

# NovoLog<sup>®</sup> Mix 70/30

70% insulin aspart protamine suspension and  
30% insulin aspart injection, (rDNA origin)

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use NovoLog<sup>®</sup> Mix 70/30 safely and effectively. See full prescribing information for NovoLog<sup>®</sup> Mix 70/30.**

**NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])**

**Suspension for subcutaneous injection**

**Initial U.S. Approval: 2001**

### RECENT MAJOR CHANGES

- Indications and Usage (1) 5/2010
- Dosage and Administration (2.1) 5/2010

### INDICATIONS AND USAGE

NovoLog<sup>®</sup> Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus.

Important Limitations of Use: In premix insulins, such as NovoLog<sup>®</sup> Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments (1).

### DOSAGE AND ADMINISTRATION

- Only for subcutaneous injection (2.1)
  - Type 1 DM: dose within 15 minutes before meal initiation.
  - Type 2 DM: dose within 15 minutes before or after starting a meal.
- Do not administer intravenously (2.1).
- Do not use in insulin infusion pumps (2.1).
- Must be resuspended immediately before use (2.2).

### DOSAGE FORMS AND STRENGTHS

Each presentation contains 100 Units of insulin aspart per mL (U-100) (3)

- 10 mL vials
- 3 mL NovoLog<sup>®</sup> Mix 70/30 FlexPen<sup>®</sup>

### CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog<sup>®</sup> Mix 70/30 or one of its excipients (4).

### WARNINGS AND PRECAUTIONS

- NovoLog<sup>®</sup> Mix 70/30 should not be mixed with any other insulin product (5.1).
- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision (5.1, 5.2).
- Insulin, particularly when given in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog<sup>®</sup> Mix 70/30 requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5).
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog<sup>®</sup> Mix 70/30 (5.6).

### ADVERSE REACTIONS

Adverse reactions observed with insulin therapy 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](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- The following may increase the blood glucose lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), sulfonamide antibiotics (7).
- The following may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (7).

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

**Revised: 5/2010**

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

NovoLog® Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus.

#### Important Limitations of Use:

In premix insulins, such as NovoLog® Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosing

NovoLog® Mix 70/30 is an insulin analog with an earlier onset and intermediate duration of action in comparison to the basal human insulin premix. The addition of protamine to the rapid-acting aspart insulin analog (NovoLog®) results in insulin activity that is 30% short-acting and 70% long-acting. NovoLog® Mix 70/30 is typically dosed on a twice-daily basis (with each dose intended to cover 2 meals or a meal and a snack). The dosage of NovoLog® Mix 70/30 must be individualized. The written prescription for NovoLog® Mix 70/30 should include the full name, to avoid confusion with NovoLog® (insulin aspart) and Novolin® 70/30 (human premix).

NovoLog® Mix 70/30 should appear uniformly white and cloudy. Do not use it if it looks clear or if it contains solid particles. NovoLog® Mix 70/30 should not be used after the printed expiration date.

NovoLog® Mix 70/30 should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. NovoLog® Mix 70/30 has a faster onset of action than human insulin premix 70/30 and should be dosed within 15 minutes before meal initiation for patients with type 1 diabetes. For patients with type 2 diabetes, dosing should occur within 15 minutes before or after meal initiation. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog® Mix 70/30 should not be administered intravenously or used in insulin infusion pumps. Dose regimens of NovoLog® Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's recommended glucose treatment goals, metabolic needs, eating habits, and other lifestyle variables.

#### 2.2 Resuspension

NovoLog® Mix 70/30 is a suspension that must be visually inspected and resuspended immediately before use.

The NovoLog® Mix 70/30 vial should be rolled gently in your hands in a horizontal position 10 times to mix it. The rolling procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Resuspension is easier when the insulin has reached room temperature.

The NovoLog® Mix 70/30 FlexPen® should be rolled 10 times gently between your hands in a horizontal position. Thereafter, turn the NovoLog® Mix 70/30 FlexPen® upside down so that the glass ball moves from one end of the reservoir to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the disposable NovoLog® Mix 70/30 FlexPen® upside down so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the suspension appears uniformly white and cloudy. Inject immediately.

