

NOVOLOG- insulin aspart injection, solution

Novo Nordisk

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 injection), for subcutaneous or intravenous use

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

- NOVOLOG is rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1).

DOSAGE AND ADMINISTRATION

See Full Prescribing Information for important administration and dosage instructions (2.1,2.2,2.3,2.4,2.5).

- *Subcutaneous injection (2.2):*
 - Inject subcutaneously within 5-10 minutes before a meal into the abdominal area, thigh, buttocks or upper arm.
 - Rotate injection sites within the same region from one injection to the next.
 - Should generally be used in regimens with an intermediate- or long-acting insulin.
- *Continuous Subcutaneous Infusion (Insulin Pump) (2.2):*
 - 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.
 - Do not mix with other insulins or diluents in the pump
- *Intravenous Administration (2.2):*
 - Dilute NOVOLOG to concentrations from 0.05 unit/mL to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags.
 - NOVOLOG is stable in infusion fluids such as 0.9% sodium chloride.
- Individualize and adjust the dosage of NOVOLOG based on route of administration, the individual's metabolic needs, blood glucose monitoring results and glycemic control goal (2.4).
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness (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)
- 3 mL NOVOLOG FlexTouch® (3)

CONTRAINDICATIONS

- During episodes of hypoglycemia (4).
- Hypersensitivity to NOVOLOG or one of its excipients.

WARNINGS AND PRECAUTIONS

- *Never share* a NOVOLOG FlexPen or a NOVOLOG Flex Touch, PenFill cartridge or PenFill cartridge device between patients, even if the needle is changed (5.1).
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairments and hypoglycemia unawareness (5.3).
- *Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection (5.4).

- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, may occur. Discontinue NOVOLOG, treat, and monitor, if indicated (5.6).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated (5.6).
- *Fluidretention and heart failure with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).
- *Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:* Monitor glucose and administer NOVOLOG by subcutaneous injection if pump malfunction occurs (5.8).

----- **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** -----

- *Drugs that may increase the risk of hypoglycemia:* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7).
- *Drugs that may decrease the blood glucose lowering effect:* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7).
- *Drugs that may increase or decrease the blood glucose lowering effect:* Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7).
- *Drugs that may blunt the signs and symptoms of hypoglycemia:* 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: 3/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NOVOLOG is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin labels before administration [*see Warnings and Precautions (5.4)*].
- Inspect NOVLOG visually before use. It should appear clear and colorless. Do not use NOVLOG if particulate matter or coloration is seen.
- Do NOT mix NOVLOG with other insulins when administering using a continuous subcutaneous infusion pump.

2.2 Route of Administration

Subcutaneous Injection

- Inject NOVLOG subcutaneously within 5-10 minutes before a meal into the abdominal area, thigh, buttocks or upper arm.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [*see Adverse Reactions (6.1)*].
- NOVLOG administered by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
- NOVLOG may be diluted with Insulin Diluting Medium for NOVLOG for subcutaneous injection. Diluting one part NOVLOG to nine parts diluent will yield a concentration one-tenth that of NOVLOG (equivalent to U-10). Diluting one part NOVLOG to one part diluent will yield a concentration one-half that of NOVLOG (equivalent to U-50).

Continuous Subcutaneous Infusion (Insulin Pump)

- Train patients using continuous subcutaneous insulin fusion pump therapy to administer insulin by injection and have alternate insulin therapy available in case of pump failure.
- Administer NOVLOG by continuous subcutaneous infusion into the subcutaneous tissue of the abdominal wall. Rotate infusion sites within the same region to reduce the risk of lipodystrophy [*see Adverse Reactions (6.1)*].
- Follow healthcare provider recommendations when setting basal and meal time infusion rate.
- Do NOT dilute or mix NOVLOG when administering by continuous subcutaneous infusion.
- Change the NOVLOG in the reservoir at least every 6 days
- Change the infusion sets and the infusion set insertion site at least every 3 days.
- Do NOT expose NOVLOG in the pump reservoir to temperatures greater than 98.6°F (37°C).
- Follow the NOVLOG-specific information (e.g., in-use time, frequency of changing infusion sets) because NOVLOG-specific information may differ from general pump manual instructions.
- The following insulin pumps† have been used in NOVLOG clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NOVLOG:
 - Medtronic Paradigm® 512 and 712
 - MiniMed 508

Intravenous Administration

- Dilute NOVLOG to concentrations from 0.05 unit/mL to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags. NOVLOG is stable in infusion fluids such as 0.9% sodium chloride.
- Administer NOVLOG intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5.3, 5.6) and How Supplied/Storage and Handling (16.2)*].

2.3 Dosage Information

- Individualize and adjust the dosage of NOVLOG based on route of administration, the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness [see *Warnings and Precautions (5.2, 5.3) and Use in Specific Populations (8.6, 8.7)*].
- Dosage adjustment may be needed when switching from another insulin to NOVLOG [see *Warnings and Precautions (5.2)*].

2.4 Dosage Adjustment Due to Drug Interactions

- Dosage adjustment may be needed when NOVLOG is coadministered with certain drugs [see *Drug Interactions (7)*].

2.5 Instructions for Mixing with Other Insulins

NOVLOG subcutaneous injection route	<p>NOVLOG may be mixed with NPH insulin preparations <u>ONLY</u>.</p> <p>• If NOVLOG is mixed with NPH insulin, draw NOVLOG into the syringe first and inject immediately after mixing.</p>
NOVLOG continuous subcutaneous infusion route (Insulin Pump)	<p><u>Do NOT mix NOVLOG with any other insulin.</u></p>

3 DOSAGE FORMS AND STRENGTHS

NOVLOG 100 units per mL (U-100) is available as a clear and colorless solution for injection in:

- 10 mL vials
- 3 mL PenFill cartridges for the 3 mL PenFill cartridge delivery device with NovoFine[®] disposable needles
- 3 mL NOVLOG FlexPen
- 3 mL NOVLOG FlexTouch

4 CONTRAINDICATIONS

NOVLOG is contraindicated:

- During episodes of hypoglycemia [see *Warnings and Precautions (5.3)*]
- In patients with hypersensitivity to NOVLOG or one of its excipients, [see *Warnings and Precautions (5.5)*]

5 WARNINGS AND PRECAUTIONS

5.1 Never Share NOVLOG FlexPen, NOVLOG FlexTouch, PenFill Cartridge or PenFill Cartridge Device Between Patients

NOVLOG FlexPen, NOVLOG FlexTouch, PenFill cartridge, and PenFill cartridge devices should never be shared between patients, even if the needle is changed. Patients using NOVLOG vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-

borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [See *Warnings and Precautions (5.3)*] or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant anti-diabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse effect of all insulin therapies, including NOVLOG. Severe hypoglycemia can cause seizures, may lead to unconsciousness may be life threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g. driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see *Drug Interactions (7)*], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of NOVLOG may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see *Clinical Pharmacology (12.2)*]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions (7)*]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations (8.6, 8.7)*].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia, increased frequency of blood glucose monitoring is recommended. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between NOVLOG and other insulin products have been reported. To avoid medication errors between NOVLOG and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including NOVLOG. If hypersensitivity reactions occur, discontinue NOVLOG; treat per standard of care and monitor until symptoms and signs resolve [see *Adverse Reactions (6)*]. NOVLOG is contraindicated in patients who have had hypersensitivity reactions to insulin aspart or one of the excipients [see *Contraindications (4)*].

5.6 Hypokalemia

All insulin products, including NOVLOG, can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentration).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including NOVLOG, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction

Malfunction of the insulin pump or insulin infusion set or insulin degradation can rapidly lead to hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with NOVLOG may be required. 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 [see *How Supplied/Storage and Handling (16.2)* and *Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia [see *Warning and Precautions (5.3)*]
- Hypersensitivity and allergic reactions [see *Warning and Precautions (5.5)*]
- Hypokalemia [see *Warning and Precautions (5.6)*]

6.1 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. The safety of NOVLOG was evaluated in two treat-to-target trials of 6 months duration, conducted in subjects with type 1 diabetes or type 2 diabetes [see *Clinical Studies (14)*].

The data in Table 1 reflect the exposure of 596 patients with type 1 diabetes to NOVLOG in one clinical trial with a mean exposure duration to NOVLOG of 24 weeks. The mean age was 38.9 years. Fifty-one percent were male, 94% were Caucasian, 2% were Black and 4% were other races. The mean body mass index (BMI) was 25.6 kg/m². The mean duration of diabetes was 15.7 years and the mean HbA_{1c} at baseline was 7.9%.

The data in Table 2 reflect the exposure of 91 patients with type 2 diabetes to NOVLOG in one clinical trial with a mean exposure duration to NOVLOG of 24 weeks. The mean age was 56.6 years. Sixty-three percent were male, 76% were Caucasian, 9% were Black and 15% were other races. The mean BMI was 29.7 kg/m². The mean duration of diabetes was 12.7 years and the mean HbA_{1c} at baseline was 8.1%.

Common adverse reactions were defined as events occurring in ≥5%, excluding hypoglycemia, of the population studied. Common adverse events occurring at the same rate or greater for NOVLOG-treated subjects than on comparator-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus (other than hypoglycemia) are listed in Table 1 and Table 2,

respectively.

