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

·····RECENT MAJOR CHANGES·····

Indications and Usage (1)……..03/2021
Dosage and Administration (2.2)……...10/2021
Warnings and Precautions (5.3, 5.4, 5.5, 5.6)…….....…….03/2021

·····INDICATIONS AND USAGE·····

- NOVOLOG is rapid acting human insulin analog indicated to improve glycemic control in adults and pediatric patients 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 to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
  - Should generally be used in regimens with an intermediate- or long-acting insulin.
- *Continuous Subcutaneous Infusion (Insulin Pump) (2.2)*
  - Refer to the insulin infusion pump user manual to see if NOVOLOG can be used. Use in accordance with the insulin pump instructions for use.
  - Administer by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer.
  - Rotate the injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis.
  - 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 Injection, USP.
- 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·····

Injection: 100 units/mL (U-100) of insulin aspart available as:

- 10 mL multiple-dose vial (3)
- 3 mL single-patient-use PenFill® cartridges for the 3 mL PenFill cartridge device (3)
- 3 mL single-patient-use NOVOLOG FlexPen® (3)
- 3 mL single-patient-use 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 FlexTouch, PenFill cartridge or PenFill cartridge device between patients, even if the needle is changed (5.1).
- *Hyperglycemia or hypoglycemia with changes in insulin regimen* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased 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 (5.5).
- *Hypokalemia* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated (5.6).
- *Fluid retention 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, 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).

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

Revised: 10/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2 1 Important Administration Instructions
2 2 Route of Administration
2 3 Dosage Information
2.4 Dosage Adjustment Due to Drug Interactions
2 5 Instructions for Mixing with Other Insulins
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5 1 Never Share a NOVOLOG FlexPen, NOVOLOG FlexTouch, PenFill Cartridge, or PenFill Cartridge Device between Patients
5 2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen
5 3 Hypoglycemia
5.4 Hypoglycemia Due to Medication Errors
5 5 Hypersensitivity Reactions
5.6 Hypokalemia
5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists
5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction
6 ADVERSE REACTIONS
6 1 Clinical Trial Experience
6 2 Immunogenicity
6 3 Post Marketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Overview of Clinical Studies
14.2 Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes and Subcutaneous Daily Injections
14.3 Clinical Studies in Adults with Type 2 Diabetes and Subcutaneous Daily Injections
14.4 Clinical Studies in Adults and Pediatrics with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion (CSII) by External Pump
14.5 Clinical Studies in Adults with Type 2 Diabetes Using Continuous Subcutaneous Insulin Infusion (CSII) by External Pump
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Recommended Storage
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NOVOLOG is indicated to improve glycemic control in adults and pediatric patients 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 NOVOLOG visually before use. It should appear clear and colorless. Do not use NOVOLOG if particulate matter or coloration is seen.
- Use NOVOLOG FlexPen and NOVOLOG FlexTouch with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
- Use PenFill cartridges with caution in patients with visual impairment.
- Do NOT mix NOVOLOG with other insulins when administering using a continuous subcutaneous infusion pump.

2.2 Route of Administration

Subcutaneous Injection

- Inject NOVOLOG 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 and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1, 6.3)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- The NOVOLOG FlexPen and FlexTouch dial in 1-unit increments.
- NOVOLOG administered by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
- NOVOLOG may be diluted with Insulin Diluting Medium for NOVOLOG for subcutaneous injection. Diluting one part NOVOLOG to nine parts diluent will yield a concentration one-tenth that of NOVOLOG (equivalent to U-10). Diluting one part NOVOLOG to one part diluent will yield a concentration one-half that of NOVOLOG (equivalent to U-50).

Continuous Subcutaneous Infusion (Insulin Pump)

- Refer to the continuous subcutaneous insulin infusion pump user manual to see if NOVOLOG can be used with the insulin pump. Use NOVOLOG in accordance with the insulin pump system's instructions for use.
- 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 NOVOLOG by continuous subcutaneous infusion in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1, 6.3)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Follow healthcare provider recommendations when setting basal and meal time infusion rate.

- Change the NOVOLOG in the reservoir at least every 7 days or according to the pump user manual, whichever is shorter.
- Change the infusion set and the infusion set insertion site according to the manufacturer's user manual.
- Do NOT dilute or mix NOVOLOG when administering by continuous subcutaneous infusion.
- Do NOT expose NOVOLOG in the pump reservoir to temperatures greater than 98.6°F (37°C).

