CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-172

Final Printed Labeling

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:

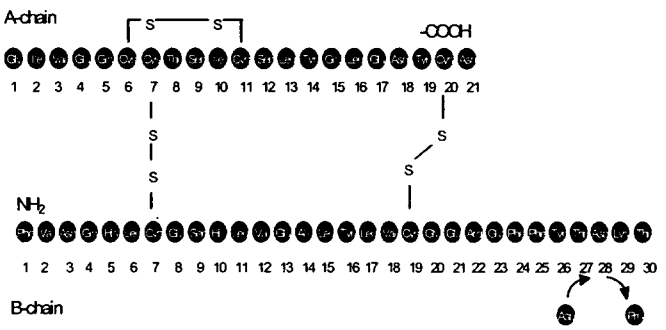

Figure 1. Structural formula of insulin aspart

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 32.7µg/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.

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).

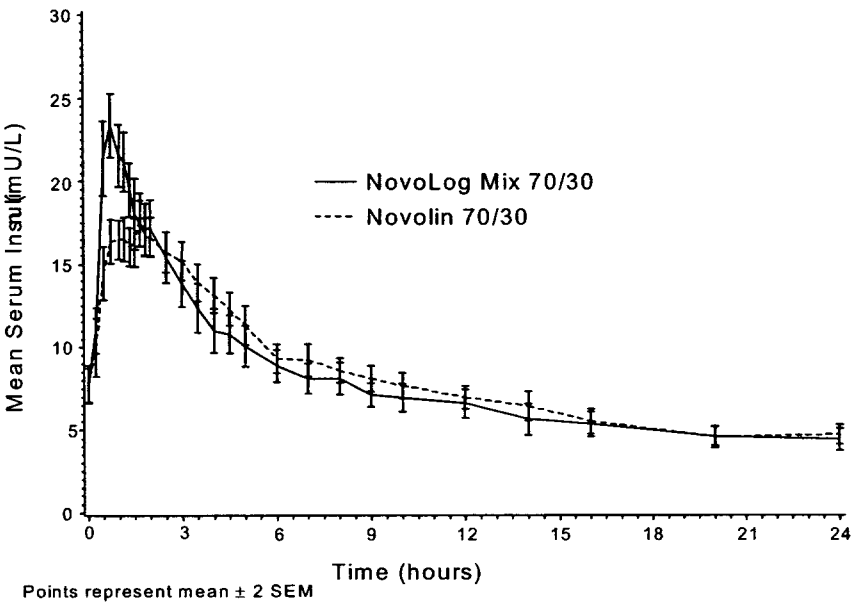

Figure 2. Pharmacokinetic Profiles of NovoLog Mix 70/30 and Novolin® 70/30

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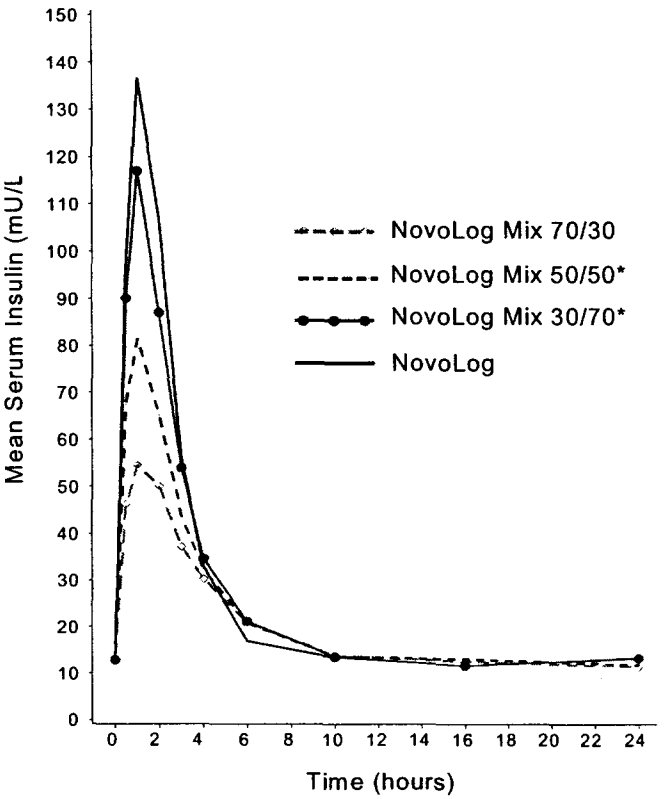

Figure 3 Pharmacokinetic profiles for NovoLog Mix 70/30 and other proportional mixes (* investigational drugs, not marketed).