Table 1: Adverse reactions occurring in $\geq 5\%$ of Type 1 Diabetes Mellitus Adult Patients treated with NOVLOG and at the same rate or greater on NOVLOG than on comparator

	NOVLOG + NPH (%) (n= 596)	Regular Human Insulin + NPH (%) (n= 286)
Headache	12	10
Injury accidental	11	10
Nausea	7	5
Diarrhea	5	3

Table 2: Adverse reactions occurring in $\geq 5\%$ of Type 2 Diabetes Mellitus Adult Patients treated with NOVLOG and at the same rate or greater on NOVLOG than on comparator

	NOVLOG + NPH (%) (n= 91)	Human Regular Insulin + NPH (%) (n= 91)
Hyporeflexia	11	7
Onychomycosis	10	5
Sensory disturbance	9	7
Urinary tract infection	8	7
Chest pain	5	3
Headache	5	3
Skin disorder	5	2
Abdominal pain	5	1
Sinusitis	5	1

Severe hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NOVLOG [see *Warnings and Precautions (5.3)*]. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for NOVLOG with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

Severehypoglycemia was defined as hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

The incidence of severe hypoglycemia in adult and pediatric patients receiving subcutaneous NOVLOG with type 1 diabetes mellitus was 17% at 24 weeks and 6% at 24 weeks, respectively [see *Clinical Studies (14)*].

The incidence of severe hypoglycemia in adult patients receiving subcutaneous NOVLOG with type 2 diabetes mellitus was 10% at 24 weeks.

The incidence of severe hypoglycemia in adult and pediatric patients with type 1 diabetes mellitus, receiving NOVLOG via continuous subcutaneous insulin infusion by external pump was 2% at 16 weeks and 10% at 16 weeks respectively.

No severe hypoglycemic episodes were reported in adult patients with type 2 diabetes mellitus

receiving NOVLOG via continuous subcutaneous insulin infusion by external pump at 16 weeks.

Allergic Reactions

Some patients taking insulin therapy, including NOVLOG have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting. Severe cases of generalized allergy (anaphylaxis) have been reported [see *Warning and Precautions (5.5)*].

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

Administration of insulin, including NOVLOG, subcutaneously and via subcutaneous insulin infusion by external pump, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients [see *Dosage and Administration (2.2)*].

Peripheral Edema

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

Weight gain

Weight gain has occurred with some insulin therapies including NOVLOG and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NOVLOG in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a 6-month study with a 6 month extension in adult subjects with type 1 diabetes, 99.8% of patients who received NOVLOG were positive for anti-insulin antibodies (AIA) at least once during the study, including 97.2% that were positive at baseline. A total of 92.1% of patients who received NOVLOG were positive for anti-drug antibodies (ADA) at least once during the study, including 64.6% that were positive at baseline.

In a phase 3 type 1 diabetes clinical trial of NOVLOG, initial increase in titers of antibodies to insulin, followed by a decrease to baseline values, was observed in regular human insulin and insulin aspart treatment groups with similar incidences. These antibodies did not cause deterioration in glycemic control or necessitate increases in insulin dose.

6.3 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of NOVLOG. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins have been accidentally substituted for NOVLOG [see *Warnings and Precautions (5.4)*].

7 DRUG INTERACTIONS

Drugs That May Increase the Risk of Hypoglycemia	
<i>Drugs:</i>	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when NOVOLOG is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of NOVOLOG	
<i>Drugs:</i>	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when NOVOLOG is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of NOVOLOG	
<i>Drugs:</i>	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when NOVOLOG is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
<i>Drugs:</i>	Beta-blockers, clonidine, guanethidine and reserpine
<i>Intervention:</i>	Increased frequency of glucose monitoring may be required when NOVOLOG is co-administered with these drugs.

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 NOVLOG did not differ from those observed with subcutaneous regular human insulin. NOVLOG caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 units/kg/day for rats and equal to the human subcutaneous dose of 1.0 units/kg/day for rabbits, based on units/body surface area.

8.3 Nursing Mothers

Endogenous insulin is present in human milk; it is unknown whether insulin aspart is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when NOVLOG is administered to a nursing woman. Use of NOVLOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NOVLOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump [See *Clinical Studies (14.1, 14.2)*]. NOVLOG has not been studied in pediatric patients younger than 2 years of age. NOVLOG has not been studied in pediatric patients with type 2 diabetes.

8.5 Geriatric Use

Of the total number of patients (n= 1,375) treated with NOVLOG 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 NOVLOG, as compared to regular human insulin, did not differ by age.

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent NOVLOG dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent NOVLOG dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see *Warnings and Precautions (5.3, 5.6)*]. 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 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 $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

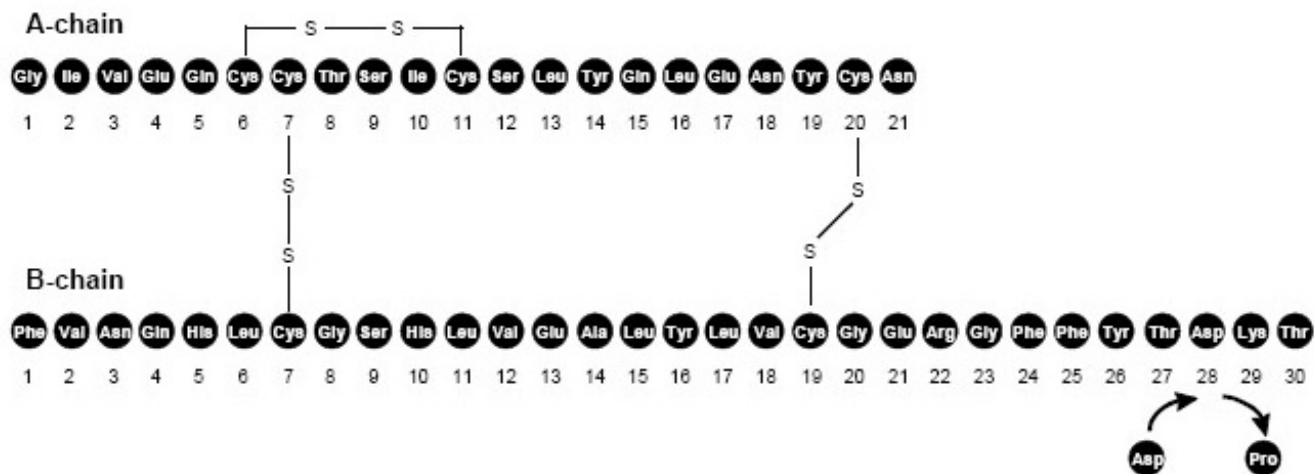


Figure 1. Structural formula of insulin aspart.

NOVOLOG is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart 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 insulin, including NOVOLOG is the regulation of glucose metabolism. Insulin, and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

Subcutaneous administration

The pharmacodynamic profile of NOVOLOG given subcutaneously in 22 patients with type 1 diabetes is shown in Figure 2. The maximum glucose-lowering effect of NOVOLOG occurred between 1 and 3 hours after subcutaneous injection (0.15 units/kg). 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 (5.3)].

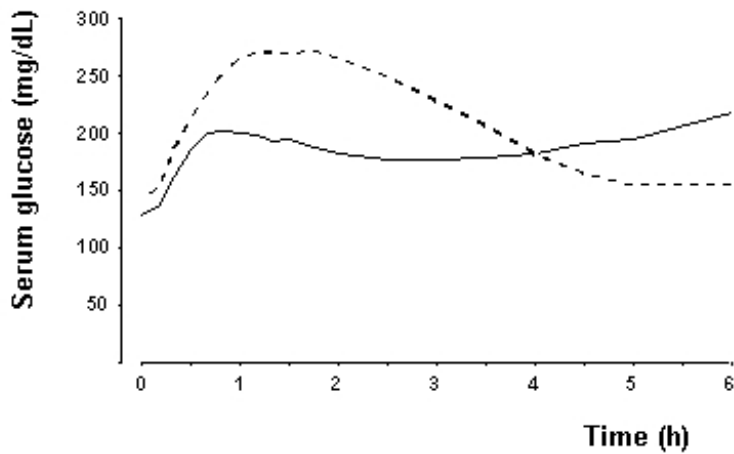
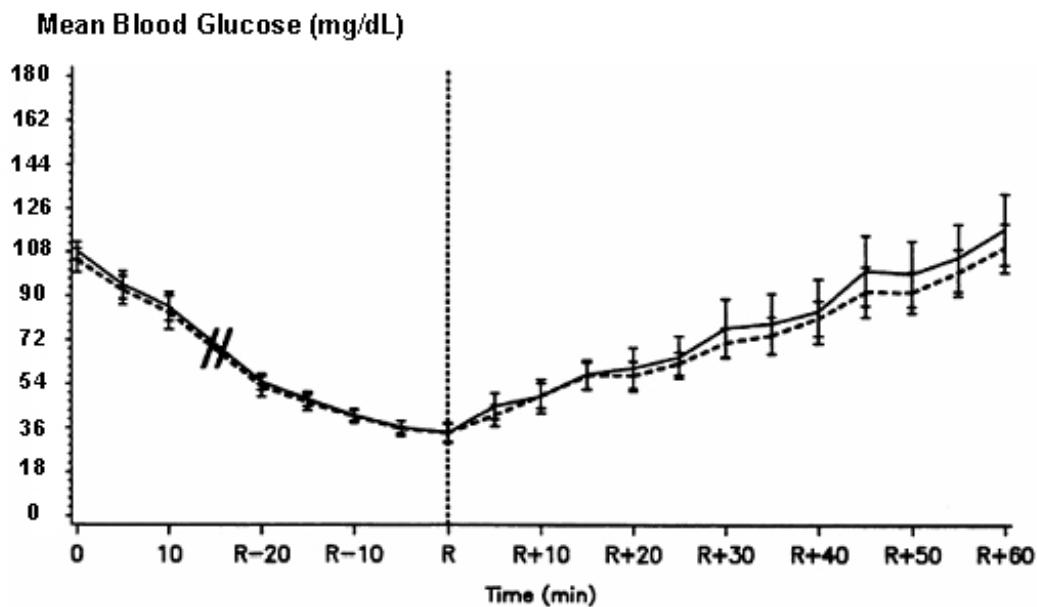


Figure 2. Serial mean serum glucose collected up to 6 hours following a single 0.15 units/kg pre-meal dose of NOVOLOG (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

Intravenous administration

A double-blind, randomized, two-way crossover 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).