Intravenous Administration

- 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 Injection, USP.
- Administer NOVOLOG 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 NOVOLOG 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 NOVOLOG *[see Warnings and Precautions (5.2)]*.

2.4 Dosage Adjustment Due to Drug Interactions

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

2.5 Instructions for Mixing with Other Insulins

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) is a clear and colorless solution available as:

- 10 mL multiple-dose vial
- 3 mL single-patient-use PenFill cartridges for the 3 mL PenFill cartridge delivery device with NovoFine® disposable needles
- 3 mL single-patient-use NOVOLOG FlexPen
- 3 mL single-patient-use NOVOLOG FlexTouch

4 CONTRAINDICATIONS

NOVOLOG is contraindicated:

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

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a NOVOLOG FlexPen, NOVOLOG FlexTouch, PenFill Cartridge, or PenFill Cartridge Device between Patients

NOVOLOG FlexPen, NOVOLOG FlexTouch, PenFill cartridge, and PenFill cartridge devices should never be shared between patients, even if the needle is changed. Patients using NOVOLOG 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 an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia *[see Adverse Reactions (6.1, 6.3)]*.
Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. 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 insulins, including NOVOLOG. 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 insulins, the glucose lowering effect time course of NOVOLOG 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 insulin products have been reported. To avoid medication errors between NOVOLOG and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity Reactions

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

5.6 Hypokalemia

All insulins, including NOVOLOG, 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 NOVOLOG, 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 NOVOLOG 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 Warnings and Precautions (5.3)]*
- Hypoglycemia Due to Medication Errors *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings 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 NOVOLOG 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 NOVOLOG in one clinical trial with a mean exposure duration to NOVOLOG 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/m^2. 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 NOVOLOG in one clinical trial with a mean exposure duration to NOVOLOG 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/m^2. 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 NOVOLOG-treated subjects than in 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 ≥ 5% of Type 1 Diabetes Mellitus Adult Patients treated with NOVOLOG and at the same rate or greater on NOVOLOG than on comparator

	NOVOLOG + 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 ≥ 5% of Type 2 Diabetes Mellitus Adult Patients treated with NOVOLOG and at the same rate or greater on NOVOLOG than on comparator

	NOVOLOG + 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 NOVOLOG. 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 NOVOLOG 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.

Severe hypoglycemia 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 NOVOLOG 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 NOVOLOG 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 NOVOLOG 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 NOVOLOG via continuous subcutaneous insulin infusion by external pump at 16 weeks.

Allergic Reactions

Some patients taking insulin, including NOVOLOG 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.

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 NOVOLOG, 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
Insulins, including NOVOLOG, 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 insulins, including NOVOLOG, 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 NOVOLOG 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 NOVOLOG 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 NOVOLOG 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 NOVOLOG, 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 NOVOLOG. 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 NOVOLOG.

Localized cutaneous amyloidosis at the injection site has occurred with insulin aspart. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7 DRUG INTERACTIONS

Drugs That May Increase the Risk of Hypoglycemia

Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	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	
Drugs:	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.
Intervention:	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	
Drugs:	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.
Intervention:	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	
Drugs:	Beta-blockers, clonidine, guanethidine and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when NOVOLOG is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available information from published randomized controlled trials with insulin aspart use during the second trimester of pregnancy have not reported an association with insulin aspart and major birth defects or adverse maternal or fetal outcomes *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, administration of subcutaneous insulin aspart to pregnant rats and rabbits during the period of organogenesis did not cause adverse developmental effects at exposures 8-times and equal to the human subcutaneous dose of 1 unit/kg/day, respectively.

Pre- and post-implantation losses and visceral/skeletal abnormalities were seen at higher exposures, which are considered secondary to maternal hypoglycemia. These effects were similar to those observed in rats administered regular human insulin *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1c} >7% and has been reported to be as high as 20-25% in women with a HbA_{1c} >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from 5 randomized controlled trials of 441 pregnant women with diabetes mellitus treated with insulin aspart during the late 2nd trimester of pregnancy did not identify an association of insulin aspart with major birth defects or adverse maternal or fetal outcomes. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including a variable duration of treatment and small size of the majority of the trials.

