# NovoLog Mix 70/30

**(70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)**

## DESCRIPTION

NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection) is a human insulin analogue suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a blood glucose-lowering agent with a rapid 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) as the production organism. Insulin aspart (NovoLog®) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 Da.

Structural formula:

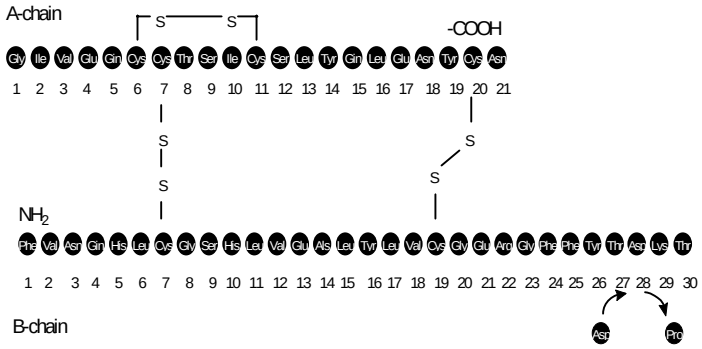


***Figure 1. Structural formula of insulin aspart***

NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analogue) 100 Units/mL, 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 0.33 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.

## CLINICAL PHARMACOLOGY

### Mechanism of action

The primary activity of NovoLog Mix 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog Mix 70/30, exert their specific action through binding to insulin receptors. Insulin binding activates mechanisms to lower blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat, simultaneously inhibiting the output of glucose from the liver.

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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.

**Pharmacokinetics**

Bioavailability and absorption

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.

The relative bioavailability of NovoLog Mix 70/30 compared to NovoLog® and Novolin 70/30 indicates that they are absorbed to similar degrees. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with 0.2 U/kg of NovoLog Mix 70/30, a mean maximum serum concentration (Cmax) of 23.4 ± 5.3 mU/L was reached after 60 minutes. The mean half-life (t1/2) 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. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with 0.3 U/kg of NovoLog Mix 70/30. A Cmax 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 Cmax and the area under the insulin concentration-time curve (AUC) after administration of NovoLog Mix 70/30 differed by approximately 20% from those after administration of NovoLog Mix 50/50 (investigational drug, not marketed.) and Novolin 70/30 (see Fig. 2 and 3 for pharmacokinetic profiles).

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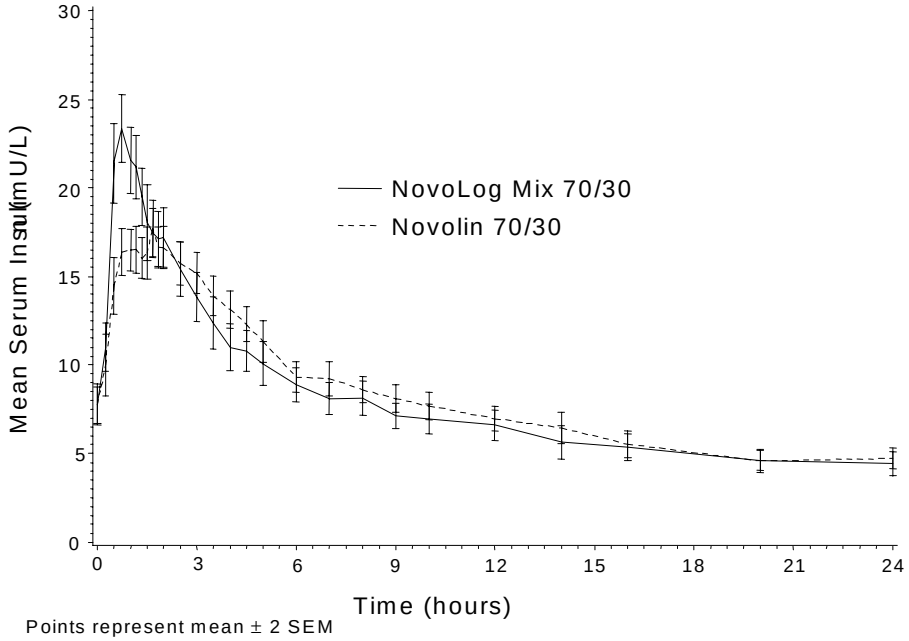