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

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

Subcutaneous administration

Absorption and Bioavailability

In studies in healthy volunteers (total n=107) and patients with type 1 diabetes (total n=40), the median time to maximum concentration of NOVLOG in these trials was 40 to 50 minutes versus 80 to 120 minutes, for regular human insulin respectively.

The relative bioavailability of NOVLOG (0.15 units/kg) compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

In a clinical trial in patients with type 1 diabetes, NOVLOG and regular human insulin, both administered subcutaneously at a dose of 0.15 units/kg body weight, reached mean maximum concentrations of 82 and 36 mU/L, respectively.

Distribution

Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin.

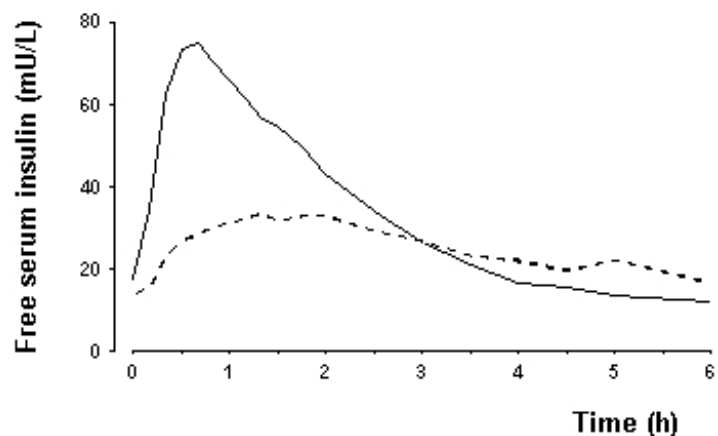


Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single 0.15 units/kg pre-meal dose of NOVLOG (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

Metabolism and Elimination

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 NOVLOG 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 NOVLOG group and 1.2 L/h/kg for the regular human insulin group.

After subcutaneous administration in normal male volunteers (n=24), NOVLOG was eliminated with an average apparent half-life of 81 minutes.

Specific Populations

Pediatrics - The pharmacokinetic and pharmacodynamic properties of NOVLOG 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 NOVLOG and regular human insulin were similar to those in healthy adult subjects and adults with type 1 diabetes.

Geriatrics: The pharmacokinetic and pharmacodynamic properties of NOVLOG and regular human insulin were investigated in a single dose study in 18 subjects with type 2 diabetes who were ≥ 65 years of age. The relative differences in pharmacokinetics and pharmacodynamics in geriatric patients with type 2 diabetes between NOVLOG and regular human insulin were similar to those in younger adults.

Gender: In healthy volunteers given a single subcutaneous dose of NOVOLG 0.06 units/kg, no difference in insulin aspart levels was seen between men and women based on comparison of AUC (0-10h) or C_{max} .

Obesity: A single subcutaneous dose of 0.1 units/kg NOVOLG was administered in a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m²). The pharmacokinetic parameters, AUC and C_{max} , of NOVOLG were generally unaffected by BMI in the different groups – BMI 19-23 kg/m² (N=4); BMI 23-27 kg/m² (N=7); BMI 27-32 kg/m² (N=6) and BMI >32 kg/m² (N=6). Clearance of NOVOLG was reduced by 28% in patients with BMI >32 kg/m² compared to patients with BMI <23 kg/m².

Renal Impairment: – A single subcutaneous dose of 0.08 units/kg NOVOLG was administered in a study to subjects with either normal renal function (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 study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of NOVOLG.

Hepatic Impairment: – A single subcutaneous dose of 0.06 units/kg NOVOLG 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 study, there was no correlation between the degree of hepatic impairment and any NOVOLG pharmacokinetic parameter.

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 NOVOLG. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NOVOLG at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, NOVOLG increased the incidence of mammary gland tumors in females when compared to untreated controls. The relevance of these findings to humans is unknown.

NOVOLG 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 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/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 NOVOLG has the same glucose-lowering effect as one unit of regular human insulin.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The safety and effectiveness of subcutaneous NOVOLG was compared to regular human insulin in 596 type 1 diabetes adult, 187 pediatric type 1 diabetes, and 91 adult type 2 diabetes patients using NPH as basal insulin (see Tables 3,4,5). The reduction in glycated hemoglobin (HbA_{1c}) was similar to regular human insulin.

The safety and effectiveness of NOVOLG administered by continuous subcutaneous insulin infusion

(CSII) by external pump was compared to buffered regular human insulin (administered by CSII), to lispro (administered by CSII) and compared to NOVLOG injections and NPH injection. Overall, the reduction in HbA_{1c} was similar to the comparator.

14.2 Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes and Subcutaneous Daily Injections

Type 1 Diabetes – Adults (see Table 3)

Two 24 week, open-label, active-controlled studies were conducted to compare the safety and efficacy of NOVLOG to regular human insulin injection 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).

The mean age of the trial population was 38.9 years and mean duration of diabetes was 15.7 years. Fifty-one percent were male. Ninety-four percent were Caucasian, 2% were Black and 4% were Other. The mean BMI was approximately 25.6 kg/m².

NOVLOG 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} were comparable for the two treatment regimens in this study (Table 3).

Table 3. Type 1 Diabetes Mellitus – Adult (NOVLOG plus NPH insulin vs. regular human insulin plus NPH insulin)

	NOVLOG + NPH (N=596)	Regular Human Insulin+ NPH (N=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)	

*Values are Mean ± SD

Type 1 Diabetes – Pediatric (see Table 4)

The efficacy of NOVLOG to improve glycemic control in pediatric patients with type 1 diabetes mellitus is based on an adequate and well-controlled trial of regular human insulin in pediatric patients with type 1 diabetes mellitus (Table 4). This 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: NOVLOG (n=187) or regular human insulin (n=96). NPH insulin was administered as the basal insulin. Similar effects on HbA_{1c} were observed in both treatment groups (Table 4).

Subcutaneous administration of NOVLOG 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}.

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

	NOVLOG + NPH (N=187)	Regular Human Insulin+ NPH (N=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)	-0.2 (-0.5, 0.1)	

*Values are Mean ± SD

14.3 Clinical Studies in Adults with Type 2 Diabetes and Subcutaneous Daily Injections

Type 2 Diabetes—Adults (see Table 5)

Onesix-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NOVOLOG to regular human insulin in patients with type 2 diabetes (Table 5).

The mean age of the trial population was 56.6 years and mean duration of diabetes was 12.7 years. Sixty-three percent were male. Seventy-six percent were Caucasian, 9% were Black and 15% were Other. The mean BMI was approximately 29.7 kg/m².

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} were comparable for the two treatment regimens.

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

	NOVOLOG + NPH (N=90)	Regular Human Insulin + NPH (N=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)	

*Values are Mean ± SD

14.4 Clinical Studies in Adults and Pediatrics with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

Type 1 Diabetes – Adult (see Table 6)

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 mean age of the trial population was 42.3 years. Thirty-nine percent were male. Ninety-eight percent were Caucasian and 2% were Black.

The two treatment regimens had comparable changes in HbA_{1c}.

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

	NOVOLOG (N=59)	Buffered human insulin (N=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)	0.2 (-0.1, 0.4)	

*Values are Mean ± SD

Type 1 Diabetes – Pediatric (see Table 7)

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} (see Table 7).

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

	NOVOLOG (N=198)	Lispro (N=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)	

*Values are Mean ± SD

14.5 Clinical Studies in Adults with Type 2 Diabetes Using Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

Type 2 Diabetes – Adults (see Table 8)

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 mean age of the trial population was 55.1 years. Sixty-four percent were male. Eighty percent were Caucasian, 12% were Black and 8% were Other. The mean BMI was approximately 32.2 kg/m².

The two treatment groups had similar reductions in HbA_{1c} (Table 8).

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

	NOVOLOG pump (N=66)	NOVOLOG + NPH (N=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 (-0.3, 0.4)	

*Values are Mean ± SD

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NOVOLOG 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution for injection in:

10 mL vials	NDC 0169-7501-11
3 mL PenFill cartridges*	NDC 0169-3303-12
3 mL NOVOLOG FlexPen	NDC 0169-6339-10
3 mL NOVOLOG FlexTouch	NDC 0169-6338-10

*NOVOLOG PenFill cartridges are designed for use with Novo Nordisk insulin delivery devices with

NovoFine disposable needles. FlexPen and FlexTouch can be used with NovoFine or NovoTwist disposable needles. NOVOLOG FlexPen, NOVOLOG FlexTouch, PenFill cartridge, and PenFill cartridge insulin delivery devices manufactured by Novo Nordisk must never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Unused NOVOLOG should be stored in a refrigerator between 2° and 8°C (36° to 46°F). **Do not freeze NOVOLOG and do not use NOVOLOG if it has been frozen.** Do not expose NOVOLOG to excessive heat or light.

NOVOLOG should not be drawn into a syringe and stored for later use.

Always remove and discard the needle after each injection from the NOVOLOG FlexPen or NOVOLOG FlexTouch and store without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing.

