial (100 Units/mL, U-100)

Before starting, gather all of the supplies that you will need to use for preparing and giving your insulin injection.

Never re-use syringes and needles.

How should I use the NovoLog vial?

1. Check to make sure that you have the correct type of insulin. This is especially important if you use different types of insulin.
2. Look at the vial and the insulin. The insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap had been removed before your first use of the vial, or if the insulin is cloudy or colored, do not use it and call Novo Nordisk at 1-800-727-6500
3. Wash your hands with soap and water. If you clean your injection site with an alcohol swab, let the injection site dry before you inject. Talk with your healthcare provider about how to rotate injection sites and how to give an injection.
4. If you are using a new vial, pull off the tamper-resistant cap. Wipe the rubber stopper with an alcohol wipe.
5. Do not roll or shake the vial. Shaking right before the dose is drawn into the syringe may cause bubbles or froth. This can cause you to draw up the wrong dose of insulin.
6. Pull back the plunger on the syringe until the black tip reaches the marking for the number of units you will inject.
7. Push the needle through the rubber stopper of the vial, and push the plunger all the way in to force air into the vial.
8. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond correct dose.
9. If there are any air bubbles, tap the syringe gently with your finger to raise the air bubbles to the top. Then slowly push the plunger to the marking for your correct dose. This process should move any air bubbles present in the syringe back into the vial.
10. Check to make sure you have the right dose of NovoLog in the syringe.
11. Pull the syringe out of the vial's rubber stopper.
12. Your doctor should tell you if you need to pinch the skin before inserting the needle. This can vary from patient to patient so it is important to ask your doctor if you did not receive instructions on pinching the skin**.** Insert the needle into the pinched skin. Press the plunger of the syringe to inject the insulin. When you are finished injecting the insulin, pull the needle out of your skin. You may see a drop of NovoLog at the needle tip. This is normal and has no effect on the dose you just received. If you see blood after

you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol wipe. **Do not rub the area.**

13. After your injection, do not recap the needle. Place used syringes, needles and used insulin vials in a disposable puncture-resistant sharps container, or some type of hard plastic or metal container with a screw on cap such as a detergent bottle or coffee can.
14. Ask your healthcare provider about the right way to throw away used syringes and needles. There may be state or local laws about the right way to throw away used syringes and needles. Do not throw away used needles and syringes in household trash or recycle.

How should I mix insulins?

NovoLog should be mixed only when injections with syringes are used. NovoLog can be mixed with NPH human insulin right before use. The NovoLog should be drawn into the syringe before you draw up the NPH insulin. **NovoLog should not be mixed with any other insulin except NPH.**

1. Add together the doses (total number of units) of NPH and NovoLog that you need to inject. The total dose will determine the final amount (volume) in the syringe after drawing up both insulins into the syringe. For example, if you need 5 units of NPH and 2 units of NovoLog, the total dose of insulin in the syringe would be 7 units.
2. Roll the NPH vial between your hands until the liquid is equally cloudy throughout.
3. Draw into the syringe the same amount of air as the NPH dose. Inject this air into the NPH vial and then remove the needle from the vial but do not withdraw any of the NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog vial and may change how quickly it works.)
4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into the NovoLog vial. With the needle in place, turn the vial upside down and withdraw the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the full dose and not an air dose.
5. After withdrawing the needle from the NovoLog vial, insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe and needle still in it. Withdraw the correct dose of NPH.
6. Inject right away to avoid changes in how quickly the insulin works.

How do I use NovoLog in a pump?

- Checking your blood sugar is very important for patients using pumps. Pump or infusion set problems can result in you not getting enough insulin. This can quickly cause you to have high blood sugar and diabetic ketoacidosis.
- Use insulin from a new vial of NovoLog if unexplained high blood sugar or pump alarms do not respond to all of the following:

  - a repeat dose (injection or bolus) of NovoLog
  - a change in the infusion set, including the NovoLog in the reservoir
  - a change in the infusion site
- If these measures do not work, you may need to go back to injecting NovoLog with syringes, or insulin pens. Continue to monitor your blood sugars and ketones. If problems continue, you must contact your healthcare provider.
- When NovoLog is used in pumps, **use only pumps that are recommended by your healthcare provider.** The infusion set and infusion site should be changed at least every 3 days. The insulin in the reservoir should be changed at least every 6 days even if you have not used all of the insulin. The reservoir, the infusion set, and infusion site should also be changed:
  - with unexpected high blood sugar
  - when the alarm sounds (see your pump manual)
  - if the insulin or pump has been exposed to temperatures over 98.6°F (37°C), such as in a sauna, with long showers, or on an unusually hot day.
  - if the insulin or pump could have absorbed heat, for example from sunlight, that would heat the insulin to over 98.6°F (37°C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may also affect the temperature

Patients who develop local skin reactions may need to change infusion sites more often than every 3 days.

Use only insulin pumps that have been specially tested with NovoLog. Follow your healthcare provider or pharmacist instructions for which insulin pumps may be used.

Check with your healthcare provider or pharmacist to see if your pump and infusion set can be used with NovoLog.

1. Check to make sure that you have the right type of insulin.
2. Look at the vial and insulin. The insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap had been removed before your first use, or if the insulin is cloudy or colored, do not use it and call Novo Nordisk at 1-800-727-6500.
3. Wash your hands with soap and water.
4. Fill the reservoir-syringe with 2 days worth of NovoLog plus about 25 extra units to prime the pump and the infusion tubing.
5. Remove air bubbles from the reservoir by following the pump manufacturers' instructions.
6. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the infusion set until you see a drop of insulin coming out of the

infusion needle-catheter. Follow the pump manufacturers' instructions for priming and removing air bubbles.

7. Clean your insertion site with an alcohol swab and let the site dry before you insert the needle-catheter. Talk with your healthcare provider about how to rotate insertion sites and how to insert the needle-catheter into the skin.
8. Insert the needle-catheter into the skin, remove the needle and prime the catheter according to the pump manufacturers' instructions. Do not insert the needle-catheter into skin that is reddened, itchy, bumpy, or thickened.
9. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin infusion according to instructions from your healthcare provider and the manufacturer of your pump equipment.
10. Change the infusion site and infusion set at least every 3 days, and change the insulin in the reservoir at least every 6 days even if you have not used all of the insulin. This will help ensure that NovoLog and the pump work well.
11. Change the infusion site, the infusion set, the insulin reservoir and the insulin if you experience a pump alarm, catheter blockage, high blood sugars, or if your pump insulin has been exposed to heat greater than 98.6^{o}F (37^{o}C).
12. If you have high blood sugar (hyperglycemia) when you check your blood sugar, this may be the first sign of a problem with the pump, infusion set, or NovoLog. If you have high blood sugar without a pump alarm, you must still check the pump because alarms may not detect all the changes to NovoLog that could result in high blood sugar. You may need to start insulin injections with syringes if the cause of the problem cannot be found quickly or fixed. Long lengths of infusion-set tubing increase the risk for kinking and expose the insulin in the tubing to more changes in temperature.