### 3 DOSAGE FORMS AND STRENGTHS

NovoLog® Mix 70/30 is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL NovoLog® Mix 70/30 FlexPen®

### 4 CONTRAINDICATIONS

NovoLog® Mix 70/30 is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog® Mix 70/30 or one of its excipients.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Administration

The short and long-acting components of insulin mixes, including NovoLog® Mix 70/30, cannot be titrated independently. Because NovoLog® Mix 70/30 has peak pharmacodynamic activity between 1-4 hours after injection, it should be administered within 15 minutes of meal initiation [see *Clinical Pharmacology* (12)]. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients who require more frequent meals.

NovoLog® Mix 70/30 should not be mixed with any other insulin product.

NovoLog® Mix 70/30 should not be used intravenously.

NovoLog® Mix 70/30 should not be used in insulin infusion pumps.

Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. Changes may also be necessary during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Needles and NovoLog® Mix 70/30 FlexPen® must not be shared.

#### 5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog® Mix 70/30. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog® Mix 70/30.

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

Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [see *Drug Interactions* (7)].

#### 5.3 Hypokalemia

All insulin products, including NovoLog® Mix 70/30, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g. patients using potassium-lowering medications or patients taking medications sensitive to potassium concentrations).

#### 5.4 Renal Impairment

Clinical or pharmacology studies with NovoLog® Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog® Mix 70/30 may be reduced in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

#### 5.5 Hepatic Impairment

Clinical or pharmacology studies with NovoLog® Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog® Mix 70/30 may be reduced in patients with hepatic impairment [see *Clinical Pharmacology* (12.3)].

### 5.6 Hypersensitivity and Allergic Reactions

*Local Reactions* - As with other insulin therapy, patients may experience reactions such as erythema, edema or pruritus at the site of NovoLog® Mix 70/30 injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog® Mix 70/30. In some instances, these reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

*Systemic Reactions* - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

#### 5.7 Antibody Production

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in a 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog® Mix 70/30 than with Novolin® 70/30 but these changes did not correlate with change in HbA<sub>1c</sub> or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog® Mix 70/30.

### 6 ADVERSE REACTIONS

#### Clinical Trial Experience

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

##### • *Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® Mix 70/30 [see *Warnings and Precautions* (5.2)]. NovoLog® Mix 70/30 should not be used during episodes of hypoglycemia [see *Contraindications* (4) and *Warnings and Precautions* (5)].

##### • *Insulin initiation and glucose control intensification*

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

##### • *Lipodystrophy*

Long-term use of insulin, including NovoLog® Mix 70/30, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy.

##### • *Weight gain*

Weight gain can occur with some insulin therapies, including NovoLog® Mix 70/30, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

##### • *Peripheral Edema*

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

##### • *Frequencies of adverse drug reactions*

The frequencies of adverse drug reactions during a clinical trial with NovoLog® Mix 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below. The trial was a three-month, open-label trial in patients with Type 1 or Type 2 diabetes who were treated twice daily (before breakfast and before supper) with NovoLog® Mix 70/30.

**Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 diabetes mellitus (Adverse events with frequency  $\geq$  5% are included.)**

Preferred Term	NovoLog® Mix 70/30 (N=55)		Novolin® 70/30 (N=49)	
	N	%	N	%
Hypoglycemia	38	69	37	76
Headache	19	35	6	12
Influenza-like symptoms	7	13	1	2
Dyspepsia	5	9	3	6
Back pain	4	7	2	4
Diarrhea	4	7	3	6
Pharyngitis	4	7	1	2
Rhinitis	3	5	6	12
Skeletal pain	3	5	2	4
Upper respiratory tract infection	3	5	1	2

**Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 diabetes mellitus (Adverse events with frequency  $\geq$  5% are included.)**

Preferred Term	NovoLog® Mix 70/30 (N=85)		Novolin® 70/30 (N=102)	
	N	%	N	%
Hypoglycemia	40	47	51	50
Upper respiratory tract infection	10	12	6	6
Headache	8	9	8	8
Diarrhea	7	8	2	2
Neuropathy	7	8	2	2
Pharyngitis	5	6	4	4
Abdominal pain	4	5	0	0
Rhinitis	4	5	2	2

## Postmarketing Data

Additional adverse reactions have been identified during post-approval use of NovoLog® Mix 70/30. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. They include medication errors in which other insulins have been accidentally substituted for NovoLog® Mix 70/30 [see Patient Counseling Information (17)].

