

NovoLog[®] Mix 50/50

50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)

DESCRIPTION

NovoLog[®] Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]) is an insulin analog suspension containing 50% insulin aspart protamine crystals and 50% soluble insulin aspart. NovoLog[®] Mix 50/50 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 C₂₅₆H₃₈₁N₆₅O₇₉S₆ and a molecular weight of 5825.8 Da.

Structural formula:

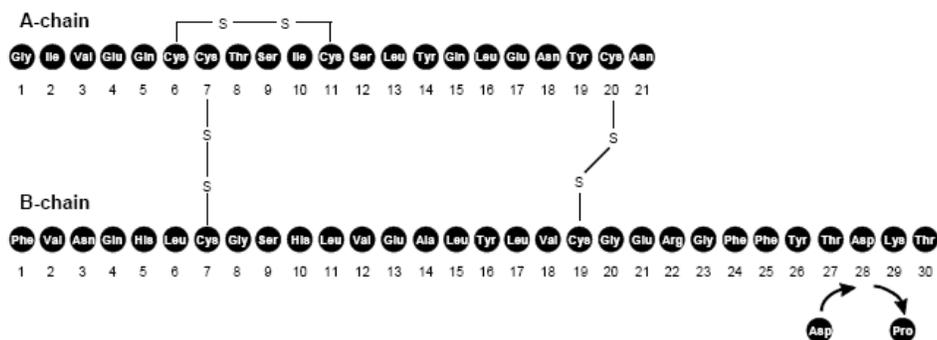


Figure 1. Structural formula of insulin aspart.

NovoLog[®] Mix 50/50 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/ml, 16 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 19.6 µg zinc, 1.25 mg disodium hydrogen phosphate dihydrate, 1.17 mg sodium chloride, and 0.23 mg protamine sulfate. NovoLog[®] Mix 50/50 has a pH of 7.10 – 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action

The primary activity of NovoLog[®] Mix 50/50 is the regulation of glucose metabolism. Insulin products including the insulin in NovoLog[®] Mix 50/50, 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 while simultaneously inhibiting the output of glucose from the liver.

In standard biological assays in mice and rabbits, one unit of NovoLog[®] (insulin aspart) has the same glucose-lowering effect as one unit of regular human insulin.

Pharmacokinetics

Bioavailability and Absorption

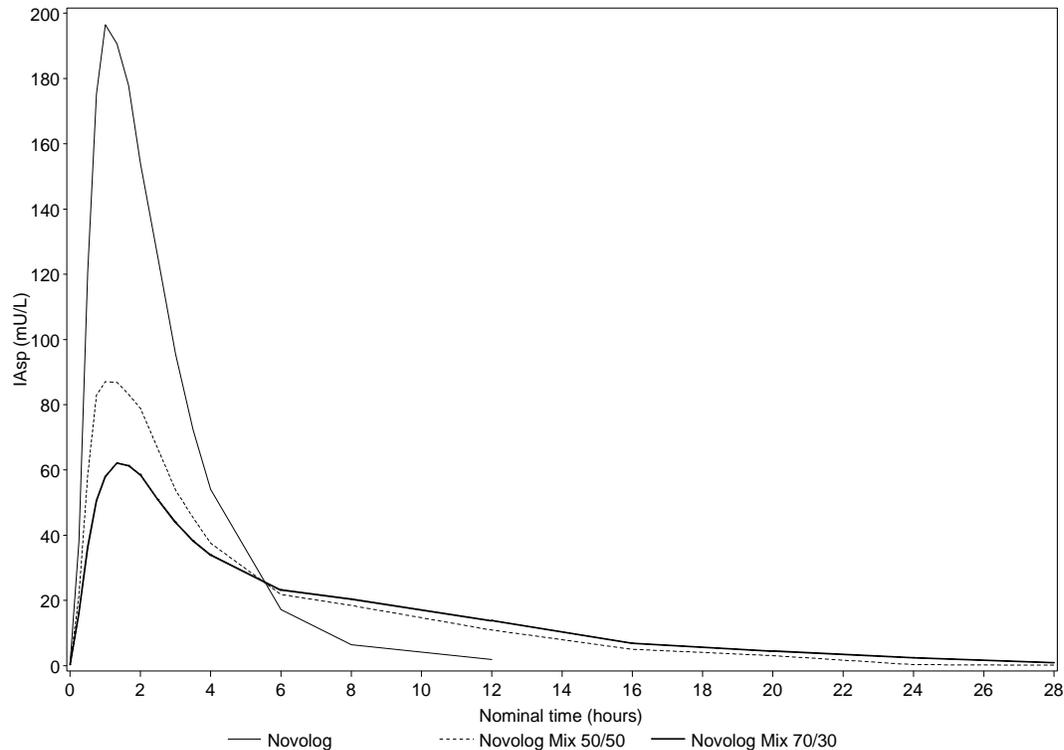
The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog[®]) reduces the molecule's tendency to form hexamers as observed with regular human insulin. This results in more rapid absorption from the subcutaneous spaces than seen with regular human insulin. The rapid absorption characteristics of NovoLog[®] are maintained by NovoLog[®] Mix 50/50, containing 50% insulin aspart in soluble form. The remaining 50% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