The storage conditions are summarized in the following table:

Table 9. Storage conditions for vial, PenFill cartridges, NOVOLOG FlexPen, and NOVOLOG FlexTouch

NOVOLOG presentation	Not in-use (unopened) Room Temperature (below 30°C [86°F])	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C [86°F])
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NOVOLOG FlexPen	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NOVOLOG FlexTouch	28 days	Until expiration date	28 days (Do not refrigerate)

Storage in External Insulin 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.

Storage of Diluted NOVOLOG

NOVOLOG diluted with Insulin Diluting Medium for NOVOLOG to a concentration equivalent to U-10 or equivalent to U-50 prepared as indicated under *Dosage and Administration (2.2)* may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NOVOLOG in Intravenous Infusion Fluids

Infusion bags prepared as indicated under *Dosage and Administration (2.2)* are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Never Share a NOVOLOG FlexPen or a NOVOLOG Flex Touch, PenFill Cartridge or PenFill

Cartridge Device Between Patients

Advise patients that they must never share NOVLOG FlexPen, NOVLOG Flex Touch, PenFill cartridge or PenFill cartridge devices with another person even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens. Advise patients using NOVLOG vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens [see *Warnings and Precautions (5.1)*].

Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of NOVLOG therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia [see *Warnings and Precautions (5.3)*].

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery

Hypoglycemia with Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products [see *Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with NOVLOG. Inform patients of the symptoms of hypersensitivity reactions [see *Warnings and Precautions (5.4)*].

Women of Reproductive Potential

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Administration

NOVLOG must only be used if the solution is clear and colorless with no particles visible. Instruct patients that when injecting NOVLOG, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6 as the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, the full dose may not be delivered (a possible under-dose may occur by as much as 20%). Inform the patient to increase the frequency of checking their blood glucose and that possible additional insulin administration may be necessary.

If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would **not** have received **any** insulin – even though the dose counter has moved from the original dose that was set. Instruct the patient to change the needle as described in Section 5 of the Instructions for Use and repeat all steps in the IFU starting with Section 1: Prepare your pen with a new needle. **Make sure the patient selects the full dose needed.**

Patients Using Continuous Subcutaneous Insulin Pumps

- Train patients in both intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.
- **Instruct patients to replace insulin in the reservoir at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin**

preservative. 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.

- Instruct patients to discard insulin exposed to temperatures higher than 37°C (98.6°F).
- Instruct patients to inform physician and select a new site for infusion if infusion site becomes erythematous, pruritic, or thickened.
- Instruct patients of the risk of rapid hyperglycemia and ketosis due to pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their physician [*see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].
- Instruct patients of the risk of hypoglycemia from pump malfunction. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their physician [*see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

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

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

Rx only

Date of Issue: March 16, 2017

Version: 25

Novo Nordisk[®], NOVOLOG[®], PenFill[®], Novolin[®], FlexPen[®], FlexTouch[®], NovoFine[®], and NovoTwist[®] are registered trademarks of Novo Nordisk A/S.

Patent Information: <http://novonordisk-us.com/patients/products/product-patents.html>

[†]The brands listed are the registered trademarks of their respective owners and are not trademarks of Novo Nordisk A/S.

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Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about NOVOLOG contact:

Novo Nordisk Inc.

800 Scudders Mill Road

Plainsboro, New Jersey 08536

1-800-727-6500

www.novonordisk-us.com

PATIENT INFORMATION

NovoLog® (NŌ-vō-log)

(insulin aspart injection)

Do not share your NovoLog FlexPen, NovoLog FlexTouch, PenFill cartridge or PenFill cartridge compatible insulin delivery device with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

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 take NovoLog?

Do not take NovoLog if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to NovoLog or any of the ingredients in NovoLog.

Before taking NovoLog, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking NovoLog, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take NovoLog?

- **Read the Instructions for Use** that come with your NovoLog.
- Take NovoLog exactly as your healthcare provider tells you to.
- **NovoLog starts acting fast.** You should eat a meal within 5 to 10 minutes after you take your dose of NovoLog.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share your needles with other people.** You may give other people a serious infection or get a serious infection from them.

What should I avoid while taking NovoLog?

While taking NovoLog do not:

- Drive or operate heavy machinery, until you know how NovoLog affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of NovoLog?

NovoLog may cause serious side effects that can lead to death, including:

Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:

- dizziness or light-headedness
- blurred vision
- anxiety, irritability, or mood changes
- sweating
- slurred speech
- hunger
- confusion
- shakiness
- headache
- fast heart beat

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Other common side effects of NovoLog may include:

- low potassium in your blood (hypokalemia), reactions at the injection site, itching, rash, serious allergic reactions (whole body reactions), skin thickening or pits at the injection site (lipodystrophy), weight gain, and swelling of your hands and feet.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of NovoLog. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of NovoLog.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about NovoLog that is written for health professionals. 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 that you have. It may harm them.

What are the ingredients in NovoLog?

Active Ingredient: insulin aspart

Inactive Ingredients: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride and water for injection

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

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 03/2017

INSTRUCTIONS FOR USE

NovoLog[®] (NŌ-vō-log)

(insulin aspart injection)

10 mL vial (100 Units/mL, U-100)

Read this Instructions for Use before you start taking NovoLog[®] and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Supplies you will need to give your NovoLog[®] injection:

- 10 mL NovoLog[®] vial
- insulin syringe and needle
- alcohol swab



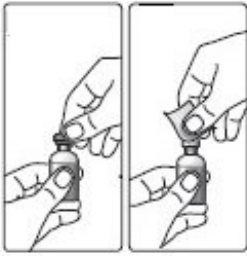
Preparing your NovoLog[®] dose:

- Wash your hands with soap and water.
- Before you start to prepare your injection, check the NovoLog[®] label to make sure that you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- NovoLog[®] should look clear and colorless. **Do not** use NovoLog[®] if it is thick, cloudy, or is colored.
- **Do not** use NovoLog[®] past the expiration date printed on the label.



Step 1: Pull off the tamper resistant cap (See Figure A).

Step 2: Wipe the rubber stopper with an alcohol swab (See Figure B).



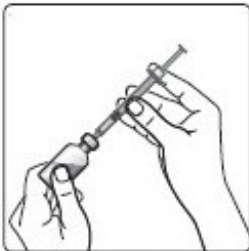
(Figure A Figure B)

Step 3: Hold the syringe with the needle pointing up. Pull down on the plunger until the black tip reaches the line for the number of units for your prescribed dose (See Figure C).



(Figure C)

Step 4: Push the needle through the rubber stopper of the NovoLog[®] vial (See Figure D).



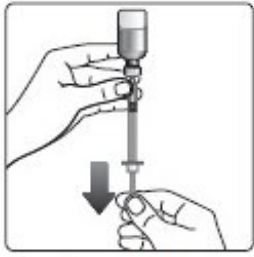
(Figure D)

Step 5: Push the plunger all the way in. This puts air into the NovoLog[®] vial (See Figure E).



(Figure E)

Step 6: Turn the NovoLog[®] vial and syringe upside down and slowly pull the plunger down until the black tip is a few units past the line for your dose (See Figure F).



(Figure F)

- If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top (See Figure G).



(Figure G)

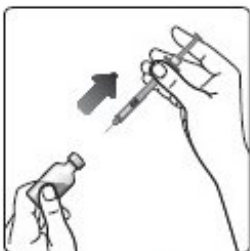
Step 7: Slowly push the plunger up until the black tip reaches the line for your NovoLog[®] dose (See Figure H).



(Figure H)

Step 8: Check the syringe to make sure you have the right dose of NovoLog[®].

Step 9: Pull the syringe out of the vial's rubber stopper (See Figure I).

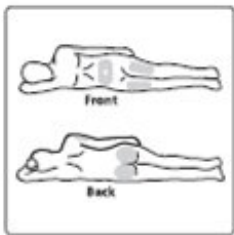


(Figure I)

Giving your Injection:

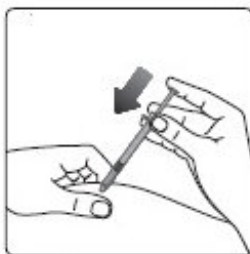
- Inject your NovoLog[®] exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- NovoLog[®] can be injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms, infused in an insulin pump, or given through a needle in your arm (intravenously) by your healthcare provider.
- If you inject NovoLog[®], change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.
- If you use NovoLog[®] in an insulin pump, you should change your insertion site 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.
- If you use NovoLog[®] in an insulin pump, see your insulin pump manual for instructions or talk to your healthcare provider.
- NPH insulin is the only type of insulin that can be mixed with NovoLog[®]. **Do not** mix NovoLog[®] with any other type of insulin.
- NovoLog[®] should **only** be mixed with NPH insulin if it is going to be injected right away under your skin (subcutaneously).
- NovoLog[®] should be drawn up into the syringe **before** you draw up your NPH insulin.
- Talk to your healthcare provider if you are not sure about the right way to mix NovoLog[®] and NPH insulin.

Step 10: Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure J).



(Figure J)

Step 11: Insert the needle into your skin. Push down on the plunger to inject your dose (See Figure K). **Needle should remain in the skin for at least 6 seconds to make sure you have injected all the insulin.**

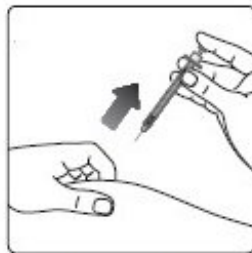


(Figure K)

Step 12: Pull the needle out of your skin. After that, you may see a drop of NovoLog[®] at the needle tip.

This is normal and does not affect the dose you just received (See Figure L).

- 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 swab. **Do not** rub the area.