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.

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).

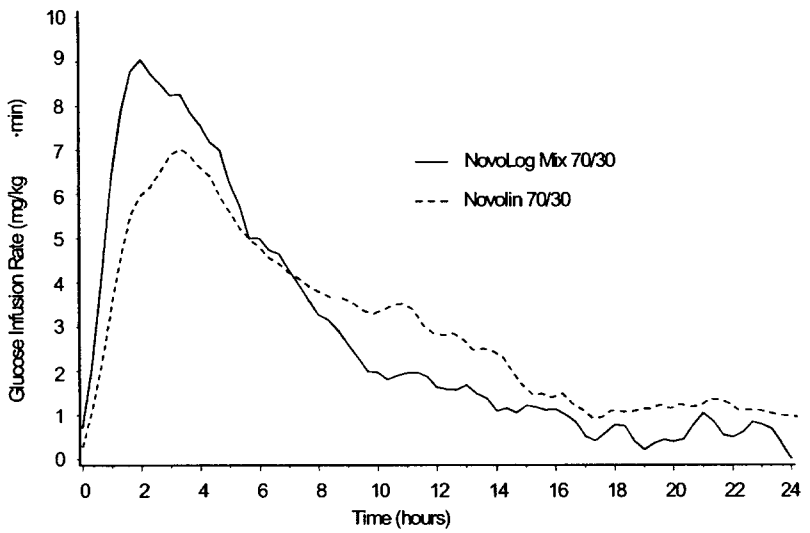

Fig 4: Pharmacodynamic Activity Profile of NovoLog Mix 70/30 and Novolin 70/30 in healthy subjects.

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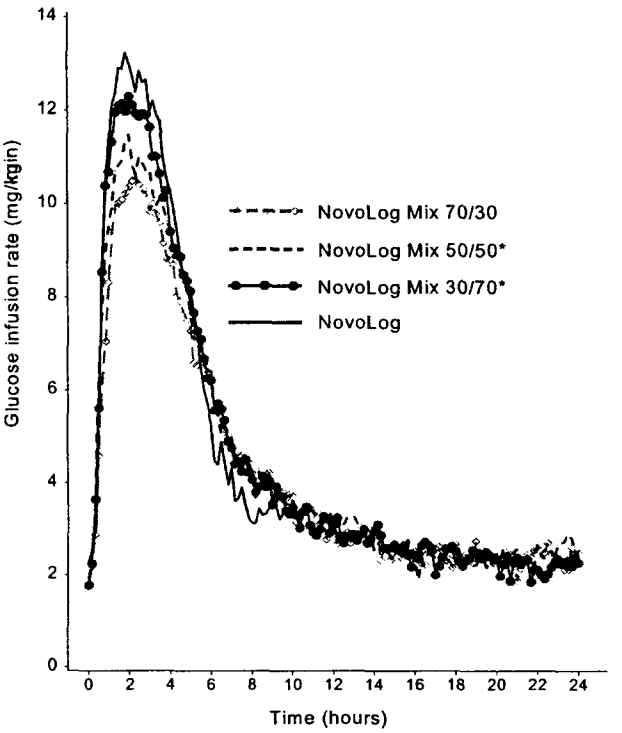

Figure 5. Pharmacodynamic Activity Profiles for NovoLog Mix 70/30 and other proportional mixes (* investigational drugs, not marketed)

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).

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.

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.

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.

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, 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

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.

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 (hoursafter 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, prefilled syringes, and vials:
PenFill® Cartridges for3 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)

Disposable NovoLog 70/30 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 prefilled syringe between your palms 10 times. Thereafter, turn the disposable 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 Prefilled® syringe upside down 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 prefilled syringes should not be recapped.**

Vial: NovoLog Mix 70/30 vial must be resuspended immediately before use. Roll the vial gently 10 times in your hand to mix it. The resuspended liquid must appear uniformly white and cloudy.