In an euglycemic clamp study in patients with type 1 diabetes (n=32) after dosing with 0.4 U/kg of NovoLog[®] Mix 70/30, 50/50, and NovoLog[®] on three different study days, a C_{max} of 98 ± 29 mU/L was reached after approximately 80 minutes for NovoLog[®] Mix 50/50 (See Table 1). There was diminishing distinction in pharmacokinetics between the two NovoLog Mix formulations at later time points (See Figure 2).

Table 1: Pharmacokinetic Parameters comparing NovoLog[®] Mix 50/50 to NovoLog[®] Mix 70/30 and NovoLog[®] in patients with Type 1 diabetes mellitus

| | NovoLog [®] Mix 50/50 versus NovoLog [®] Mix 70/30 | NovoLog [®] versus NovoLog [®] Mix 50/50 |
|---------------------|---|---|
| C _{max} | 1.49 [1.34; 1.65] | 2.04 [1.84; 2.26] |
| AUC _{0-2h} | 1.48 [1.35; 1.64] | 2.01 [1.82; 2.22] |

Values are expressed as mean ratios [95% confidence intervals]



x14/sun5070-us/current - 07SEP2007 - f_lda_sep_07_1746.sas/fda_sep_07/fda_sep_07_1746_iasp.cgm

Figure 2. Pharmacokinetic profiles of NovoLog[®] Mix 50/50, 70/30, and NovoLog[®] in Patients with Type 1 diabetes mellitus

The bioavailability of insulin aspart is decreased with increasing protamine sulfate concentration in any NovoLog[®] Mix formulation. Consequently, exposure of a subcutaneous dose of NovoLog[®] Mix 50/50 may be reduced in comparison to the comparable dose of insulin aspart (NovoLog[®]) and an intermediate insulin that are mixed by the patient prior to injection. No clinical studies have been conducted comparing NovoLog[®] Mix 50/50 to proportionate doses of insulin aspart (NovoLog[®]) and an intermediate-acting insulin that are mixed by the patient prior to injection. Switching to a regimen that contains a NovoLog[®] Mix formulation will require careful blood glucose monitoring to ensure adequacy of glycemic control and to avoid hypoglycemia.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). The influence of different injection sites on the absorption of NovoLog[®] Mix 50/50 has not been investigated.

Distribution and Elimination

NovoLog[®] Mix 50/50 is a biphasic insulin which contains 50% soluble insulin aspart. NovoLog[®] has a low binding to plasma proteins, 0 – 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.