**Figure 2. Pharmacokinetic Profiles of NovoLog Mix 70/30 and Novolin® 70/30**

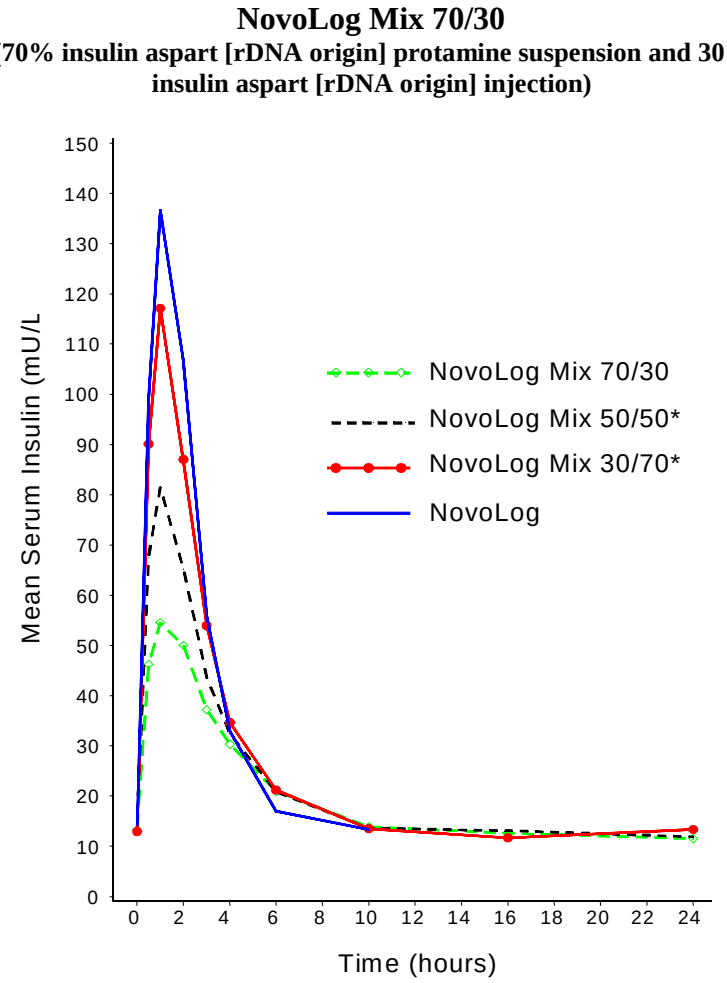


**Figure 3 Pharmacokinetic profiles for NovoLog Mix 70/30 and other proportional mixes (* investigational drugs, not marketed).**

Pharmacokinetic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin kinetics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacokinetics between NovoLog Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

*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.

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## Pharmacodynamics

The two euglycemic clamp studies described above assessed glucose utilization after dosing of healthy volunteers. NovoLog Mix 70/30 has a more rapid onset of action than regular human insulin in studies of normal volunteers and patients with diabetes. The peak pharmacodynamic effect of NovoLog Mix 70/30 occurs between 1 and 4 hours after injection. The duration of action may be as long as 24 hours (see Figures 4 and 5).