(Figure L)

After your injection:

- **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.
- Throw away empty insulin vials, used syringes, and needles in a sharps container or some type of hard plastic or metal container with a screw on cap such as a detergent bottle or empty coffee can. Check with your healthcare provider about the right way to throw away the container. There may be local or state laws about how to throw away used syringes and needles. Do not throw away used syringes and needles in household trash or recycling bins.

How should I store NovoLog[®]?

Do not freeze NovoLog[®]. **Do not** use NovoLog[®] if it has been frozen.

- Keep NovoLog[®] away from heat or light.
- Store opened and unopened NovoLog[®] vials in the refrigerator at 36^oF to 46^oF (2^oC to 8^oC). Opened NovoLog[®] vials can also be stored out of the refrigerator below 86^oF (30^oC).
- Unopened vials may be used until the expiration date printed on the label, if they are kept in the refrigerator.
- Opened NovoLog[®] vials should be thrown away after 28 days, even if they still have insulin left in them.

General information about the safe and effective use of NovoLog[®]

- Always use a new syringe and needle for each injection.
- Do not share syringes or needles.
- Keep NovoLog[®] vials, syringes, and needles out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

NovoLog[®] is a registered trademark of Novo Nordisk A/S.

Patent Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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For information about NovoLog[®] contact:

Novo Nordisk Inc.

800 Scudders Mill Road

Plainsboro, New Jersey 08536

1-800-727-6500

www.novonordisk-us.com

Revised: March 2017

INSTRUCTIONS FOR USE

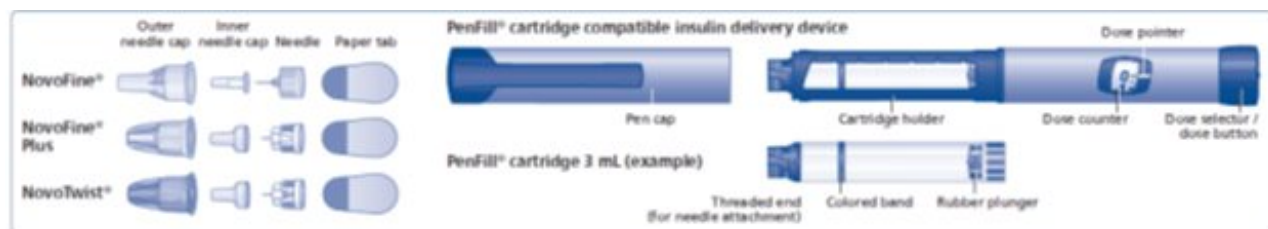
NovoLog[®] (NŌ-vō-log) PenFill[®] 3 mL cartridge 100 Units/mL (U-100)

(insulin aspart injection)

- **Do not share your PenFill cartridge or PenFill cartridge compatible insulin delivery device with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**
- Your healthcare provider should show you or your caregiver how to inject NovoLog the right way before you inject it for the first time.
- **NovoLog PenFill cartridge 100 Units/mL is a prefilled cartridge** containing 300 units of NovoLog (insulin aspart injection) 100 Units/mL insulin.
- After you insert the PenFill cartridge in your device, you can use it for multiple injections. Read the **instruction manual** that comes with your insulin delivery device for complete instructions on how to use the PenFill cartridge with the device.
- This PenFill cartridge is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product and your insulin delivery device.
- If using a **new** NovoLog PenFill cartridge, start with **Step 1**.
- If the NovoLog PenFill cartridge has already been **used**, start with **Step 2**.

Supplies you will need to give your NovoLog injection:

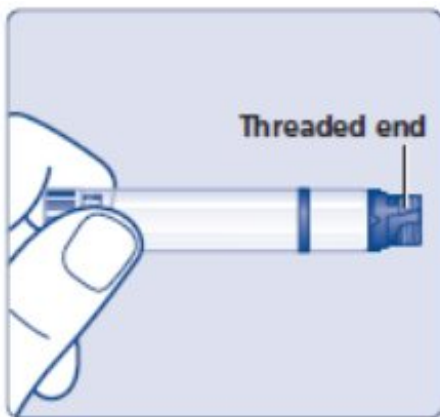
- NovoLog PenFill cartridge
- Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery device
- 1 new NovoFine[®], NovoFine[®] Plus, or NovoTwist[®] needle
- Alcohol swab
- Adhesive bandage
- Cotton gauze
- A sharps container for throwing away used PenFill cartridges and needles. **See “After your injection” at the end of these instructions.**



(Figure A)

How to use the NovoLog PenFill cartridge

- Wash your hands with soap and water.
- Before you start to prepare your injection, **check the NovoLog PenFill cartridge label** to make sure that it contains the insulin you need. This is especially important if you take more than 1 type of insulin.
- The tamper-resistant foil should be in place before the first use. If the foil has been broken or removed before your first use of the cartridge, **do not** use it. Call Novo Nordisk at 1-800-727-6500.
- Carefully look at the cartridge and the insulin inside it. Check that the NovoLog cartridge:
 - is not damaged, for example cracked or leaking
 - is not loose on the threaded end
- NovoLog should look clear and colorless. **Do not** use NovoLog if it is cloudy or colored or if the threaded end is loose (See Figure B).



(Figure B)

Step 1:

- Insert a 3 mL cartridge with the threaded end first into your Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery device (See Figure C).
- If you drop your device, check the insulin cartridge for damage such as cracks or leaking. If your cartridge is damaged, throw it away and use a new one.

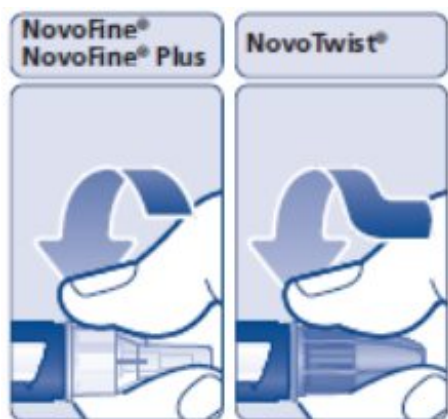


(Figure C)

Prepare your device with a new needle

Step 2:

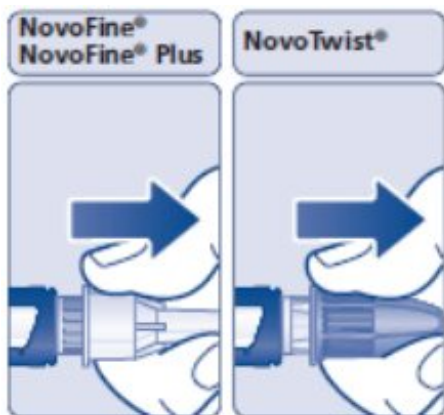
- Take a **new needle**, and tear off the paper tab. Always use a new needle for each injection to make sure the needle is free of germs (sterile) and to prevent blocked needles. **Do not attach a new needle** to your device until you are ready to give your injection. **Do not reuse or share your needles with other people. You may give others a serious infection, or get a serious infection from them.**
- Be careful not to bend or damage the needle before you use it.
- Push the needle straight onto the device. Turn the needle clockwise until it is on tight(See Figure D).



(Figure D)

Step 3:

- **Pulloff the outer needle cap** (See Figure E). **Do not** throw it away. You will need it after the injection to safely remove the needle.

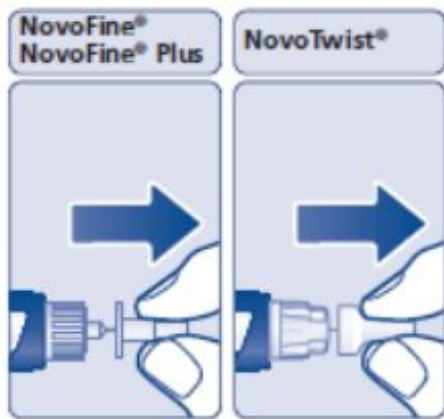


(Figure E)

Step 4:

- **Pulloff the inner needle cap** and throw it away (See Figure F). **Do not** try to put the inner needle

cap back on the needle.



(Figure F)

A drop of insulin may appear at the needle tip. This is normal, but you must still check the insulin flow.

Check the insulin flow

Step 5:

- Small amounts of air may collect in the cartridge during normal use. You must do an airshot before each injection to avoid injecting air and to make sure you receive the prescribed dose of your medicine.
- Do the airshot as described in the instruction manual that comes with your device.
- Keep testing your Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery device until you see insulin at the needle tip. If you still do not see a drop of insulin after 6 times, change the needle and repeat this step. This makes sure that any air bubbles are removed and that insulin is getting through the needle (See Figure G).



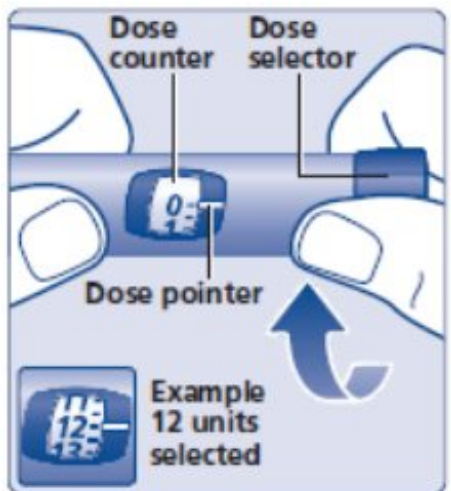
(Figure G)

Select your dose

Step 6:

- **Check to make sure that the dose counter is set to 0.**
- **Turn the dose selector clockwise to select the dose you need to inject** (See Figure H). The pointer should line up with your dose. When turning the dose selector, be careful not to press the dose button as insulin will come out. You will hear a click for every single unit dialed. **Do not** set the dose by counting the number of clicks you hear because you may get an incorrect dose.