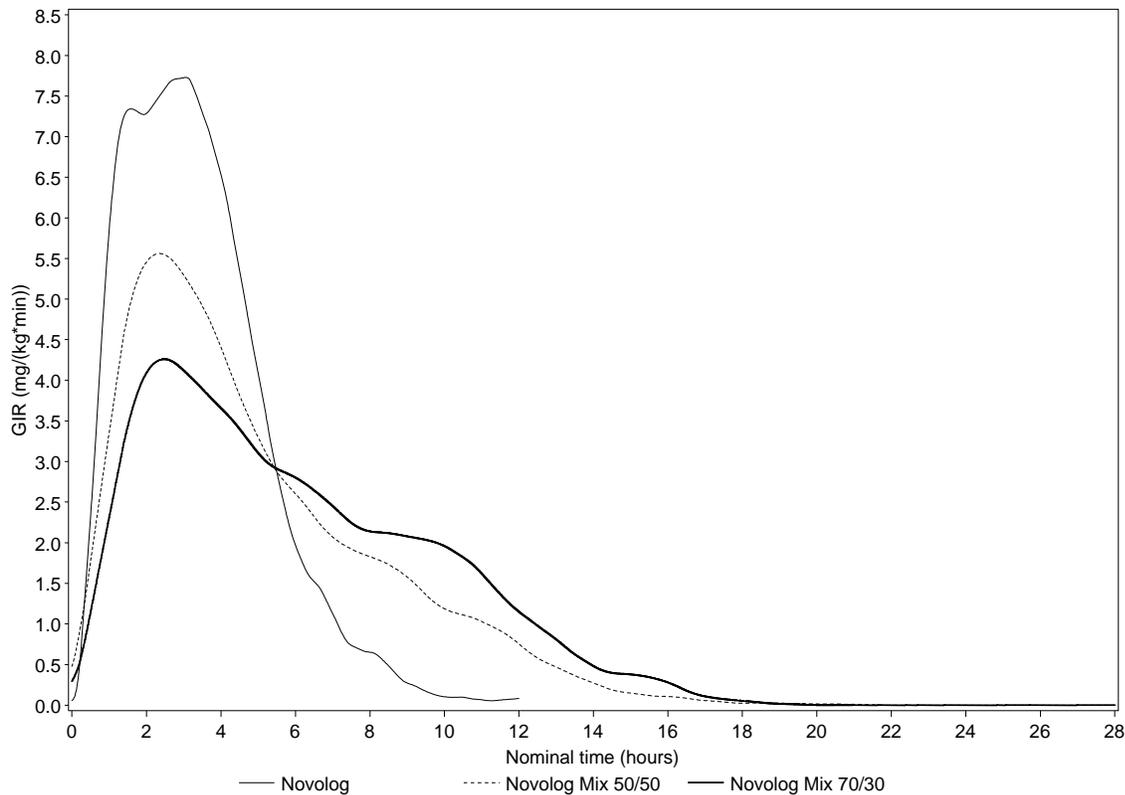
Pharmacodynamics

In an euglycemic clamp study in subjects with type 1 diabetes, a maximum glucose infusion rate (GIR_{max}) of 6.0 ± 1.7 mg/kg/min was reached after approximately 2.5 hours for NovoLog[®] Mix 50/50 (See Table 2). There was diminishing distinction in pharmacodynamics between the two NovoLog[®] Mix formulations at later time points (See Figure 3).

Table 2: Pharmacodynamic Parameters comparing NovoLog[®] Mix 50/50 to NovoLog[®] Mix 70/30 and NovoLog[®] in patients with Type 1 diabetes mellitus

| | NovoLog [®] Mix 50/50 versus NovoLog [®] Mix 70/30 | NovoLog [®] versus NovoLog [®] Mix 50/50 |
|-------------------------|---|---|
| GIR _{max} | 1.29 [1.17; 1.43] | 1.49 [1.35; 1.65] |
| AUC _{GIR,0-2h} | 1.52 [1.31; 1.78] | 1.44 [1.23; 1.67] |

Values are expressed as mean ratios [95% confidence intervals]



x14/sum5070-us/current - 07SEP2007 - f_fda_sep_07_1746.sas/fda_sep_07/f_fda_sep_07_1746_gir.cgm

Figure 3. Pharmacodynamic profiles of NovoLog[®] Mix 50/50, 70/30, and NovoLog[®] in patients with Type 1 diabetes mellitus

Special populations

Children and adolescents – The pharmacokinetic and pharmacodynamic properties of NovoLog[®] Mix 50/50 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 50/50 has not been studied.

Gender – The effect of gender on the pharmacokinetics and pharmacodynamics of NovoLog[®] Mix 50/50 has not been studied.

Obesity – The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of NovoLog[®] Mix 50/50 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 50/50 has not been studied.

Renal impairment – The effect of renal function on the pharmacokinetics and pharmacodynamics of NovoLog[®] Mix 50/50 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 50/50 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 50/50 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 50/50, 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 50/50 has not been studied (see PRECAUTIONS, Pregnancy).

Smoking – The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoLog[®] Mix 50/50 has not been studied.

INDICATIONS AND USAGE

NovoLog[®] Mix 50/50 is indicated as an adjunct to diet and exercise to improve glycemic control in patients with diabetes mellitus.

CONTRAINDICATIONS

NovoLog[®] Mix 50/50 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog[®] Mix 50/50 or any of the excipients.

WARNINGS

Because NovoLog[®] Mix 50/50 has peak pharmacodynamic activity between 1 and 4 hours after injection, it should be administered with meals.

NovoLog[®] Mix 50/50 should not be administered intravenously.

NovoLog[®] Mix 50/50 is not to be used in insulin infusion pumps.

NovoLog[®] Mix 50/50 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog[®] Mix 50/50. 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, premixed), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Fluid retention and heart failure with concomitant use of PPAR gamma agonists: Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including NovoLog[®] Mix 50/50, and a PPAR-gamma antagonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reductions of the PPAR-gamma agonist must be considered.

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 50/50 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). 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. 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.

Insulin may cause sodium retention and edema (swelling of hands and feet), particularly if previously poor metabolic control is improved by intensified insulin therapy. Lipodystrophy at the injection site 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 50/50. 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 50/50 in patients with diabetes with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog[®] Mix 50/50 may be reduced in patients with renal impairment.