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).

10 ml vials	NDC xxxx-xxxx-xx
3 ml PenFill® cartridges*	NDC xxxx-xxxx-xx
3 ml NovoLog Mix 70/30 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**. Once a cartridge is punctured, it may be used for up to 14 days if it is kept at room temperature below 30°C (86°F). Cartridges in use must not be stored in the refrigerator. Vials in use may be used for up to 28 days if kept at room temperature below 30°C (86°F).

The cartridge or vial in use should not be exposed to excessive heat or sunlight. Unpunctured cartridges or vials can be used until the expiration date printed on the label.

Rx Only.

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

Manufactured for:
Novo Nordisk Pharmaceuticals, Inc.
Princeton, NJ 08540

www.novonordisk-us.com

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Final
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AP: 11/01/01

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

What is the most important information I should know about NovoLog Mix 70/30?

WARNINGS

THIS NOVO NORDISK® HUMAN INSULIN ANALOG MIXTURE IS DIFFERENT FROM OTHER INSULIN MIXTURES IN THAT ITS ONSET OF ACTION IS VERY QUICK. THE QUICK ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF NOVOLOG MIX 70/30 (70% INSULIN ASPART [rDNA ORIGIN] PROTAMINE SUSPENSION AND 30% INSULIN ASPART [rDNA ORIGIN] INJECTION) WITHIN 15 MINUTES OF A MEAL.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF NOVOLOG MIX 70/30.

PATIENTS TAKING NOVOLOG MIX 70/30 MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

What is NovoLog Mix 70/30?

NovoLog Mix 70/30 (NO-voe-log-MIX-SEV-en-tee-THIR-tee) is a mixed insulin analog similar to human insulin mixes used to treat diabetes. The active ingredient in NovoLog Mix 70/30 is insulin aspart, which is made through biotechnology. Another ingredient, protamine, is used to slow the absorption of the insulin analog by your body.

NovoLog Mix 70/30 comes in:

- 10 ml vials (small bottles) for use with a syringe
- 3ml PenFill® cartridges for use with 3 mL PenFill® cartridge compatible delivery devices* (see **3mL PenFill® cartridge compatible delivery devices section**)
- 3 ml NovoLog Mix 70/30 Prefilled syringe

Who should not take NovoLog Mix 70/30?

Do not take NovoLog Mix 70/30 if:

- Your blood sugar is too low (hypoglycemia).

- You are allergic to NovoLog Mix 70/30 or any of its ingredients. Check with your doctor or pharmacist if you want information about ingredients.
- You are not planning to eat within 15 minutes of your injection.

Tell your doctor if:

- **You have liver or kidney problems.** Your dose may need to be changed.
- **You are pregnant or planning to become pregnant.** It is not known whether NovoLog Mix 70/30 can cause any harm to the baby if it is taken during pregnancy.
- **You are breast-feeding or planning to breast-feed.** It is not known whether NovoLog Mix 70/30 is passed through in human milk as is human insulin. Many drugs, including human insulin, are present in human milk, and may affect the baby.
- **You take any other medicines**, including prescription and non-prescription medicines and herbal supplements. Your NovoLog Mix 70/30 needs may change if you take other medicines. Be sure to mention if you take the following:
  - oral hypoglycemic medicines (medicines you take by mouth to treat non insulin-dependent [Type 2] diabetes)
  - monoamine oxidase (MAO) inhibitors (used to treat depression)
  - some beta-blocking agents (used to treat certain heart conditions or high blood pressure)
  - angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions, or high blood pressure)
  - salicylates, including aspirin (used to relieve pain ~~and~~ or lower fever)
  - anabolic steroids and glucocorticoids
  - oral contraceptives (used for birth control)
  - diuretics such as thiazides (used to treat high blood pressure or swelling [edema])
  - thyroid hormones (used to treat thyroid gland problems)
  - danazol (used to treat endometriosis)
  - octreotide (used to treat gigantism or other rare endocrine tumors)
  - sulfa antibiotics (used to treat infections)

How should I take NovoLog Mix 70/30?