- Refer to your insulin delivery device manual if necessary.

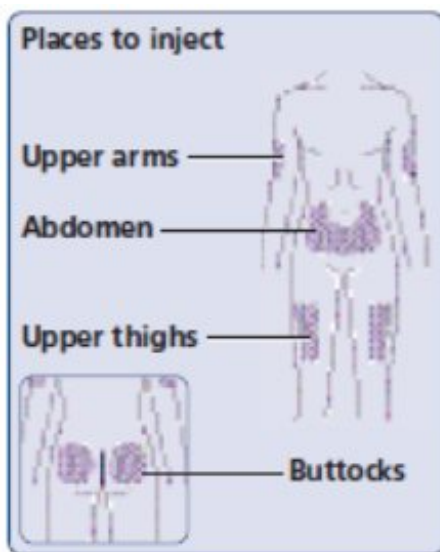


(Figure H)

Inject your dose

Step 7:

- **Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.**
- **NovoLog can be injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs (thighs), or upper arms (See Figure I).**

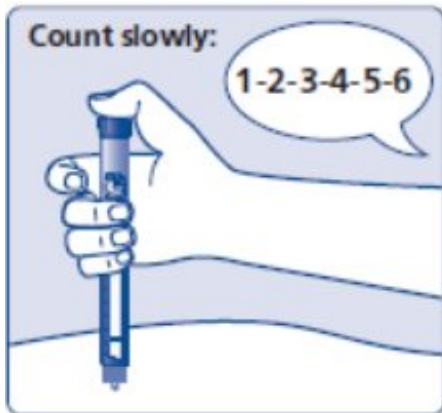


(Figure I)

- **For each injection, change (rotate) your injection site within the area of skin that you use. Do not use the same injection site for each injection.**
- **Clean your injection site with an alcohol swab. Let your skin dry. Do not touch this area again before injecting.**
- **Insert the needle into your skin. Press and hold down the dose button until the dose counter**

shows “0”. Continue to keep the dose button pressed and keep the needle in your skin and slowly count to 6 (see Figure J).

- Remove the needle from your skin.



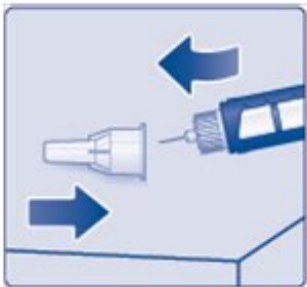
(Figure J)

You may see a drop of NovoLog at the needle tip after injecting. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a cotton gauze and cover with an adhesive bandage, if necessary. **Do not rub the area.**

After your injection

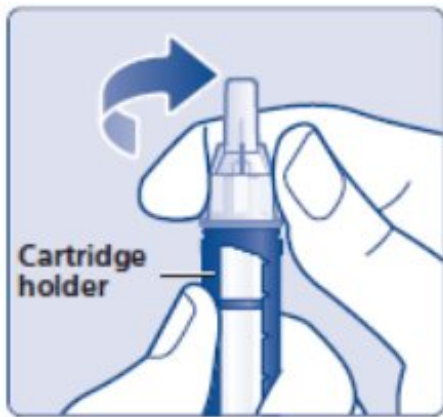
Step 8:

- Lay your outer needle cap on a flat surface. Carefully, lead the needle tip into the outer needle cap without touching the needle (See Figure K) and push the outer needle cap completely on.



(Figure K)

- Hold the black cartridge holder on the insulin delivery device and unscrew the needle counterclockwise (See Figure L).



(Figure L)

- Throw away (dispose of) the needle in an FDA-cleared sharps container as your healthcare professional has instructed you.
- Put your empty NovoLog PenFill cartridge and used needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and PenFill cartridges in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles or syringes with other people. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Step 9:

- Keep the 3 mL PenFill cartridge in the device. **Do not** store your device with a needle attached. This will prevent infection or leakage of insulin and will make sure that you receive the right dose of NovoLog.
- **Put the pen cap on** your device after each use to protect the insulin from light (See Figure M).



(Figure M)

How should I store my NovoLog PenFill cartridge?

Before use:

- Store unused NovoLog PenFill cartridges in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze NovoLog. **Do not** use NovoLog if it has been frozen.
- Unused PenFill cartridges may be used until the expiration date printed on the label, if kept in the refrigerator.
- If NovoLog is stored mistakenly outside of refrigeration between 47°F (9°C) to 86°F (30°C) prior to first use, it should be used within 28 days or thrown away.

PenFill cartridges in use:

- Store the PenFill cartridge you are currently using in the insulin delivery device at room temperature below 86°F (30°C) for up to 28 days. Do not refrigerate.
- Keep NovoLog away from heat or light.
- The NovoLog PenFill cartridge you are using should be thrown away after 28 days, even if it still has insulin left in it.

General Information about the safe and effective use of NovoLog.

- **Keep NovoLog PenFill cartridges and needles out of the reach of children.**
- **Do not** share NovoLog PenFill cartridges or needles with other people. You may give other people a serious infection, or get a serious infection from them.
- **Always carry extra insulin of the same type(s) you use in case of loss or damage.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

Revised: 03/2017

INSTRUCTIONS FOR USE

NovoLog® (NŌ-vō-log) FlexTouch® Pen

(insulin aspart injection)

- **Do not share your NovoLog FlexTouch Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from**

them.

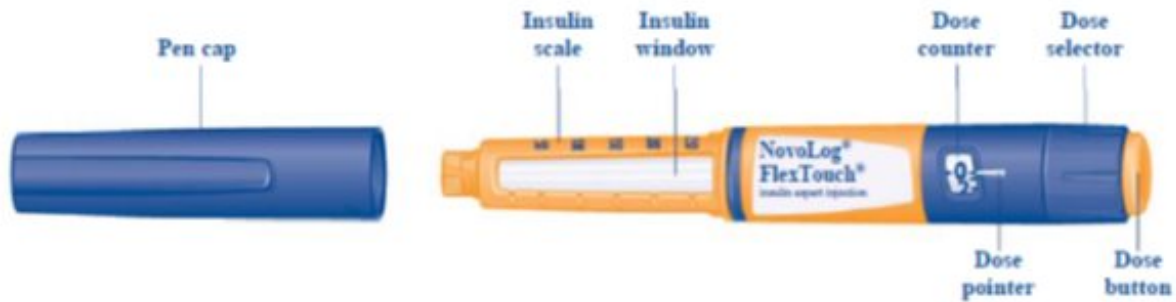
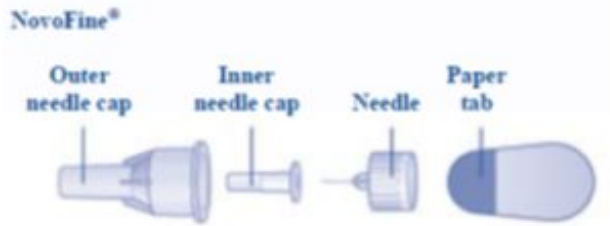
- **NovoLog FlexTouch Pen (“Pen”)** is a **prefilled disposable pen** containing 300 units of U-100 NovoLog (insulin aspart injection) insulin. You can inject from 1 to 80 units in a single injection.
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

Supplies you will need to give your NovoLog injection:

- NovoLog FlexTouch Pen
- a new NovoFine, NovoFine Plus or NovoTwist needle
- alcohol swab
- 1 sharps container for throwing away used Pens and needles. **See “Disposing of used NovoLog FlexTouch Pens and needles” at the end of these instructions.**

Preparing your NovoLog FlexTouch Pen:

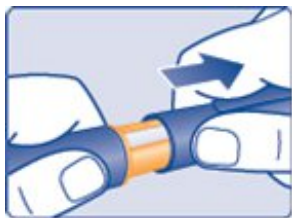
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the NovoLog FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- NovoLog should look clear and colorless. **Do not** use NovoLog if it is thick, cloudy, or is colored.
- **Do not** use NovoLog past the expiration date printed on the label or 28 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.**



(Figure A)

Step 1:

- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

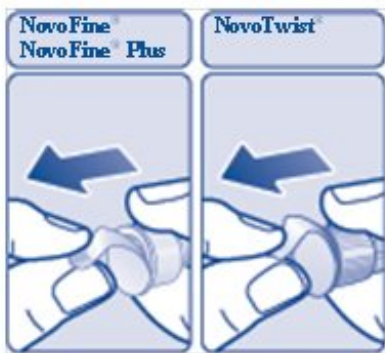
- **Check the liquid in the Pen** (See Figure C). NovoLog should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

Step 3:

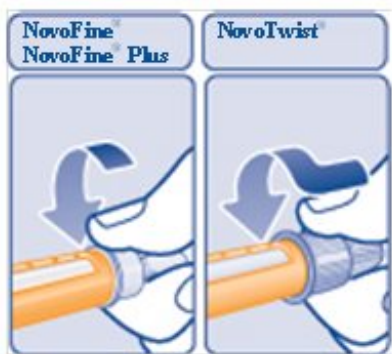
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

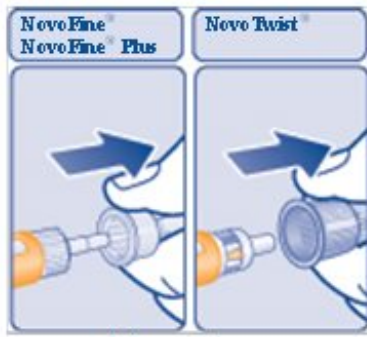
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

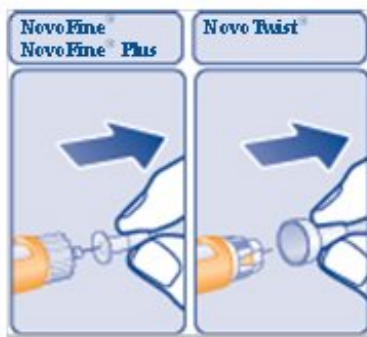
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your NovoLog FlexTouch Pen:

Step 7:

- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows “0”. The “0” must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
 - If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
 - If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

Selecting your dose:

Step 10:

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
 - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
 - The **even** numbers are printed on the dial.
 - The **odd** numbers are shown as lines.