Hepatic Impairment – Clinical or pharmacology studies with NovoLog[®] Mix 50/50 in patients with diabetes with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog[®] Mix 50/50 may be reduced in patients with hepatic impairment.

Allergy - Local reactions: Erythema, swelling, and pruritus at the injection site have been observed with 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 – Antibodies have not been extensively investigated during the clinical development of NovoLog[®] Mix 50/50. Antibodies specific to NovoLog[®] and cross-reactive with both NovoLog[®] and human insulin have been evaluated previously in connection with the clinical development of NovoLog[®]. In addition, specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial between NovoLog[®] Mix 70/30 and human pre-mixed insulin and NovoLog[®] as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog[®] Mix 70/30 than with human pre-mixed insulin but these changes did not correlate with change in HbA_{1c} 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 - Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetes complications. Patients should consult with their healthcare provider before using NovoLog[®] Mix 50/50 as a mealtime insulin; the decision should be based on the patient's insulin needs for that particular meal. Patients should be informed that alcohol, including beer and wine, may affect their blood sugar when taking NovoLog[®] Mix 50/50. Patients should be informed about potential

risks and advantages of NovoLog[®] Mix 50/50 therapy including the possible side effects. Patients should be informed that hypoglycemia may impair the ability to concentrate and react, which may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

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 dosage, 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 50/50 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

Laboratory Tests – The therapeutic response to NovoLog[®] Mix 50/50 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, 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).

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 50/50 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 50/50. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog[®], the rapid-acting component of NovoLog[®] Mix 50/50, 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:

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. Insulin mixtures, including NovoLog Mix 50/50, may be limited in their ability to provide near-normal glycemic control, as recommended during pregnancy. Careful monitoring of glucose control is essential in patients with diabetes during pregnancy.

It is not known whether NovoLog[®] Mix 50/50 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 50/50 in pregnant women.

Animal reproduction studies have not been conducted with NovoLog[®] Mix 50/50. However, reproductive toxicology and teratology studies have been performed with NovoLog[®] (the rapid-acting component of NovoLog[®] Mix 50/50) 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.

Nursing mothers - It is unknown whether NovoLog[®] Mix 50/50 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog[®] Mix 50/50 or NovoLog[®] in lactating women.

Pediatric Use - Safety and effectiveness of NovoLog[®] Mix 50/50 in children have not been established.

Geriatric Use - Safety and effectiveness of NovoLog[®] Mix 50/50 in geriatric population have not been studied. 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

During clinical trials the overall adverse event profile of NovoLog[®] Mix 50/50 was comparable to Novolin[®] 70/30. Adverse events commonly associated with human insulin therapy include the following:

Body as whole: *allergic reactions* (see PRECAUTIONS, Allergy).

Skin and Appendages: *Injection site reaction, lipodystrophy, pruritus, rash* (see PRECAUTIONS, Allergy).

Hypoglycemia: see WARNINGS and PRECAUTIONS.

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

The written prescription for NovoLog[®] Mix 50/50 should include the full name, to avoid confusion with NovoLog[®] (insulin aspart) and NovoLog[®] Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin).

NovoLog[®] Mix 50/50 should be administered within 15 minutes of meal initiation up to three times daily. It is intended only for subcutaneous injection into the abdominal wall, thigh, or upper arm. NovoLog[®] Mix 50/50 should not be administered intravenously.

No clinical studies have been conducted comparing NovoLog[®] Mix 50/50 to proportionate doses of insulin aspart (NovoLog[®]) and an intermediate-acting insulin that are mixed by the patient prior to injection. Initiating or switching to a regimen that contains a NovoLog[®] Mix formulation, as with any change in an insulin regimen, will require careful blood glucose monitoring to ensure adequacy of glycemic control and to avoid hypoglycemia.

Dose regimens of NovoLog[®] Mix 50/50 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.

Administration using PenFill[®] Cartridges for 3 mL PenFill[®] cartridge compatible delivery devices and NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes:

PenFill[®] Cartridges for 3 mL PenFill[®] cartridge compatible delivery devices*:

NovoLog[®] Mix 50/50 PenFill[®] suspension should be visually inspected and resuspended immediately before use. The resuspended NovoLog[®] Mix 50/50 must appear uniformly white and cloudy. Before inserting the cartridge into the insulin delivery system, roll the cartridge between your palms 10 times.

The cartridge should be kept horizontal while rolling. 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 suspension appears uniformly white and cloudy. Mixing is easier when the insulin has reached room temperature. 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 at least 10 times until the suspension appears uniformly white and cloudy. Inject immediately.