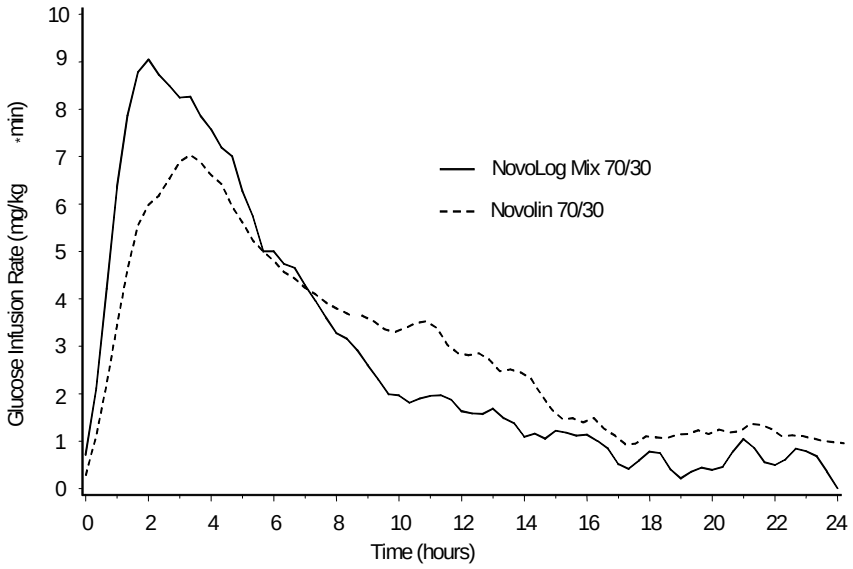


**Fig 4: Pharmacodynamic Activity Profile of NovoLog Mix 70/30 and Novolin 70/30 in healthy subjects.**

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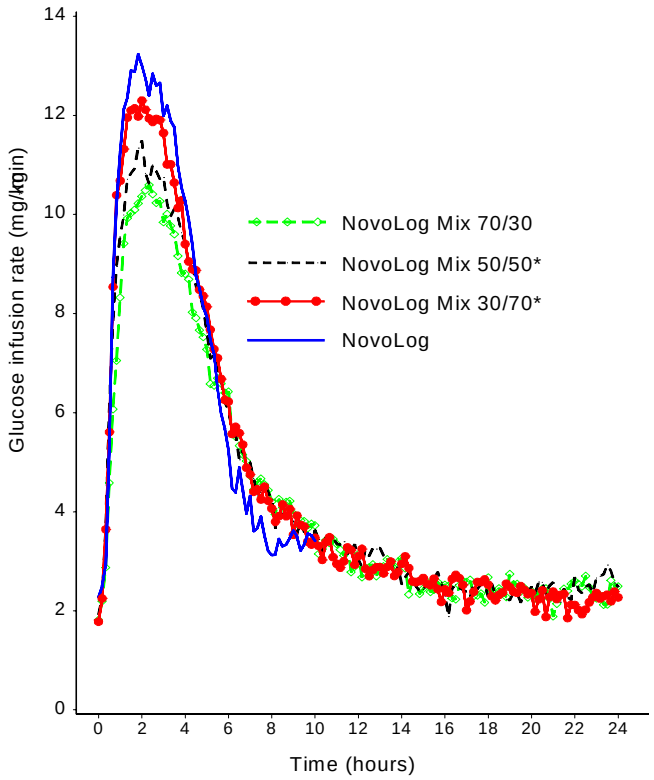


**Figure 5. Pharmacodynamic Activity Profiles for NovoLog Mix 70/30 and other proportional mixes (* investigational drugs, not marketed)**

Pharmacodynamic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin pharmacodynamics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

**Special populations**

*Children and adolescents*-The pharmacokinetic and pharmacodynamic properties of NovoLog Mix 70/30 have not been assessed in children and adolescents less than 18 years of age.

*Geriatrics*-The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

*Gender*- The effect of gender on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

*Obesity*-The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid acting component (NovoLog®) show no significant effect.

*Ethnic origin*-The effect of ethnic origin on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

*Renal impairment*-The effect of renal function on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid acting component (NovoLog®) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

*Hepatic impairment*- The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid-acting component (NovoLog®) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

*Pregnancy*-The effect of pregnancy on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied (see PRECAUTIONS, Pregnancy).

*Smoking*-The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

## CLINICAL STUDIES

In a three-month, open-label trial, patients with Type 1 (n=146) or Type 2 (n=178) diabetes were treated BID (before breakfast and before supper) with NovoLog Mix 70/30 or Novolin® 70/30. The small changes in glycemic control (HbA1c) were comparable across the treatment groups (see Table 1).

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Table 1: Glycemic Parameters at the End of Treatment ~~(~~[Mean (SD)]

| | NovoLog Mix 70/30 | Novolin 70/30 |
|---|---|---|
| Type 1, N=92 | | |
| Fasting Blood Glucose (mg/dL) | 173 (62.3) | 141 (58.7) |
| 1.5 Hour Post Breakfast | 185 (80.1) | 198 (80.1) |
| 1.5 Hour Post Dinner | 158 (76.5) | 169 (65.9) |
| HbA1c (%) | 8.4 (1.1) | 8.3 (1.0) |
| Type 2, N=169 | | |
| Fasting Blood Glucose (mg/dL) | 151 (39.2) | 151 (67.6) |
| 1.5 Hour Post Breakfast | 180 (64.1) | 198 (80.1) |
| 1.5 Hour Post Dinner | 166 (49.8) | 189 (49.8) |
| HbA1c (%) | 7.9 (1.0) | 8.1 (1.1) |

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~~.~~ (see PRECAUTIONS, Allergy).