(Figure K)

- The NovoLog FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

- **To see how much insulin is left in your NovoLog FlexTouch Pen:**
 - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
 - If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your NovoLog exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- NovoLog can be injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs (thighs) or upper arms.

- For each injection, change (rotate) your injection site within the area of skin that you use. **Do not** use the same injection site for each injection.

Step 11:

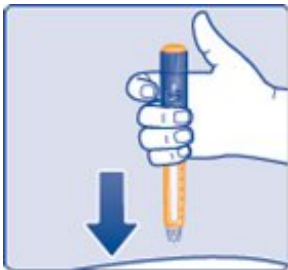
- Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).



(Figure M)

Step 12:

- **Insert the needle into your skin** (See Figure N).
 - **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

- **Press and hold down the dose button until the dose counter shows “0”** (See Figure O).
 - The “0” must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

- **Keep the needle in your skin after** the dose counter has returned to “0” and **slowly count to 6** (See Figure P).

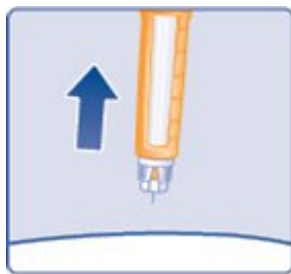


(Figure P)

- **When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.**
- **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
- **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**

Step 14:

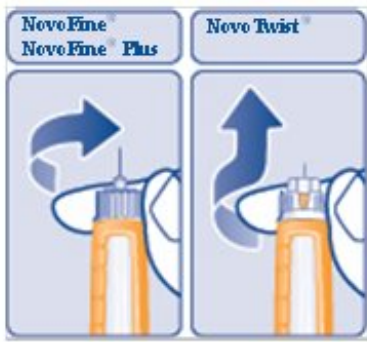
- **Pull the needle out of your skin** (See Figure Q).
- If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

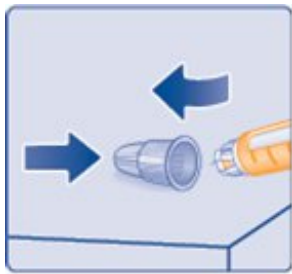
Step 15:

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
- **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

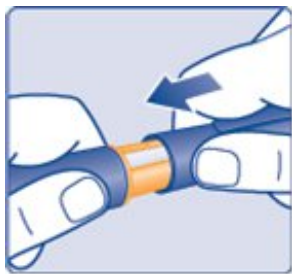


(Figure S)

- **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- You can put your used NovoLog FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container

that is:

- made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles or syringes with other people. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>
 - Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my NovoLog FlexTouch Pen?

- Store unused NovoLog FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Store the Pen you are currently using out of the refrigerator below 86°F.
- **Do not** freeze NovoLog. **Do not** use NovoLog if it has been frozen.
- Keep NovoLog away from heat or light.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- The NovoLog FlexTouch Pen you are using should be thrown away after 28 days, even if it still has insulin left in it.

General Information about the safe and effective use of NovoLog.

- **Keep NovoLog FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not share** your NovoLog FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

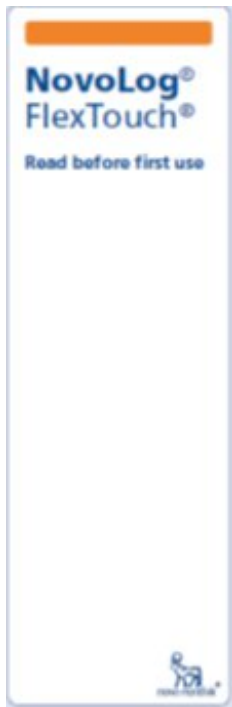
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 03/2017



For more information go to

www.novotrainig.com/novologflectouch/us02



INSTRUCTIONS FOR USE

NovoLog® FlexPen®

Introduction

Please read the following instructions carefully before using your NovoLog® FlexPen®.

Do not share your NovoLog FlexPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

NovoLog FlexPen is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. NovoLog FlexPen is designed to be used with NovoFine®, NovoFine® Plus or NovoTwist® needles.

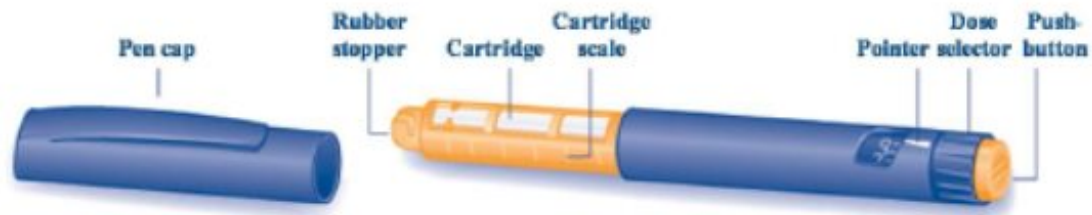
Δ NovoLog FlexPen should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog FlexPen the right way.

Getting ready

Make sure you have the following items:

- NovoLog FlexPen
- New NovoFine, NovoFine Plus or NovoTwist needle
- Alcohol swab

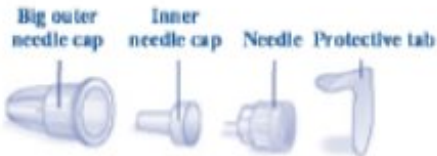
NovoLog® FlexPen®



NovoFine®



NovoFine® Plus



NovoTwist®



Preparing your NovoLog FlexPen

Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog should look clear.

A. Pull off the pen cap (see diagram A).

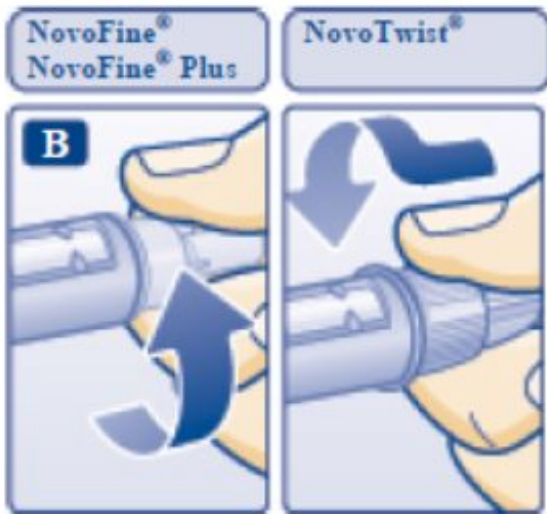


Wipe the rubber stopper with an alcohol swab.

B. Attaching the needle

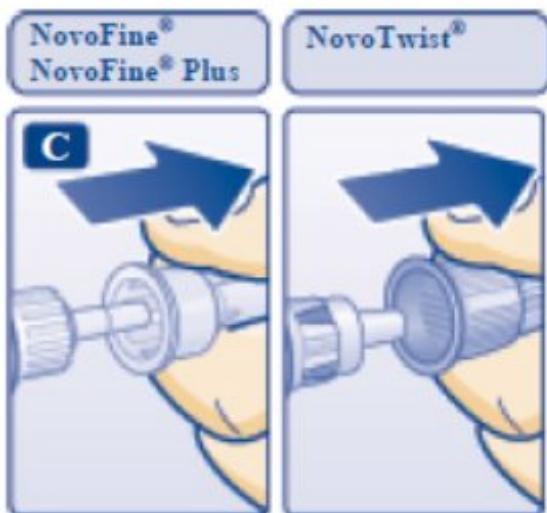
Remove the protective tab from a disposable needle.

Screw the needle tightly onto your FlexPen. It is important that the needle is put on straight (see diagram B).

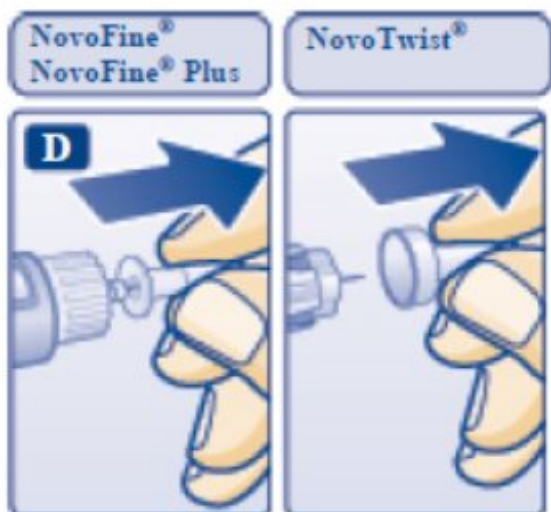


Never place a disposable needle on your NovoLog FlexPen until you are ready to take your injection.

C. Pull off the big outer needle cap (see diagram C).



D. Pull off the inner needle cap and dispose of it (see diagram D).



Δ Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.

Δ Be careful not to bend or damage the needle before use.

Δ To reduce the risk of unexpected needle sticks, **never put the inner needle cap back on the needle.**

Giving the airshot before each injection

Before each injection small amounts of air may collect in the cartridge during normal use. To avoid injecting air and to ensure proper dosing:

E. Turn the dose selector to select 2 units (see diagram E).



F. Hold your NovoLog FlexPen with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram F).



G. Keep the needle pointing upwards, press the push-button all the way in (see diagram G). The dose selector returns to 0.