## 7 DRUG INTERACTIONS

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

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), sulfonamide antibiotics.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics.
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category B.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

An open-label, randomized study compared the safety and efficacy of NovoLog® (the rapid-acting component of NovoLog® Mix 70/30) versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies (NovoLog: 157, human insulin: 165)). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA<sub>1c</sub> of ~6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Animal reproduction studies have not been conducted with NovoLog® Mix 70/30. However, subcutaneous reproduction and teratology studies have been performed with NovoLog® (the rapid-acting component of NovoLog® Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog® was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog® did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32-times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits based on U/body surface area.

Female patients should be advised to discuss with their physician if they intend to, or if they become pregnant. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 in pregnant women.

### 8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk as occurs with human insulin. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 or NovoLog® in lactating women. Women with diabetes who are lactating may require adjustments of their insulin doses.

### 8.4 Pediatric Use

Safety and effectiveness of NovoLog® Mix 70/30 have not been established in pediatric patients.

### 8.5 Geriatric Use

Clinical studies of NovoLog® Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

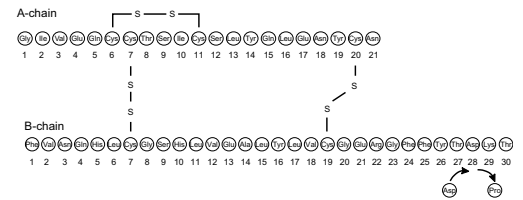
## 10 OVERDOSAGE

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

## 11 DESCRIPTION

NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog® Mix 70/30

is a blood glucose-lowering agent with an earlier onset and an intermediate duration of action. Insulin aspart 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 (NovoLog®) has the empirical formula C<sub>256</sub>H<sub>381</sub>N<sub>65</sub>O<sub>79</sub>S<sub>6</sub> and a molecular weight of 5825.8 Da.



**Figure 1. Structural formula of insulin aspart**

NovoLog® Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart 100 Units/mL.

Inactive ingredients for the 10 mL vial are mannitol 36.4 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL, and protamine sulfate 0.32 mg/mL.

Inactive ingredients for the NovoLog® Mix 70/30 FlexPen® are glycerol 16.0 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.877 mg/mL, and protamine sulfate 0.32 mg/mL. NovoLog® Mix 70/30 has a pH of 7.20 - 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

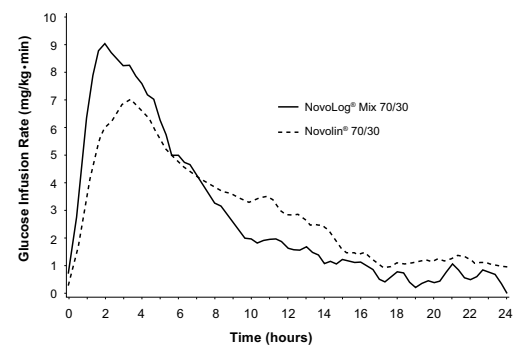
## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The primary activity of NovoLog® Mix 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog® Mix 70/30, bind to the insulin receptors on muscle, liver and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

### 12.2 Pharmacodynamics

The two euglycemic clamp studies described below [see Clinical Pharmacology (12.3)] assessed glucose utilization after dosing of healthy volunteers. NovoLog® Mix 70/30 has an earlier onset of action than human premix 70/30 in studies of normal volunteers and patients with diabetes. The onset of action is between 10-20 minutes for NovoLog® Mix 70/30 compared to 30 minutes for Novolin® 70/30. The mean  $\pm$  SD time to peak activity for NovoLog® Mix 70/30 is 2.4 hr  $\pm$  0.8 hr compared to 4.2 hr  $\pm$  0.4 hr for Novolin® 70/30. The duration of action may be as long as 24 hours (see Figure 2).