- Follow your doctor's instructions about monitoring your blood sugar.
- Before injecting, make sure that you have the correct type and strength of insulin. Carefully follow the instructions on how to use your insulin syringe or pen
- **Inject your NovoLog Mix 70/30 fifteen-minutes or less before a meal.**
- Inject NovoLog Mix 70/30 under your skin (subcutaneously). Never inject it into a vein.
- The effect of an injected insulin dose may occur faster if the insulin is injected into your abdomen (stomach area). However, you may also inject under the skin of your thigh, or upper arm.
- Change (rotate) injection sites within the same body area.
- Measure your blood sugar level as directed by your doctor.

- Carefully follow the instructions given by your doctor about the type of insulin you are using, its dose, and time of its injection. Any change in insulin should be made cautiously and only with your doctor's guidance. Your insulin needs may change due to a number of factors, such as illness, stress, medicines, or changes in diet or exercise routines. Follow your doctor's instructions to make these changes in your dose regimen.
- Clean your hands and the injection site with soap and water or with alcohol before you start the injection process.

See the end of this patient information for instructions about preparing and giving the injection.

What should I do during illness?

Even if you have a short term (acute) illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups. If you can, eat small amounts of bland foods. Test your urine for glucose and ketones and, if possible, test your blood glucose. Note the results and contact your health care provider for possible insulin dose adjustment. If you have severe and continued vomiting, get emergency medical care.

What should I avoid while taking NovoLog Mix 70/30?

Alcohol, including beer and wine, may increase and lengthen the risk of hypoglycemia (too low blood sugar) when you take NovoLog Mix 70/30.

Be careful when you drive a car or operate machinery. Your ability to concentrate or react may be reduced if you have hypoglycemia. Ask your doctor if you should drive if you have:

- frequent hypoglycemia
- reduced or absent warning signs of hypoglycemia

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What are the possible side effects of NovoLog Mix 70/30?

Common side effects include blood sugar that is too low (hypoglycemia).
Hypoglycemia (too little glucose in the blood) is one of the most frequent problems experienced by insulin users. It can be brought about by:

1. Missing or delaying meals.
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or kidney or liver disease that is getting worse
7. Interactions with other drugs that lower blood glucose, such as oral (taken by mouth) antidiabetic medicines, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants
8. Drinking of alcohol

What are symptoms of **mild to moderate** hypoglycemia:

- Sweating
- Dizziness
- Palpitation (fast heart beat)
- Tremor (shakiness)
- Hunger
- Restlessness
- Tingling in the hands, feet, lips, or tongue
- Lightheadedness
- Trouble concentrating
- Headache
- Drowsiness
- Sleep problems
- Anxiety
- Blurred vision
- Slurred speech
- Depressed mood
- Irritability
- Abnormal behavior
- Unsteady movement
- Personality change

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What are symptoms of **severe** hypoglycemia:

- Disorientation
- Unconsciousness
- Seizures (convulsions)
- Death

Get medical help right away, if you develop serious hypoglycemic reactions.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More sever hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility. You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that your experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Common side effects include blood sugar that is too high (hyperglycemia) and diabetic ketoacidosis.

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by any of the following:

1. Not taking your insulin or taking less than the doctor has prescribed
2. Eating much more than your meal plan suggests
3. Developing a fever, infection, or being under stress

In patients with type 1 or insulin-dependent diabetes, long-lasting hyperglycemia can cause diabetic ketoacidosis (DKA). The first symptoms of DKA usually come on slowly, over a period of hours or days, and include feeling drowsy, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, long-lasting hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of consciousness, or even death. Therefore, it is important that you obtain medical help right away.

Other possible side effects include the following:

- **Serious allergic reaction.**
  Get medical help right away if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating. These are signs of a dangerous allergic reaction (systemic allergic reaction). These reactions are not common.

- **Reaction at the injection site** (local allergic reaction). You may get redness, swelling and itching at the injection site. If you have serious or continuing reactions, you may need to stop using NovoLog Mix 70/30 and use another insulin. Do not inject insulin into skin sites with these reactions. No type of insulin should be injected into skin sites with these reactions.

- **Skin thickens or pits at the injection site**, especially if the injection site is not rotated (changed).