## INDICATIONS AND USAGE

NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

## CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog Mix 70/30 or one of its excipients.

## WARNINGS

Because NovoLog Mix 70/30 has peak pharmacodynamic activity one hour after injection, it should be administered with meals.

NovoLog Mix 70/30 should not be administered intravenously.

NovoLog Mix 70/30 is not to be used in insulin infusion pumps.

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

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

## PRECAUTIONS

### General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog Mix 70/30 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level)

Fixed ratio insulins are typically dosed on a twice daily basis, i.e. before breakfast and supper, with each dose intended to cover two meals or a meal and snack (see DOSAGE AND ADMINISTRATION). Because there is diurnal variation in insulin resistance and endogenous insulin secretion, variability in the time and content of meals, and variability in the time and extent of exercise, fixed ratio insulin mixtures may not provide optimal glycemic control for all patients. 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 (e.g. pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed 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.

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

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**Hypoglycemia**-As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog Mix 70/30. Rapid changes in serum glucose concentrations 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.

**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.

**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.

***Allergy***-
Local Reactions- Erythema, swelling, and pruritus at the injection site have been observed with NovoLog Mix 70/30 as with other insulin therapy. 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.

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. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

**Antibody production**-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. 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 HbA1c 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.

**Information for patients**-
Patients should be informed about potential risks and advantages of NovoLog Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.

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Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog Mix 70/30 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

*Laboratory Tests*- The therapeutic response to NovoLog Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

*Drug Interactions* A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), sulfonamide antibiotics.

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

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

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

**Mixing of insulins**
NovoLog Mix 70/30 should not be mixed with any other insulin product.

**Carcinogenicity, Mutagenicity, 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 for NovoLog® was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog® was not genotoxic in the following tests: Ames test,

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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.

**Pregnancy: Teratogenic Effects: Pregnancy Category C:**
Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, reproductive toxicology 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.

It is not known whether NovoLog Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog® in pregnant women. NovoLog Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nursing mothers*-It is unknown whether NovoLog Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog® in lactating women.

*Pediatric Use*-Safety and effectiveness of NovoLog Mix 70/30 in children have not been established.

*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.

**ADVERSE REACTIONS**

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Clinical trials comparing NovoLog Mix 70/30 with Novolin® 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.
Adverse events commonly associated with human insulin therapy include the following:

**Body as whole**: *allergic reactions* (see PRECAUTIONS, Allergy).
**Skin and Appendages**: *Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog Mix 70/30 and 5% on Novolin® 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug.* (see PRECAUTIONS, Allergy).
**Hypoglycemia:** see WARNINGS and PRECAUTIONS.
**Other**: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog® controlled clinical trials. There have been no clinical consequences of these laboratory findings.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

General:
Fixed ratio insulins are typically dosed on a twice daily basis, i.e. before breakfast and supper, with each dose intended to cover two meals or a meal and snack. NovoLog Mix 70/30 is intended only for subcutaneous injection (into the abdominal wall, thigh, or upper arm). NovoLog Mix 70/30 should not be administered intravenously. The absorption rate of NovoLog Mix 70/30 from the subcutaneous tissue allows dosing within 15 minutes of meal initiation.

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 metabolic needs, eating habits, and other lifestyle variables. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity and conditioning.