**Figure 2. Pharmacodynamic Activity Profile of NovoLog® Mix 70/30 and Novolin® 70/30 in healthy subjects.**

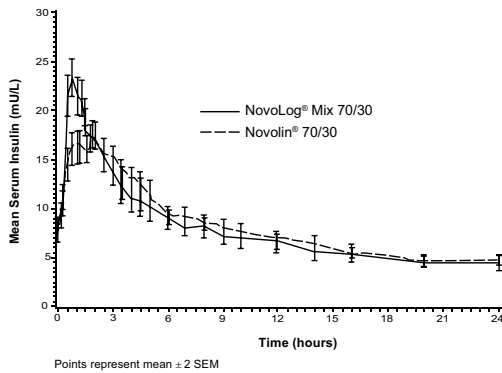
### 12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog®) reduces the molecule's tendency to form hexamers as observed with regular human insulin. The rapid absorption characteristics of NovoLog® are maintained by NovoLog® Mix 70/30. The insulin aspart in the soluble component of NovoLog® Mix 70/30 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

**Bioavailability and Absorption** - The relative bioavailability of NovoLog® Mix 70/30 compared to NovoLog® and Novolin®

70/30 indicates that the insulins are absorbed to similar extent. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with NovoLog® Mix 70/30 (0.2 U/kg), a mean maximum serum concentration (C<sub>max</sub>) of 23.4 ± 5.3 mU/L was reached after 60 minutes. The mean half-life (t<sub>1/2</sub>) of NovoLog® Mix 70/30 was about 8 to 9 hours. Serum insulin levels returned to baseline 15 to 18 hours after a subcutaneous dose of NovoLog® Mix 70/30. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with NovoLog® Mix 70/30 (0.3 U/kg). A C<sub>max</sub> of 61.3 ± 20.1 mU/L was reached after 85 minutes. Serum insulin levels returned to baseline 12 hours after a subcutaneous dose.

The C<sub>max</sub> and the area under the insulin concentration-time curve (AUC) after administration of NovoLog® Mix 70/30 was approximately 20% greater than those after administration of Novolin® 70/30, (see Fig. 3 for pharmacokinetic profiles).



**Figure 3. Pharmacokinetic Profiles of NovoLog® Mix 70/30 and Novolin® 70/30**

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

The effect of sex, age, obesity, ethnic origin, renal and hepatic impairment, pregnancy, or smoking, on the pharmacodynamics and pharmacokinetics of NovoLog® Mix 70/30 has not been studied.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog® Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog, the rapid-acting component of NovoLog® Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog® increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors found with NovoLog® was not significantly different from that found with regular human insulin. The relevance of these findings to humans is not known.

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

In fertility studies in male and female rats, NovoLog® at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

#### 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. However, the effect of NovoLog® Mix 70/30 is more rapid in onset compared to Novolin® (human insulin) 70/30 due to its faster absorption after subcutaneous injection.

## 14 CLINICAL STUDIES

### 14.1 NovoLog® Mix 70/30 versus Novolin® 70/30

In a three-month, open-label trial, patients with Type 1 (n=104) or Type 2 (n=187) diabetes were treated twice daily (before breakfast and before supper) with NovoLog® Mix 70/30 or Novolin® 70/30. Patients had received insulin for at least 24 months before the study. Oral hypoglycemic agents were not allowed within 1 month prior to the study or during the study. The small changes in HbA<sub>1c</sub> were comparable across the treatment groups (see Table 3).

**Table 3: Glycemic Parameters at the End of Treatment [Mean ± SD (N subjects)]**

	NovoLog® Mix 70/30	Novolin® 70/30
<b>Type 1, N=104</b>		
Fasting Blood Glucose (mg/dL)	174 ± 64 (48)	142 ± 59 (44)
1.5 Hour Post Breakfast (mg/dL)	187 ± 82 (48)	200 ± 82 (42)
1.5 Hour Post Dinner (mg/dL)	162 ± 77 (47)	171 ± 66 (41)
HbA <sub>1c</sub> (%) Baseline	8.4 ± 1.2 (51)	8.5 ± 1.1 (46)
HbA <sub>1c</sub> (%) Week 12	8.4 ± 1.1 (51)	8.3 ± 1.0 (47)
<b>Type 2, N=187</b>		
Fasting Blood Glucose (mg/dL)	153 ± 40 (76)	152 ± 69 (93)
1.5 Hour Post Breakfast (mg/dL)	182 ± 65 (75)	200 ± 80 (92)
1.5 Hour Post Dinner (mg/dL)	168 ± 51 (75)	191 ± 65 (93)
HbA <sub>1c</sub> (%) Baseline	8.1 ± 1.2 (82)	8.2 ± 1.3 (98)
HbA <sub>1c</sub> (%) Week 12	7.9 ± 1.0 (81)	8.1 ± 1.1 (96)