Always remove the needle after each injection and store the 3 mL PenFill[®] cartridge compatible delivery device without a needle attached. This prevents contamination and/or infection, entry of air into the insulin reservoir, or leakage of insulin and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination. Used needles or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

*NovoLog[®] Mix 50/50 PenFill[®] cartridges are designed for use with Novo Nordisk 3 mL PenFill[®] cartridge compatible insulin delivery devices, with or without the addition of a NovoPen[®] 3 PenMate[®], and NovoFine[®] disposable needles.

Disposable NovoLog[®] Mix 50/50 FlexPen[®] Prefilled Syringes:

NovoLog[®] Mix 50/50 suspension should be visually inspected and resuspended immediately before use. The resuspended NovoLog[®] Mix 50/50 must appear uniformly white and cloudy. Before use, roll the disposable NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe between your palms 10 times. This procedure should be carried out with the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe in a horizontal position. Thereafter, turn the disposable NovoLog[®] Mix 50/50 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 suspension appears uniformly white and cloudy. Mixing is easier when the insulin has reached room temperature. Inject immediately. Before each subsequent injection, turn the disposable NovoLog[®] Mix 50/50 FlexPen[®] 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 suspension appears uniformly white and cloudy. Inject immediately.

Always remove the needle after each injection and store the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled Syringe without a needle attached. This prevents contamination and/or infection, entry of air into the insulin reservoir, or leakage of insulin and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination. Used needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

HOW SUPPLIED

NovoLog[®] Mix 50/50 is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).

| | |
|--|------------------|
| 3 mL PenFill [®] cartridges* | NDC 0169-3672-12 |
| 3 mL NovoLog [®] Mix 50/50 FlexPen [®] Prefilled Syringe | NDC 0169-3676-19 |

* NovoLog[®] Mix 50/50 PenFill[®] cartridges are designed for use with Novo Nordisk 3 mL PenFill[®] cartridge compatible insulin delivery devices, with or without the addition of a NovoPen[®] 3 PenMate[®], and NovoFine[®] disposable needles.

RECOMMENDED STORAGE

Unused NovoLog[®] Mix 50/50 should be stored in a refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze or use NovoLog[®] Mix 50/50 if it has been frozen.**

PenFill[®] cartridges or NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes:

Once a cartridge or a NovoLog[®] Mix 50/50 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 50/50 FlexPen[®] Prefilled syringes in use should not be stored in the refrigerator. Keep all PenFill[®] cartridges and NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes away from direct heat and light.

Unpunctured PenFill[®] cartridges and NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes can be used until the expiration date printed on the label if they are stored in a refrigerator. After removing NovoLog[®] Mix 50/50 PenFill[®] cartridges or NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes from the refrigerator it is recommended to let the PenFill[®] cartridges or NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe reach room temperature before resuspending the insulin as recommended for first time use. Keep unused PenFill[®] cartridges and NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringes in the carton so they 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°-8° C [36° to 46°F]) | In-use (opened) Room Temperature (at or below 30°C [86°F]) |
|--------------------------------------|---|---|---|
| 3 mL PenFill [®] cartridges | 14 days | Until expiration date | 14 days (Do not refrigerate) |

| | | | |
|---|---------|-----------------------|---------------------------------------|
| 3 mL NovoLog [®] Mix 50/50 FlexPen [®] | 14 days | Until expiration date | 14 days (Do not refrigerate) |
|---|---------|-----------------------|---------------------------------------|

Rx Only

Date of issue: XXX xx, XXXX

Version: X

NovoLog[®], FlexPen[®], Novolin[®] and NovoFine[®] are registered trademarks of Novo Nordisk A/S.

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NovoLog[®] Mix 50/50 is covered by US Patent Nos. 5,547,930, 5,618,913, 5,834,422, 5,840,680 and 5,866,538 and other patents pending.

PenFill[®] is covered by US Patent No. 5,693,027.

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

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

Manufactured for:
Novo Nordisk Inc.
Princeton, NJ 08540

www.novonordisk-us.com

Patient Information for NovoLog[®] Mix 50/50
NovoLog[®] Mix 50/50 (NO-vo-log-MIX-FIF-tee-FIF-tee)
(50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

Important:

Know your insulin. Do not change the type of insulin you take unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you have the type and strength of insulin prescribed for you.

Read this Patient Information that comes with NovoLog[®] Mix 50/50 before you start taking it and each time you get a refill. There may be new information since your last refill. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog[®] Mix 50/50?

NovoLog[®] Mix 50/50 is both a rapid-acting and long-acting man-made insulin.

NovoLog[®] Mix 50/50 comes in:

- 3 mL PenFill[®] cartridges.
- 3 mL NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe.