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Table 2 Summary of pharmacodynamic properties of insulin products (pooled cross-study comparison) and recommended interval between dosing and meal initiation

| *Insulin Products* | *Dose (U/kg) Used in Study* | *Recommended interval between dosing and meal initiation (minutes)** | *Time of Peak Activity (hours after dosing) (mean± SD)* | Percent of Total Activity Occurring in the First 4 hours *(mean, range)* |
|---|---|---|---|---|
| NovoLog® | 0.3 | 10-20 | 2.2 ± 0.98 | 65% ± 11% |
| Novolin® R | 0.2 | 30 | 3.3 | 60% ± 16% |
| Novolin® 50/50 | 0.5 | 30 | 4.0 ± 0.6 | 54% ± 12% |
| NovoLog Mix 70/30 | 0.3 | 10-20 | 2.4 ± 0.80 | 45% ± 22% |
| Novolin® 70/30 | 0.3 | 30 | 4.2 ± 0.39 | 25% ± 5% |
| Novolin® N | 0.3 | -n/a | 8.0 ~~+/-~~ ±5.3 | 21% ~~+/-~~ ±11% |

*Applicable only to Novolin® R and NovoLog® alone or as components of insulin mixes.

**Administration using pens and NovoLog Mix 70/30 prefilled syringes::**

*PenFill® Cartridges for 3 mL PenFill® cartridge compatible delivery devices**: NovoLog Mix 70/30 PenFill® suspension should be visually inspected and resuspended immediately before use. The resuspended liquid must appear uniformly white and cloudy. Before insertion into the insulin delivery system, roll the cartridge between your palms 10 times. Thereafter, turn the cartridge upside down so that the glass ball moves from one end of the cartridge to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the liquid appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the 3 mL PenFill® cartridge compatible delivery devices* upside down so that the glass ball moves from one end of the cartridge to the other. Repeat this 10 times until the liquid appears uniformly white and cloudy. Inject immediately. **After use, needles on the insulin pen delivery devices should not be recapped**. ~~*(see HOW SUPPLIED)~~

* NovoLog Mix 70/30 PenFill® cartridges are for use with the following 3 mL PenFill® cartridge compatible delivery devices: NovoPen® 3, Innovo®, and InDuo™.

*Disposable NovoLog Mix 70/30 FlexPen™ Prefilled Syringes*:
NovoLog Mix 70/30 suspension should be visually inspected and resuspended immediately before use. The resuspended liquid must appear uniformly white and cloudy. Before use, roll the disposable NovoLog Mix 70/30 FlexPen prefilled syringe between your palms 10 times. Thereafter, turn the disposable NovoLog Mix 70/30 FlexPen prefilled syringe 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 liquid appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the disposable NovoLog Mix 70/30 FlexPen Prefilled® syringe upside down

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so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the liquid appears uniformly white and cloudy. Inject immediately. **After use, needles on the disposable NovoLog Mix 70/30 FlexPen prefilled syringes should not be recapped.**

**HOW SUPPLIED**

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

3 ~~ml~~ mL PenFill® cartridges* NDC xxxx-xxxx-xx
3 mL NovoLog® Mix 70/30 FlexPen® Prefilled Syringe NDC xxxx-xxxx-xx

* NovoLog Mix 70/30 PenFill® cartridges are for use with the following 3 mL PenFill® cartridge compatible delivery devices: NovoPen® 3, Innovo®, and InDuo™.

**RECOMMENDED STORAGE**

NovoLog Mix 70/30 should be stored between 2 and 8°C (36° to 46°F). *Do not freeze*. **Do not use NovoLog Mix 70/30 if it has been frozen**.

***PenFill® cartridges or NovoLog Mix 70/30 FlexPen™ Prefilled syringes:***

Once a cartridge or a NovoLog Mix 70/30 FlexPen® prefilled syringe is punctured, it may be used for up to 14 days if it is kept at room temperature below 30°C (86°F). Cartridges or NovoLog Mix 70/30 FlexPen® prefilled syringes in use must NOT be stored in the refrigerator. ~~.~~ Keep all PenFill® cartridges and disposable NovoLog® Mix 70/30 FlexPen® Prefilled syringes away from direct heat and sunlight. Unpunctured PenFill® cartridges and NovoLog Mix 70/30 FlexPen® Prefilled syringes can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused PenFill® cartridges and NovoLog® Mix 70/30 FlexPen® Prefilled syringes in the carton so they will stay clean and protected form light.

Rx Only.

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

Manufactured for:
Novo Nordisk Pharmaceuticals, Inc.

**NovoLog Mix 70/30**
**(70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)**

Princeton, NJ 08540

www.novonordisk-us.com

Add circular number

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/s/

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David Orloff

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