The significance, with respect to the long-term clinical sequelae of diabetes, of the differences in postprandial hyperglycemia between treatment groups has not been established.

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial.

### 14.2 Combination Therapy: Insulin and Oral Agents in Patients with Type 2 Diabetes

#### Trial 1:

In a 34-week, open-label trial, insulin-naïve patients with type 2 diabetes currently treated with 2 oral antidiabetic agents were switched to treatment with metformin and pioglitazone. During an 8-week optimization period metformin and pioglitazone were increased to 2500 mg per day and 30 or 45 mg per day, respectively. After the optimization period, subjects were randomized to receive either NovoLog® Mix 70/30 twice daily added on to the metformin and pioglitazone regimen or continue the current optimized metformin and pioglitazone therapy. NovoLog® Mix 70/30 was started at a dose of 6 IU twice daily (before breakfast and before supper). Insulin doses were titrated to a pre-meal glucose goal of 80-110 mg/dL. The total daily insulin dose at the end of the study was 56.9 ± 30.5 IU.

**Table 4: Combination Therapy with Oral Agents and Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]**

Treatment duration	NovoLog® Mix 70/30 + Metformin + Pioglitazone	Metformin + Pioglitazone
<b>24-weeks</b>		
HbA <sub>1c</sub>		
Baseline mean ± SD (n)	8.1 ± 1.0 (102)	8.1 ± 1.0 (98)
End-of-study mean ± SD (n) - LOCF	6.6 ± 1.0 (93)	7.8 ± 1.2 (87)
Adjusted Mean change from baseline ± SE (n)*	-1.6 ± 0.1 (93)	-0.3 ± 0.1 (87)
Treatment difference mean ± SE* 95% CI*		-1.3 ± 0.1 (-1.6, -1.0)
Percentage of subjects reaching HbA <sub>1c</sub> <7.0%	76%	24%
Percentage of subjects reaching HbA <sub>1c</sub> ≤6.5%	59%	12%

Fasting Blood Glucose (mg/dL)		
Baseline Mean ± SD (n)	173 ± 39.8 (93)	163 ± 35.4 (88)
End of Study Mean ± SD (n) - LOCF	130 ± 50.0 (90)	162 ± 40.8 (84)
Adjusted Mean change from baseline ± SE (n)*	-43.0 ± 5.3 (90)	-3.9 ± 5.3 (84)
End-of-Study Blood Glucose (Plasma) (mg/dL)		
2 Hour Post Breakfast	138 ± 42.8 (86)	188 ± 57.7 (74)
2 Hour Post Lunch	150 ± 41.5 (86)	176 ± 56.5 (74)
2 Hour Post Dinner	141 ± 57.8 (86)	195 ± 60.1 (74)
% of patients with severe hypoglycemia**	3	0
% of patients with minor hypoglycemia**	52	3
Weight gain at end of study (kg)**	4.6 ± 4.3 (92)	0.8 ± 3.2 (86)

\*Adjusted mean per group, treatment difference, and 95% CI were obtained based on an ANCOVA model with treatment, FPG stratum, and secretagogue stratum as fixed factors and baseline HbA<sub>1c</sub> as the covariate.

\*\*If metabolic control is improved by intensified insulin therapy, an increased risk of hypoglycemia and weight gain may occur.