Animal Data

Fertility, embryo-fetal and pre- and postnatal development studies have been performed with insulin aspart and regular human insulin in rats and rabbits. In a combined fertility and embryo-fetal development study in rats, insulin aspart was administered before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, 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 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1 unit/kg/day, based on human exposure equivalents). 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 unit/kg/day for rats and equal to the human subcutaneous dose of 1 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of NOVOLOG in human milk, the effects on the breastfed infant, or the effect on milk production. One small published study reported that exogenous insulin, including insulin aspart, was present in human milk. However, there is insufficient information to determine the effects of insulin aspart on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NOVOLOG, and any potential adverse effects on the breastfed infant from NOVOLOG, or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of NOVOLOG to improve glycemic control have been established in pediatric patients. Use of NOVOLOG for this indication is supported by evidence from an adequate and well-controlled study in 283 pediatric patients with type 1 diabetes mellitus aged 6 to 18 years and from studies in adults with diabetes mellitus *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

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

Insulin aspart is a rapid-acting human insulin analog homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast). Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8 Da. In vitro assay confirms the minimum potency of insulin aspart to be NLT 15 units/mg.

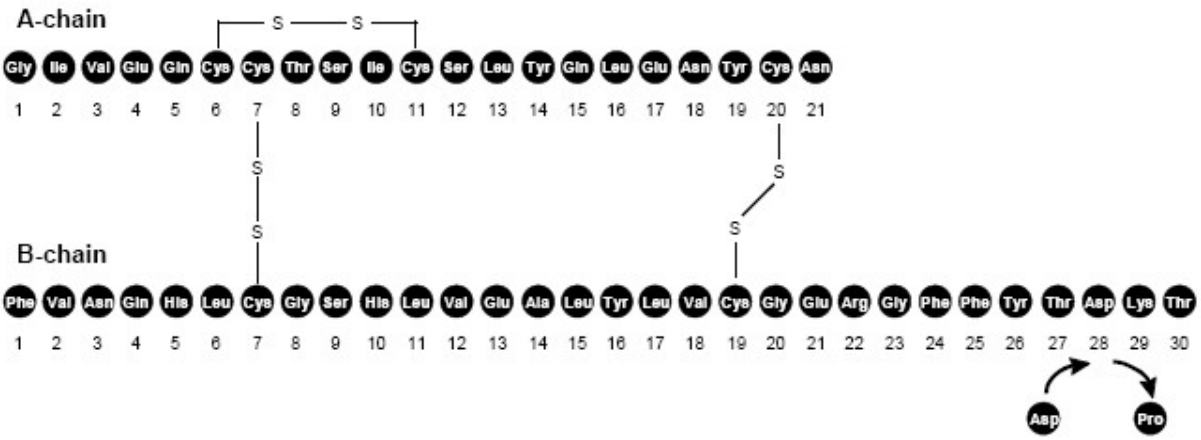


Figure 1. Structural formula of insulin aspart.

NOVOLOG (insulin aspart) injection is a sterile, clear, and colorless solution for subcutaneous or intravenous use. Each mL contains 100 units of insulin aspart and the inactive ingredients: disodium hydrogen phosphate dihydrate (1.25 mg), glycerin (16.0 mg), metacresol (1.72 mg), phenol (1.50 mg), sodium chloride (0.58 mg), zinc (19.6 mcg), and Water for Injection, USP. 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)]*.

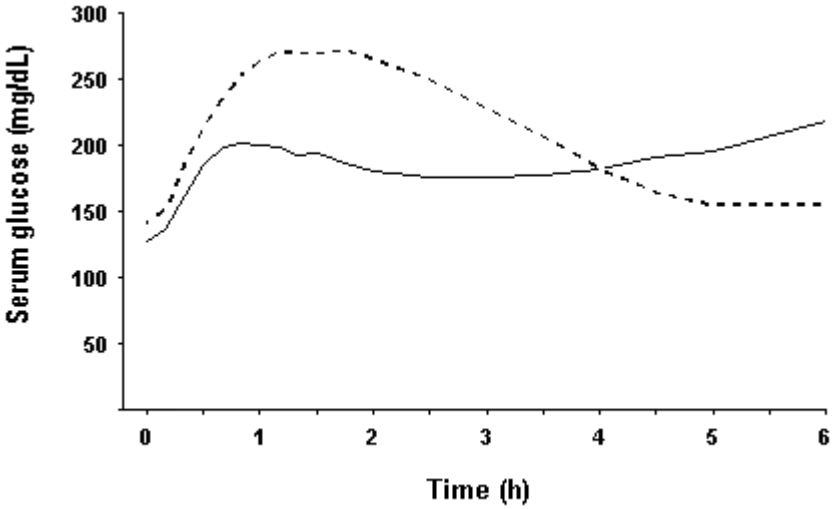


Figure 2. Serial mean serum glucose collected up to 6 hours following a single 0.15 units/kg pre-meal dose of NOVOLOG (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

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).