- **Vision changes** that may require evaluation by an ophthalmologist (medical doctor specializing in eye disease) or changes in your eyeglasses or contact lens prescription.

- **Fluid retention or swelling of your hands and feet.**

- **Low potassium in your blood** (hypokalemia)

There are other possible side effects from NovoLog Mix 70/30. Ask your doctor or pharmacist for further information. Tell your doctor or pharmacist if you have any other unwanted effects that you believe are caused by this insulin.

How should I store NovoLog Mix 70/30?

- **Unused insulin:**
  Store insulin in a refrigerator (36°F – 46°F; 2°C – 8°C), but not in the freezer. Do not use NovoLog Mix 70/30 if it has been frozen. Keep unused NovoLog Mix 70/30 Prefilled syringes, PenFill® cartridges and vials in the carton so they will stay clean and protected from light.
- **After starting to use the insulin:**
  Do not refrigerate disposable NovoLog Mix 70/30 Prefilled syringes, or PenFill® cartridges in use (the seal has been punctured). However, keep them as cool as possible (below 30°C [86°F]). The vials should be stored in a refrigerator not in a freezer. If refrigeration is not possible, the bottle that you are currently using can be kept unrefrigerated at room temperature up to 28 days, as long as it is kept as cool as possible. Keep all PenFill® cartridges, disposable NovoLog Mix 70/30 Prefilled syringes, and vials away from direct heat and sunlight.
- **Throw away unrefrigerated disposable NovoLog Mix 70/30 Prefilled syringes, and PenFill® cartridges after 14 days, even if they still contain insulin. Throw away unrefrigerated vials after 28 days, even if they still contain insulin.**

General information about NovoLog Mix 70/30

Use NovoLog Mix 70/30 only to treat your diabetes. **Do not** give it to any other person. Ask your doctor or pharmacist about any concerns you have. They can answer your questions and give you written information about NovoLog Mix 70/30 written for health care professionals.

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How should I prepare and deliver the injection using different delivery devices?

Using the 10 ml vial:

1. At your first use, remove the tamper-resistant cap of the vial. If the cap has already been removed, do not use this vial and return it to your pharmacy.
2. Wipe the rubber stopper with an alcohol swab.
3. Roll the vial gently 10 times in your hands to mix it. Do not shake it vigorously. Vigorous shaking right before the dose is drawn into the syringe may cause bubbles or froth, which could cause dosage errors. The insulin should be used only if it uniformly appears white and cloudy.
4. Pull back the plunger until the black tip reaches the marking for the number of units you will inject.
5. Push the needle through the rubber stopper into the vial.
6. Push the plunger all the way in. This inserts air into the vial.
7. Turn the vial and syringe upside down together and slowly pull the plunger back to a few units beyond the correct dose.
8. If there are air bubbles, tap the syringe gently with your finger to raise the air bubbles to the needle. Then slowly push the plunger to the correct unit marking.
9. Lift the vial off the syringe.
10. Inject right away. If there is a delay after you rolled the vial, you will have to roll it again to remix the insulin.- (See injection instructions "How should I inject NovoLog Mix 70/30 with a syringe)
11. The syringe and insulin should be disposed of properly without recapping the needle.

Using the NovoLog Mix 70/30 3mL PenFill® cartridge in 3 mL PenFill® cartridge compatible delivery devices*or the NovoLog Mix 70/30 3 mL Prefilled syringe (*see 3 mL PenFill® cartridge compatible delivery devices section):

1. Read the specific instructions for use of the NovoLog Mix 70/30 3-mL Prefilled syringe and the instruction manuals for the 3 mL PenFill® cartridge compatible delivery devices* before the device is used.

2a. For PenFill® cartridge:
Before inserting the PenFill® cartridge in the 3 mL PenFill® cartridge compatible delivery devices*for the first time, roll the cartridge between your palms 10 times. Then turn the PenFill® cartridge up and down between positions a and b (see Diagram 1) so the glass ball moves from one end of the cartridge to the other. Do this at least 10 times. The procedure must be repeated until the insulin appears uniformly white and cloudy. Insert the PenFill® cartridge into the 3 mL PenFill® cartridge compatible delivery devices*and inject right away.