Only use NovoLog[®] Mix 50/50 if all of the medicine looks white and cloudy after you mix it (resuspension) (see “Patient Instructions for Use”). If your NovoLog[®] Mix 50/50 looks clear, do not use it and call Novo Nordisk at 1-800-727-6500.

Who should not take NovoLog[®] Mix 50/50?

Do not use NovoLog[®] Mix 50/50 if:

- Your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of NovoLog[®] Mix 50/50.
- You are allergic to anything in NovoLog[®] Mix 50/50. See the end of this leaflet for a complete list of ingredients in NovoLog[®] Mix 50/50. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

- **about all of your medical conditions.** Medical conditions can affect your insulin needs and your dose of NovoLog[®] Mix 50/50.
- **if you are pregnant or breast feeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog[®] Mix 50/50 has not been studied in pregnant or nursing women.

- **about all of the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines can affect your blood sugar levels and your insulin needs. Your NovoLog[®] Mix 50/50 dose may need to change if you take other medicines.
- **if you take any other medicines, especially ones commonly called TZDs (thiazolidinediones).**
- **if you have heart failure or other heart problems.** If you have heart failure, it may get worse while you take TZDs with NovoLog[®] Mix 50/50.

Know the medicines you take. Keep a list of your medicines with you to show all your healthcare providers.

How should I take NovoLog[®] Mix 50/50?

Read the instructions for use that come with your NovoLog[®] Mix 50/50 product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog[®] Mix 50/50 before you start taking it.

- **Take NovoLog[®] Mix 50/50 exactly as prescribed.** NovoLog[®] Mix 50/50 is injected right before a meal, up to three (3) times each day.
- **NovoLog[®] Mix 50/50 starts acting fast, so inject it up to 15 minutes before you eat a meal.** Do not inject NovoLog[®] Mix 50/50 if you are not planning to eat within 15 minutes.
- **Inject NovoLog[®] Mix 50/50 under the skin of your stomach area, upper arms, or upper legs.** NovoLog[®] Mix 50/50 may affect your blood sugar levels sooner if you inject it into the skin of your stomach area.
- **Change (rotate) sites with each dose. Although you can inject insulin in the same area, do not inject into the exact same spot for each injection.**
- **Check your blood sugar levels.** Ask your healthcare provider how often you should check your blood sugar levels for hypoglycemia (too low blood sugar) and hyperglycemia (too high blood sugar).
- **If you take too much NovoLog[®] Mix 50/50, your blood sugar may fall low (hypoglycemia).** You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See “What are the most common side effects of NovoLog[®] Mix 50/50?” for more information on low blood sugar (hypoglycemia).

- **If you forget to take your dose of NovoLog[®] Mix 50/50, your blood sugar may go too high (hyperglycemia).** High blood sugar (hyperglycemia) if not treated can lead to loss of consciousness (passing out), coma or even death. Symptoms of high blood sugar may include:
 - increased thirst
 - frequent urination
 - drowsiness
 - loss of appetite
 - fruity odor on the breath
 - high amounts of sugar and ketones in your urine
 - nausea, vomiting (throwing up), or abdominal pain
 - a hard time breathing

Follow your healthcare provider's instructions for treating high blood sugar, and talk to your healthcare provider if high blood sugar is a problem for you.

Your insulin dosage may need to change because of:

- illness
- stress
- other medicines you take
- change in food intake
- change in physical activity or exercise
- surgery

Follow your healthcare provider's instructions to make changes in your insulin dose.

- **Never mix NovoLog[®] Mix 50/50 with other insulin products.**
- **Never use NovoLog[®] Mix 50/50 in an insulin pump.**
- **Never inject NovoLog[®] Mix 50/50 into a vein.**

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

What are the most common side effects of NovoLog[®] Mix 50/50?

- **Low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:
 - sweating
 - dizziness or lightheadedness
 - shakiness
 - hunger
 - fast heart beat
 - tingling of lips or tongue
 - trouble concentrating or confusion
 - blurred vision
 - slurred speech
 - anxiety, irritability or mood changes
 - headache

Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog[®] Mix 50/50.

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

- frequent hypoglycemia
- reduced or absent warning signs of hypoglycemia

Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other possible side effects include:

- **Serious allergic reaction (whole body allergic reaction).** Get medical help right away if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **Reactions at the injection site (local allergic reaction).** You may get redness, swelling and itching at the injection site. If you keep having skin reactions or they are serious, you may need to stop taking NovoLog[®] Mix 50/50 and take a different insulin. Do not inject insulin into a skin area that is red, swollen, or itchy.
- **Skin thickens or pits at the injection site (lipodystrophy).** Change (rotate) where you inject your insulin to help prevent these skin changes from happening. Do not inject insulin into this type of skin.
- **Swelling of your hands and feet.**
- **Heart Failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with NovoLog[®] Mix 50/50 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with NovoLog[®] Mix 50/50. Your healthcare provider should monitor you closely while you are taking TZDs with NovoLog[®] Mix 50/50. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
 - shortness of breath
 - swelling of your ankles or feet
 - sudden weight gain

Treatment with TZDs and NovoLog[®] Mix 50/50 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

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

These are not all of the possible side effects from NovoLog[®] Mix 50/50. Ask your healthcare provider or pharmacist for more information.