#### Trial 2:

In a 28-week, open-label trial, insulin-naïve patients with type 2 diabetes with fasting plasma glucose above 140 mg/dL currently treated with metformin ± thiazolidinedione therapy were randomized to receive either NovoLog® Mix 70/30 twice daily [before breakfast and before supper] or insulin glargine once daily (see Table 5). NovoLog® Mix 70/30 was started at an average dose of 5-6 IU (0.07 ± 0.03 IU/kg) twice daily (before breakfast and before supper), and bedtime insulin glargine was started at 10-12 IU (0.13 ± 0.03 IU/kg). Insulin doses were titrated weekly by decrements or increments of -2 to +6 units per injection to a pre-meal glucose goal of 80-110 mg/dL. The metformin dose was adjusted to 2550 mg/day. Approximately one-third of the patients in each group were also treated with pioglitazone (30 mg/day). Insulin secretagogues were discontinued in order to reduce the risk of hypoglycemia. Most patients were Caucasian (53%), and the mean initial weight was 90 kg.

**Table 5: Combination Therapy with Oral Agents and Two Types of Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]**

Treatment duration	NovoLog® Mix 70/30 + Metformin ± Pioglitazone	Insulin Glargine+ Metformin ± Pioglitazone
<b>28-weeks</b>		
Number of patients	117	116
HbA <sub>1c</sub>		
Baseline mean (%)	9.7 ± 1.5 (117)	9.8 ± 1.4 (114)
End-of-study mean (± SD)	6.9 ± 1.2 (108)	7.4 ± 1.2 (114)
Mean change from baseline	-2.7 ± 1.6 (108)	-2.4 ± 1.5 (114)
Percentage of subjects reaching HbA <sub>1c</sub> <7.0%	66%	40%
Total Daily Insulin Dose at end of study (U)	78 ± 40 (117)	51 ± 27 (116)
% of patients with severe hypoglycemia	0	0
% of minor hypoglycemia	43	16
Weight gain at end of study	5.4 ± 4.8 (117)	3.5 ± 4.5 (116)

## 15 REFERENCES

- Raskin R, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005; 28:260-265.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

NovoLog® Mix 70/30 is available in the following package sizes: each presentation contains 100 Units of insulin aspart per mL (U-100).

10 mL vials	NDC 0169-3685-12
3 mL NovoLog® Mix 70/30 FlexPen®	NDC 0169-3696-19

NovoLog® Mix 70/30 vials and NovoLog® Mix 70/30 FlexPen® are latex free.

## 16.2 Recommended Storage

Unused NovoLog® Mix 70/30 should be stored in a refrigerator between 2°C and 8°C (36°F to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze NovoLog® Mix 70/30 or use NovoLog® Mix 70/30 if it has been frozen.**

**Vials:** After initial use, a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Open vials may be refrigerated.

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

**NovoLog® Mix 70/30 FlexPen:** Once a NovoLog® Mix 70/30 FlexPen® is punctured, it should be kept at temperatures below 30°C (86°F) for up to 14 days, but should not be exposed to excessive heat or sunlight. A NovoLog® Mix 70/30 FlexPen® in use must NOT be stored in the refrigerator. Keep the disposable NovoLog® Mix 70/30 FlexPen® away from direct heat and sunlight. An unpunctured NovoLog® Mix 70/30 FlexPen® can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep any unused NovoLog® Mix 70/30 FlexPen® in the carton so it will stay clean and protected from light.

These storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30°C(86°F))	Not in-use (unopened) Refrigerated (2°C - 8°C [36°F- 46°F])	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 NovoLog® Mix 70/30 FlexPen®	14 days	Until expiration date	14 days (Do not refrigerate)

## 17 PATIENT COUNSELING INFORMATION

[see FDA-Approved Patient Labeling]

### 17.1 Physician Instructions

Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and advantages of NovoLog® Mix 70/30 therapy including the possible adverse reactions. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin. See Patient Information supplied with the product. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia, and diabetic ketoacidosis.

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

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

### Rx only

Date of Issue: May 7, 2010

### Version: 9

Novo Nordisk®, NovoLog®, FlexPen®, and Novolin®, are trademarks owned by Novo Nordisk® A/S.

NovoLog® Mix 70/30 is covered by US Patent Nos. 5,547,930; 5,618,913; 5,834,422; 5,840,680; 5,866,538 and other patents pending.

FlexPen® is covered by US Patent Nos. 6,582,404; 6,004,297; 6,235,004 and other patents pending.

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131122-R4 6/2010