A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If you do not see a drop of insulin after 6 times, do not use the NovoLog FlexPen and contact Novo Nordisk at 1-800-727-6500.

A small air bubble may remain at the needle tip, but it will not be injected.

Selecting your dose

Check and make sure that the dose selector is set at 0.

H. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram H). When turning the dose selector, be careful not to press the push-button as insulin will come out.



You cannot select a dose larger than the number of units left in the cartridge.

You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

Δ Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

Giving the injection

Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.

Novolog can be injected under the skin (subcutaneously) or your stomach area, buttocks, upper legs (thighs), or upper arms.

For each injection, change (rotate) your injection site within the area of skin that you use. **Do not** use the same injection site for each injection.

I. Insert the needle into your skin.

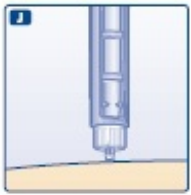
Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the button when injecting.



Turning the dose selector will not inject insulin.

J. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram J). This will make sure that the full dose has been given.

You may see a drop of insulin at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**



After the injection

Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog FlexPen after each injection and dispose of it. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

If you do not have a sharps container, carefully slip the needle into the outer needle cap. Safely remove the needle and throw it away as soon as you can.

- Put your used NovoLog FlexPen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information

about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

The NovoLog FlexPen prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

K. Put the pen cap on the NovoLog FlexPen and store the NovoLog FlexPen without the needle attached (see diagram K).

Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.



How should I store NovoLog FlexPen?

- Store unused NovoLog FlexPen in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Store the FlexPen you are currently using out of the refrigerator below 86°F (30°C) for up to 28 days.
- **Do not** freeze NovoLog. **Do not** use NovoLog if it has been frozen.
- Keep NovoLog away from heat or light.
- Unused FlexPen may be used until the expiration date printed on the label, if kept in the refrigerator.
- The NovoLog FlexPen you are using should be thrown away after 28 days, even if it still has insulin left in it.

Maintenance

For the safe and proper use of your FlexPen be sure to handle it with care. Avoid dropping your FlexPen as it may damage it. If you are concerned that your FlexPen is damaged, use a new one. You can clean the outside of your FlexPen by wiping it with a damp cloth. Do not soak or wash your FlexPen as it may damage it. Do not refill your FlexPen.

Δ Remove the needle from the NovoLog FlexPen after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.

Δ Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.

Δ Keep your NovoLog FlexPen and needles out of the reach of children.

Δ Use NovoLog FlexPen as directed to treat your diabetes.

Δ **Do not** share your NovoLog FlexPen or needles with other people. You may give other people a serious infection, or

get a serious infection from them.

Δ Always use a new needle for each injection.

Δ Novo Nordisk is not responsible for harm due to using this insulin pen with products not

recommended by Novo

Nordisk.

⚠ As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog FlexPen is lost or damaged.

⚠ Remember to keep the disposable NovoLog FlexPen with you. Do not leave it in a car or other location where it can get too hot or too cold.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 04/2015

PRINCIPAL DISPLAY PANEL - 10 mL NovoLog Vial

NDC 0169-7501-11

List 750111

NovoLog®

Insulin aspart Injection

10 mL 100 units/mL

Rx only

U-100



PRINCIPAL DISPLAY PANEL - 3 mL NovoLog PenFill

NDC 0169-3303-12 List 330312

NovoLog®

PenFill®

Insulin aspart Injection

For Single Patient Use Only

3 mL cartridges

100 units/mL (U-100)

5 cartridges per package

For use with Novo Nordisk 3 mL PenFill® cartridge compatible delivery devices, with or without the addition of a NovoPen® 3 PenMate®, and NovoFine® disposable needles.

Keep in a cold place.

Avoid freezing.

Protect from light.

Rx only



PRINCIPAL DISPLAY PANEL - 3 mL NovoLog FlexPen

NDC 0169-6339-10 List 633910

NovoLog® FlexPen®

Prefilled Syringe

Insulin aspart Injection

For Single Patient Use Only

100 units/mL (U-100)

5 x 3 mL Prefilled Insulin Syringes

Rx only

**For use with NovoFine®, NovoFine Plus® or
NovoTwist® disposable needles.**

Keep in a cold place.

Avoid freezing.

Protect from light.



PRINCIPAL DISPLAY PANEL - 3 mL NovoLog FlexTouch

NDC 0169-6338-10 List 633810

NovoLog® FlexTouch®

Insulin aspart Injection

For Single Patient Use Only

100 units/mL (U-100)

5 x 3 mL Prefilled Pens

For subcutaneous use only

Rx Only

**Recommended for use with
NovoFine®, NovoFine Plus® or
NovoTwist® disposable needles.**

Keep in a cold place until first use.

Store at 2° - 8°C (36° - 46°F).

Avoid freezing.

Protect from light.



NOVOLOG

insulin aspart injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0169-7501
Route of Administration	INTRAVENOUS, SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
INSULIN ASPART (UNII: D933668QVX) (INSULIN ASPART - UNII:D933668QVX)	INSULIN ASPART	100 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM PHOSPHATE, DIBASIC DIHYDRATE (UNII: 9425516E2T)	1.25 mg in 1 mL
GLYCERIN (UNII: PDC6A3C0OX)	16 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METACRESOL (UNII: GGO4Y809LO)	1.72 mg in 1 mL

PHENOL (UNII: 339NCG44TV)	1.5 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	0.58 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
ZINC (UNII: J41CSQ7QDS)	19.6 ug in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0169-7501-11	1 in 1 CARTON	08/27/2001	
1		10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:0169-7501-90	1 in 1 CARTON	08/27/2001	
2		10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020986	08/27/2001	

NOVOLOG

insulin aspart injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0169-3303
Route of Administration	INTRAVENOUS, SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
INSULIN ASPART (UNII: D933668QVX) (INSULIN ASPART - UNII:D933668QVX)	INSULIN ASPART	100 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM PHOSPHATE, DIBASIC DIHYDRATE (UNII: 94255I6E2T)	1.25 mg in 1 mL
GLYCERIN (UNII: PDC6A3C0OX)	16 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METACRESOL (UNII: GGO4Y809LO)	1.72 mg in 1 mL
PHENOL (UNII: 339NCG44TV)	1.5 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	0.58 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
ZINC (UNII: J41CSQ7QDS)	19.6 ug in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0169-3303-12	5 in 1 CARTON	08/27/2001	
1		3 mL in 1 CARTRIDGE; Type 0: Not a Combination Product		
2	NDC:0169-3303-91	1 in 1 CARTON	08/27/2001	
2		3 mL in 1 CARTRIDGE; Type 0: Not a Combination Product		
3	NDC:0169-3303-90	5 in 1 CARTON	08/27/2001	
3		3 mL in 1 CARTRIDGE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020986	08/27/2001	

NOVOLOG

insulin aspart injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0169-6339
Route of Administration	INTRAVENOUS, SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
INSULIN ASPART (UNII: D933668QVX) (INSULIN ASPART - UNII:D933668QVX)	INSULIN ASPART	100 [IU] in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
SODIUM PHOSPHATE, DIBASIC DIHYDRATE (UNII: 9425516E2T)	1.25 mg in 1 mL
GLYCERIN (UNII: PDC6A3C0OX)	16 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METACRESOL (UNII: GGO4Y809LO)	1.72 mg in 1 mL
PHENOL (UNII: 339NCG44TV)	1.5 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	0.58 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
ZINC (UNII: J41CSQ7QDS)	19.6 ug in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0169-6339-10	5 in 1 CARTON	01/22/2003	
1		3 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		

2	NDC:0169-6339-97	1 in 1 CARTON	01/22/2003	08/31/2017
2	NDC:0169-6339-90	3 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		
3	NDC:0169-6339-98	1 in 1 CARTON	01/22/2003	
3	NDC:0169-6339-90	3 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020986	01/22/2003	

NOVOLOG

insulin aspart injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0169-6338
Route of Administration	INTRAVENOUS, SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
INSULIN ASPART (UNII: D933668QVX) (INSULIN ASPART - UNII:D933668QVX)	INSULIN ASPART	100 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM PHOSPHATE, DIBASIC DIHYDRATE (UNII: 94255I6E2T)	1.25 mg in 1 mL
GLYCERIN (UNII: PDC6A3C0OX)	16 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METACRESOL (UNII: GGO4Y809LO)	1.72 mg in 1 mL
PHENOL (UNII: 339NCG44TV)	1.5 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	0.58 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
ZINC (UNII: J41CSQ7QDS)	19.6 ug in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0169-6338-10	5 in 1 CARTON	10/31/2030	
1		3 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:0169-6338-98	1 in 1 CARTON	10/31/2030	

2	NDC:0169-6338-90	3 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020986	10/31/2013		

Labeler - Novo Nordisk (622920320)

Establishment			
Name	Address	ID/FEI	Business Operations
Novo Nordisk Pharmaceuticals Industries, Inc.		622920320	MANUFACTURE(0169-7501, 0169-3303, 0169-6339, 0169-6338)

Establishment			
Name	Address	ID/FEI	Business Operations
Novo Nordisk A/S		305914798	MANUFACTURE(0169-7501, 0169-3303, 0169-6339, 0169-6338)

Establishment			
Name	Address	ID/FEI	Business Operations
Novo Nordisk A/S		305156788	API MANUFACTURE(0169-7501, 0169-3303, 0169-6339, 0169-6338)

Revised: 3/2017

Novo Nordisk