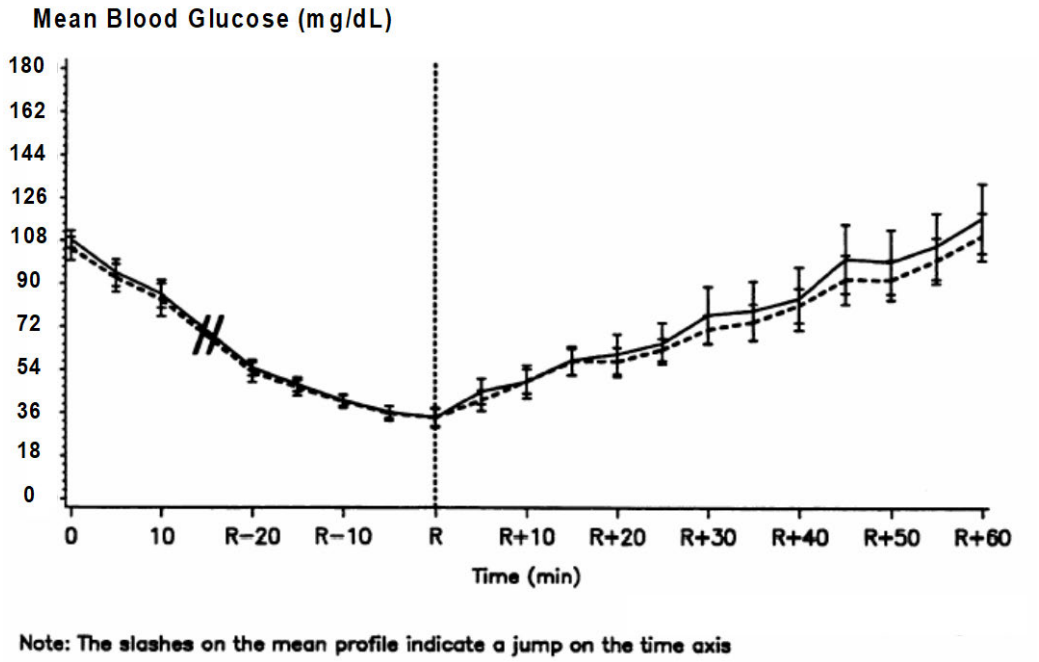


Figure 3. Mean blood glucose profiles following intravenous infusion of NOVOLOG (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

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 NOVOLOG in these trials was 40 to 50 minutes versus 80 to 120 minutes, for regular human insulin respectively.

The relative bioavailability of NOVOLOG (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, NOVOLOG 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.

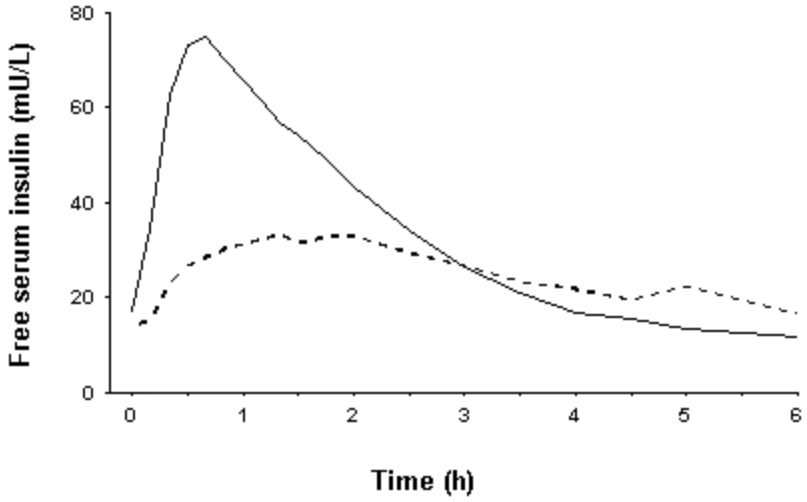


Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single 0.15 units/kg pre-meal dose of NOVOLOG (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

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 NOVOLOG or regular human insulin at 1.5 mU/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.2 L/h/kg for the NOVOLOG group and 1.2 L/h/kg for the regular human insulin group.