Diagram #1

2b. For disposable NovoLog Mix 70/30 Prefilled syringes:
Before using a disposable NovoLog Mix 70/30 Prefilled syringe for the first time, turn the disposable prefilled (syringe up and down between positions a and b (see Diagram 1) so that the glass ball moves from one end of the insulin reservoir to the other. Do this at least 10 times. This procedure must be repeated until the insulin appears uniformly white and cloudy.

3. Place the needle onto the 3 mL PenFill® cartridge compatible delivery devices* or disposable prefilled syringe immediately before use.

4. Airshots should be done prior to each injection (see "Preparing the disposable prefilled syringe").

5. Inject the insulin right away. If there is a delay after you mix the insulin and the injection, you will have to mix the insulin again before injecting the insulin. (See injection instructions "How should I inject NovoLog Mix 70/30 using a disposable prefilled syringe or 3 mL PenFill® cartridge compatible delivery devices*?" below.)

6. The needle should not be recapped to avoid needlesticks and should be disposed of after each injection.

After the first use of PenFill® cartridge or disposable prefilled syringe:

1a If the PenFill® cartridge is already in the 3 mL PenFill® cartridge compatible delivery devices*, it should be turned upside down between positions a and b (see Diagram 1), so that the glass ball moves from one end of the PenFill® cartridge to the other. Do this until the insulin appears uniformly white and cloudy.

1b If the disposable prefilled syringe is to be used for later injections, it should be turned upside down between positions a and b (see Diagram 1), so that the glass ball moves from one end of the insulin reservoir to the other. Do this until the insulin appears uniformly white and cloudy.

2. Airshots should be done prior to each injection (see Preparing the disposable prefilled syringe)
3 Inject right away. If there is a delay between mixing of the insulin and the injection, the insulin will need to be mixed again. (See injection instructions "How should I inject NovoLog Mix 70/30 with a syringe or disposable prefilled syringe or 3 mL PenFill® cartridge compatible delivery devices*?" below)
4. To avoid needlesticks, **do not** recap the needle. Throw away the needle safely after each injection.

How should I inject NovoLog Mix 70/30 insulin with a syringe or disposable prefilled syringe or 3 mL PenFill® cartridge compatible delivery devices*?

1. Pinch your skin between two fingers, push the needle into the skinfold, and push the plunger to inject the insulin under your skin. The needle should be perpendicular to the skin. This means the needle will be straight in.
2. Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.
3. If blood appears after you pull the needle from your skin, press the injection site lightly with a finger. Do not rub the area.

***3 mL PenFill® cartridge compatible delivery devices**
NovoPen® 3, Innovo®, InDuo™

Helpful information for people with diabetes is published by the American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314.

For information about NovoLog Mix 70/30 contact:
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Manufactured by
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DK-2880 Bagsvaerd, Denmark

License under U.S. Patent No. 5,618,913 and Des. 347,894

Date of Issue: October 31, 2001

Printed in USA

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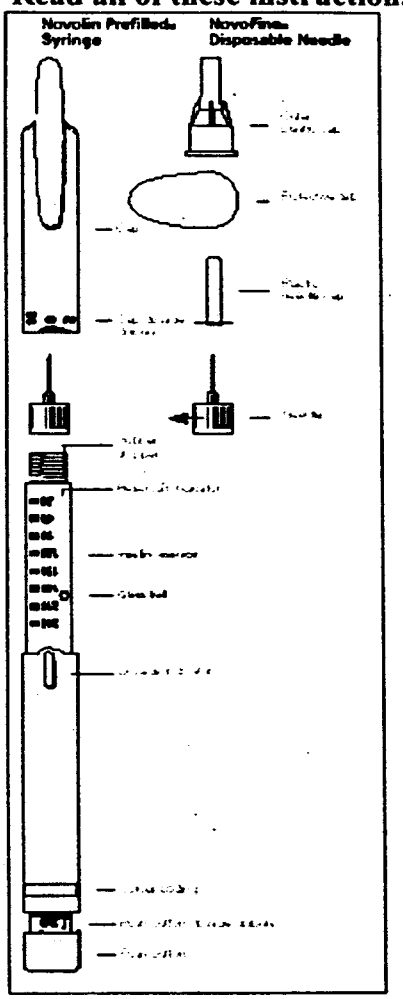
-Second page of the insert:

Using the disposable prefilled syringe:

This is a disposable dial-a-dose insulin delivery system that you can throw away. It can deliver 2-78 units in steps of 2 units. NovoLog Mix 70/30 Prefilled syringe is designed for use with NovoFine® single use disposable needles or other products specifically recommended by Novo Nordisk.