How should I store NovoLog[®] Mix 50/50?

Unopened NovoLog[®] Mix 50/50:

- Keep all unopened NovoLog[®] Mix 50/50 in the refrigerator between 36° to 46° F (2° to 8° C). Do not store in the freezer or next to the refrigerator cooling element. **Do not freeze.**
- Keep unopened NovoLog[®] Mix 50/50 in the carton to protect from light.

After the package has been opened:

- Do not put NovoLog[®] Mix 50/50 that you are using in the refrigerator. Keep at room temperature at or below 86°F (30°C) for up to 14 days.
- Keep NovoLog[®] Mix 50/50 away from direct heat or light.
- Throw away used NovoLog[®] Mix 50/50 after 14 days of use, even if there is insulin left in the cartridge or syringe.

General information about NovoLog[®] Mix 50/50

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog[®] Mix 50/50 for a condition for which it was not prescribed. Do not give NovoLog[®] Mix 50/50 to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog[®] Mix 50/50. If you would like more information about NovoLog[®] Mix 50/50 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog[®] Mix 50/50 which is written for healthcare professionals. For more information, call 1-800-727-6500 or visit www.novonordisk-us.com.

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

What are the ingredients in NovoLog[®] Mix 50/50?

- | | |
|---------------------|--|
| ▪ insulin aspart | ▪ zinc |
| ▪ glycerol | ▪ disodium hydrogen phosphate dihydrate |
| ▪ phenol | ▪ sodium chloride |
| ▪ metacresol | ▪ hydrochloric acid and/or sodium hydroxide may be added |
| ▪ protamine sulfate | |

Date of Issue: XXXX xx, XXXX

Version: X

NovoLog[®], PenFill[®], FlexPen[®], NovoPen[®], NovoFine[®], PenMate[®], are registered trademarks of Novo Nordisk A/S.

NovoLog[®] Mix 50/50 is covered by US Patent Nos. 5,547,930, 5,618,913, 5,834,422, 5,840,680 and 5,866,538 and other patents pending.

PenFill[®] is covered by US Patent No. 5,693,027.

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

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

For information about NovoLog[®] Mix 50/50 contact:
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540

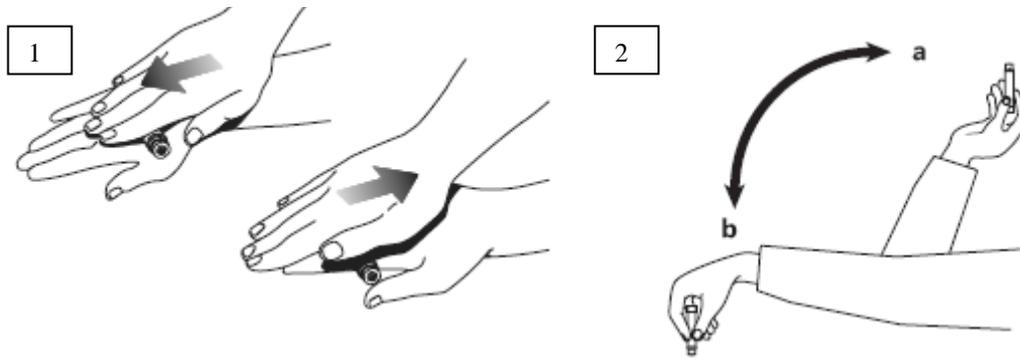
Patient Instructions for Use NovoLog[®] Mix 50/50 cartridge