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

Specific Populations

Pediatrics - The pharmacokinetic and pharmacodynamic properties of NOVOLOG and regular human insulin were evaluated in a single dose study in 18 pediatric patients with type 1 diabetes in 2 age groups: 6-12 years, n=9 and 13-17 years (Tanner grade $\geq$ 2), n=9. The relative differences in pharmacokinetics and pharmacodynamics in the pediatric patients with type 1 diabetes in both age groups between NOVOLOG 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 NOVOLOG and regular human insulin were investigated in a single dose study in 18 subjects with type 2 diabetes who were $\geq$ 65 years of age. The relative differences in pharmacokinetics and pharmacodynamics in geriatric patients with type 2 diabetes between NOVOLOG and regular human insulin were similar to those in younger adults.
Gender: In healthy volunteers given a single subcutaneous dose of NOVOLOG 0.06 units/kg, no difference in insulin aspart levels was seen between men and women based on comparison of $AUC_{(0\text{-}10h)}$ or C_{max}.

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

Renal Impairment: A single subcutaneous dose of 0.08 units/kg NOVOLOG 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 NOVOLOG.

Hepatic Impairment: A single subcutaneous dose of 0.06 units/kg NOVOLOG was administered in an open-label, single-dose study of 24 subjects (n=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this study, there was no correlation between the degree of hepatic impairment and any NOVOLOG 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 NOVOLOG. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NOVOLOG 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, NOVOLOG increased the incidence of mammary gland tumors in females when compared to untreated controls. The relevance of these findings to humans is unknown.

NOVOLOG was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes.

In fertility studies in male and female rats, at subcutaneous doses up to 200 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 NOVOLOG 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 NOVOLOG were 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 NOVOLOG administered by continuous subcutaneous insulin infusion (CSII) by external pump were compared to buffered regular human insulin (administered by CSII), to lispro (administered by CSII) and compared to NOVOLOG 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 NOVOLOG 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/m^2.

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 in this study (Table 3).

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

	NOVOLOG + 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 NOVOLOG 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 pediatric patients with type 1 diabetes (n=283), aged 6 to 18 years, compared two subcutaneous multiple-dose treatment regimens: NOVOLOG (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 NOVOLOG and regular human insulin have also been compared in pediatric patients with type 1 diabetes (n=26) aged 2 to 6 years with similar effects on HbA_{1c}.

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

	NOVOLOG + 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)
One six-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/m^2.

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 pediatric patients 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/m^2.

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

10 mL multiple-dose vial		NDC 0169-7501-11
	ReliOn® brand	NDC 0169-2100-11

3 mL single-patient-use NOVOLOG FlexPen		NDC 0169-6339-10
	ReliOn® brand	NDC 0169-2101-25
3 mL single-patient-use PenFill cartridges*		NDC 0169-3303-12
3 mL single-patient-use 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.

The NOVOLOG FlexPen and FlexTouch dial in 1-unit increments.

16.2 Recommended Storage

Dispense in the original sealed carton with the enclosed Instructions for Use.

Unused NOVOLOG should be stored in a refrigerator between 2°C and 8°C (36°F 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.

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 (up to 30°C [86°F])	**Not in-use** (unopened) Refrigerated (2°C - 8°C [36°F - 46°F])	**In-use (opened)** Room Temperature (up to 30°C [86°F])
10 mL multiple-dose vial	28 days	Until expiration date	28 days* (refrigerated/room temperature)
3 mL single-patient-use PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL single-patient-use NOVOLOG FlexPen	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL single-patient-use	28 days	Until expiration date	28 days (Do not refrigerate)

NOVOLOG FlexTouch			

***For insulin pump use, the total in-use time is 19 days, including 7 days pump in-use time.**

Storage in External Insulin Pump:

Change the NOVOLOG in the pump reservoir at least every 7 days or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 37°C (98.6°F).