People who are blind or who cannot see well should use the disposable prefilled syringe only if they have help from someone trained to use the disposable prefilled syringe

Read all of these instructions before using the disposable prefilled syringe.



NovoLog Mix 70/30 Prefilled® syringe **NovoFine® Disposable Needle**

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1. PREPARING THE DISPOSABLE PREFILLED SYRINGE:

a Pull off the cap.

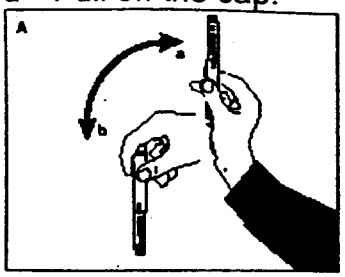

Diagram A

b To mix the insulin, turn the disposable prefilled syringe up and down between positions **a** and **b** (Diagram A) so the glass ball is moved from one end of the insulin reservoir to the other. Do this at least 10 times, until the insulin appears uniformly white and cloudy.

c Wipe the rubber stopper with an alcohol swab.

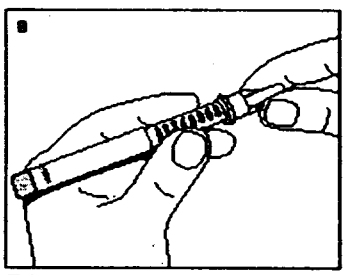

Diagram B

d Remove the protective tab from the disposable needle and screw the needle tightly onto the disposable prefilled syringe (Diagram B). Never place a disposable needle on your syringe until you are ready to give an injection. Remove the needle right after use without recapping. If the needle is not removed, some insulin may drip from the syringe, causing a change in insulin strength (concentration).

2. GIVING THE AIR SHOT BEFORE EACH INJECTION:

a Small amounts of air may collect in the needle and insulin reservoir during normal use. Remove both the plastic outer cap and the needle cap. To avoid injecting air and for proper dosing, hold the syringe with the needle pointing up and tap the syringe gently with your finger so any air bubbles collect in the top of the reservoir. See Diagram D below.

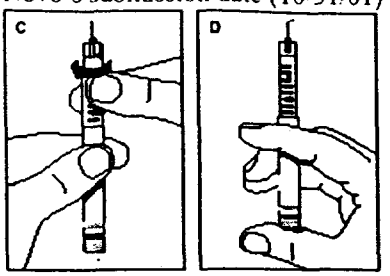

Diagram C

b Holding the syringe with the needle pointing up, slowly turn the insulin reservoir clockwise (in the direction of the arrow, see diagram. C) to the first notch where you feel resistance (1/5 of a full turn).(Diagram C)

c Still with the needle pointing up, press the push button as far as it will go and see if a drop of insulin appears at the needle tip (Diagram D).

Before the first use of the disposable prefilled syringe, you may need to perform up to 6 air shots to get a droplet of insulin at the needle tip. If you need to make more than 6 air shots, do not use the syringe, and contact Novo Nordisk® at 1-800-727-6500.

3. SETTING THE DOSE

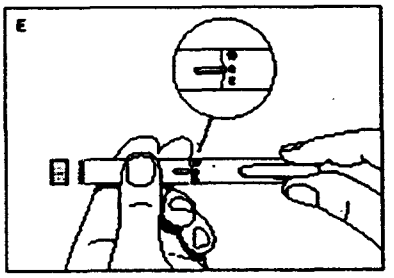

Diagram E

a Replace the cap, so **0** is opposite the dosage indicator. (Diagram E)

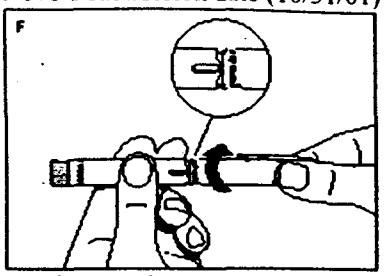

Diagram F

b Hold the syringe horizontally and turn the cap in the direction of the arrow to set the required dose. Do not put your hand over the push button when dialing the dose. If the button is not allowed to rise freely, insulin will be pushed out of the needle. The dosage display on the cap shows **0, 2, 4, 6, 8, 10, 12, 14, 16,** and **18** units. (Diagram F)

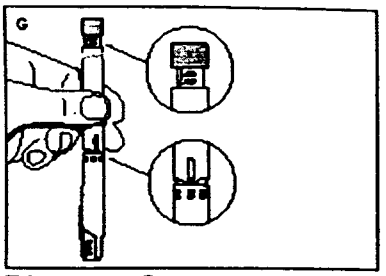

Diagram G

c As the cap is turned, the push button rises. The dosage display below the push button shows 20, 40 and 60 units (Diagram G). Every time you rotate the cap 360 degrees, 20 units are set to be delivered. A smaller amount of rotation will provide a smaller dose.

d To check the dose set, add the figure on the cap opposite the dosage indicator to the highest number showing on the push button display.

Dosage examples

- **8 units:**
  Turn the cap until **8** is opposite the dosage indicator.
- **26 units:**
  Turn the cap 1 full turn so **0** is opposite the dosage indicator. The 20-line will show on the push button scale. Continue turning until **6** is opposite the dosage indicator (see Diagram **G**).

If you have set a wrong dose, simply turn the cap forward or backwards until the right number of units has been set.

78 units is the highest dose. If you try to set a higher dose, insulin will be forced from the needle and the dose will be wrong. If you set more than 78 units, turn the cap back as far as you can until you feel resistance (it is harder to turn) and the push button is fully pushed in. If the dosage indicator is not lined up with **0** when you feel resistance, remove the cap and place it back on with **0** opposite the dosage indicator. Now start again, remembering that **78** units is the highest dose. After the dose is set, remove the cap.

4. GIVING THE INJECTION:

a Use the injection technique recommended by your doctor. Check that you have set the proper dose and after inserting the needle into your skin, push in the push button as far as it will go. When pushing the push button, you may hear a clicking sound. Do not rely on this clicking sound to set your dose. After injecting, unscrew the needle and throw it away properly **without** recapping the needle. Replace the cap with **0** opposite the dosage indicator.

For more information, see "How to inject NovoLog Mix 70/30 insulin" on the back of this *leaflet.*

5. LATER INJECTIONS:

a Always check that the push button is fully pushed in before using the syringe again. If it is not pushed in, turn the cap until the push button is completely down. Then follow steps 1-3.

b The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the syringe. Do not use these numbers to measure the insulin dose.

c You cannot set a dose greater than the number of units remaining in the reservoir.

6. IMPORTANT NOTES

NOVOLOG MIX 70/30 SHOULD NOT BE MIXED WITH ANY OTHER INSULIN PRODUCT.

- If you need to perform more than 6 airshots before the first use of NovoLog Mix 70/30 Prefilled™ syringe to get a droplet of insulin at the needle tip, do not use the syringe.

- Remember to perform an air shot before each injection. (diagrams B and C)

- Take care not to drop the syringe.

- Remember to keep the NovoLog Mix 70/30 Prefilled® syringe with you. Don't leave it in a car or other location where it can get too hot or too cold.

- NovoLog Mix 70/30 Prefilled® syringe is designed for use with NovoFine® disposable needles.

- Never place a disposable needle on this disposable prefilled syringe until you are ready to use it. Remove the needle right after use without recapping.

- **Throw away used needles properly, so other people will not be harmed.**

- Throw away the used syringe, without the needle attached.

- Always carry a spare NovoLog Mix 70/30 Prefilled® insulin syringe with you in case your prefilled syringe is damaged or lost.

Novo Nordisk is not responsible for harm due to using this insulin delivery system with products that are not recommended by Novo Nordisk.

- Keep this disposable prefilled syringe out of the reach of children.

Helpful information for people with diabetes is published by the American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314.

For information about NovoLog Mix 70/30 contact:

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

License under U.S. Patent No. 5,618,913 and Des. 347,894

Date of Issue: October 31, 2001

Printed in USA

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