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 up to 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 FlexTouch, PenFill Cartridge or PenFill Cartridge Device between Patients

Advise patients that they must never share NOVOLOG FlexPen, NOVOLOG FlexTouch, 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 NOVOLOG 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)]*.

Hyperglycemia or 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 NOVOLOG 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.

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

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 NOVOLOG. Inform patients of the symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.4)]*.

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.
- Refer to the continuous subcutaneous infusion pump user manual to see if NOVOLOG can be used with the pump. See recommended reservoir and infusion sets in the insulin pump user manual.
- Instruct patients to replace insulin in the reservoir at least every 7 days or according to the user manual, whichever is shorter; infusion sets and infusion set insertion sites should be changed according to the manufacturer's user manual. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin preservative.
- 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)]*.

Rx only

Date of Issue: 10/2021
Version: 29

Manufactured by:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500
U.S. License Number 1261

For information about NOVOLOG contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500
(Se Habla español)

www.novonordisk-us.com

Instructions for Use

NovoLog® (NŌ-vō-log)
(insulin aspart) injection
10 mL multiple-dose vial (100 Units/mL, U-100)

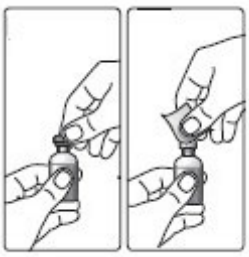
Read this Instructions for Use before you start taking NovoLog and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

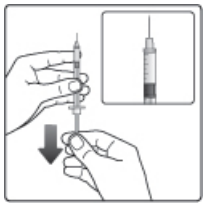
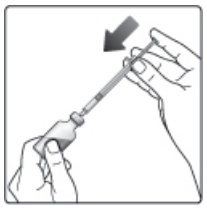
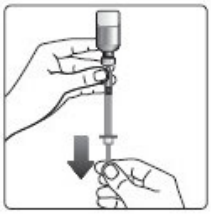
Supplies you will need to give your NovoLog injection:

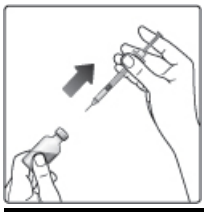
- 10 mL NovoLog vial
- insulin syringe and needle
- alcohol swabs

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.

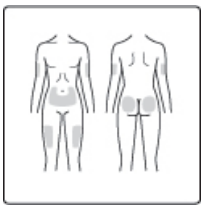
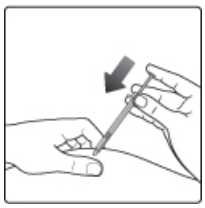
Step 1: Pull off the tamper resistant cap (See Figure A). **Step 2:** Wipe the rubber stopper with an alcohol swab (See Figure B).	 (Figure A Figure B)

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). • 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 F)  (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 (continuous subcutaneous infusion into an area of your body recommended in the instructions that come with your 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 to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. **Do not** use the same injection site for each injection. **Do not** inject where the skin has pits, is thickened, or has lumps. **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- If you use NovoLog in an insulin pump, you should change your infusion set and insertion site according to the manufacturer's user manual. NovoLog should be given into an area of your body recommended in the instructions that come with your insulin pump. Change (rotate) your insertion sites within the area you choose for each insertion to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the insertion sites. Do not insert into the exact same spot for each insertion. Do not insert where the skin has pits, is thickened, or has lumps. Do not insert where the skin is tender, bruised, scaly or hard, or into scars or damaged skin. The insulin in the reservoir should be changed at least every 7 days or according to the pump user manual, whichever is shorter, 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 (stomach area, buttocks, upper legs or upper arms) 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). **The 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.
- Put the empty insulin vials, used needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes and needles 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, and 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.

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.
- **All unopened vials:**
  - Store unopened NovoLog vials in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C).
  - Unopened vials may be used until the expiration date printed on the label, if they have been stored in the refrigerator.
  - Unopened vials should be thrown away after 28 days, if they are stored at room temperature.
- **After vials have been opened:**
  - Opened NovoLog vials can be stored in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C) or at room temperature below 86˚F (30˚C).
  - Throw away all opened NovoLog vials after 28 days, even if they still have insulin left in them.
  - If using NovoLog in a pump, throw away all opened NovoLog vials after 19 days.

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 Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500
U.S. License Number 1261

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: 10/2021