Before using the NovoLog[®] Mix 50/50 cartridge

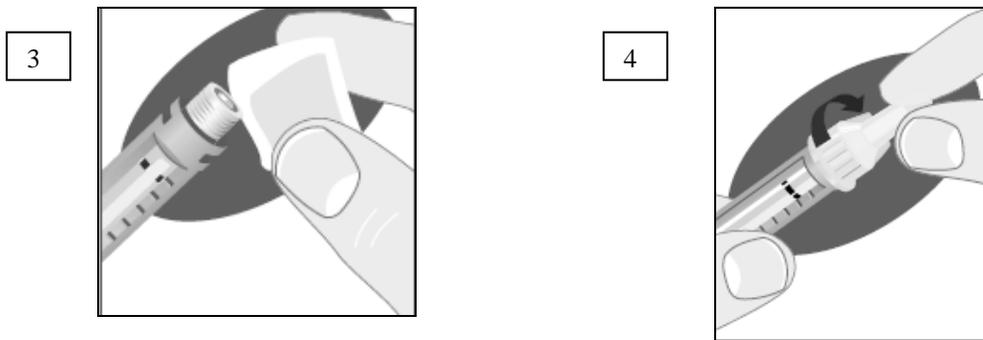
1. Talk with your healthcare provider to find out where to inject NovoLog[®] Mix 50/50 (injection sites) and how to give an injection with your insulin delivery device.
2. Read the instruction manual that comes with your insulin delivery device for complete instructions on how to use the PenFill[®] cartridge with the device.

How to use the NovoLog[®] Mix 50/50 cartridge

1. **Check your insulin.** Just before using your NovoLog[®] Mix 50/50 cartridge, check to make sure that you have the right type of insulin. This is especially important if you use different types of insulin.
2. **Carefully look at the cartridge and the insulin inside it.** The insulin should be white and cloudy (after being mixed). The tamper-resistant foil should be in place before the first use. If the foil has been broken or removed before your first use of the cartridge, or if the insulin is clear, do not use it. Call Novo Nordisk at 1-800-727-6500.
3. **Gather your supplies** for injecting NovoLog[®] Mix 50/50. You will need your NovoLog[®] Mix 50/50 PenFill[®] cartridge, your insulin delivery device, NovoFine[®] single use needles and an alcohol swab. Be sure to use an insulin delivery device that is made to work with NovoLog[®] Mix 50/50 PenFill[®] cartridges. These insulin delivery devices can be used with a NovoPen[®] 3 PenMate[®] if you would like to hide the needle from view during injection.
4. **Wash your hands** well with soap and water.
5. **Clean your injection site** with an alcohol swab and let the injection site dry before you inject.
6. Before inserting a 3 mL cartridge into your insulin delivery device for the first time, roll the cartridge between your palms 10 times. These steps should be done with the 3 mL PenFill[®] cartridge in a horizontal (flat) position (see Diagram 1 below). Then turn the PenFill[®] cartridge up and down between positions **a** and **b** (see Diagram 2 below) so the glass ball moves from one end of the cartridge to the other. Do this at least 10 times. Repeat the rolling and turning steps until the insulin looks white and cloudy. Mixing is easier when the insulin is at room temperature.



7. Insert the PenFill[®] cartridge into the insulin delivery device. Wipe the front rubber stopper of the 3 mL PenFill[®] cartridge with an alcohol swab, then screw on a new needle (see Diagram 3 below).



For NovoFine[®] needles, remove the big outer needle cap and the inner needle cap (see Diagram 4 above). Always use a new needle for each injection to prevent infection.

Giving the airshot before each injection:

To prevent the injection of air and make sure insulin is delivered; you must do an air shot before each injection. Hold the device with the needle pointing up and gently tap the PenFill[®] cartridge holder with your finger a few times to raise any air bubbles to the top of the cartridge (see Diagram 5 below). Do the airshot as described in the device instruction manual.



Giving the injection

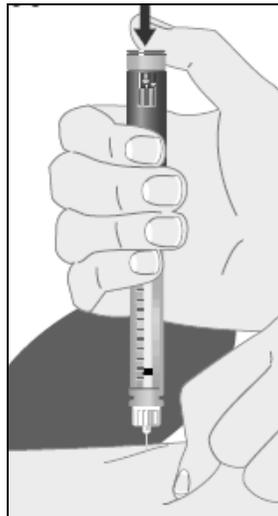
8. Dial the number of units you need to inject on the device (see Diagram 6 below). Inject right away as you were shown by your healthcare provider. If there is a delay between mixing of the insulin and the injection, the insulin will need to be mixed again.

6



9. Pinch a fold of skin between 2 fingers, then push the needle into the pinched up skin (see Diagram 7 below). Inject the dose by pressing the push button all the way in. Keep the needle in the skin for at least 6 seconds, and keep the push button pressed all the way in until the needle has been pulled out from the skin. This will make sure that the full dose has been given. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**

7



After the injection

10. Remove the needle from the insulin delivery device after each injection. Keep the 3 mL PenFill[®] cartridge in the insulin delivery device. The needle should not be attached to the insulin delivery device during storage. This will prevent

infection or leakage of insulin, and will help ensure that you receive the right dose of NovoLog[®] Mix 50/50.

11. Put the used needle in a sharps container, or some type of hard plastic or metal container that can be sealed, such as a detergent bottle or coffee can. Ask your healthcare provider how to seal and throw away these containers safely. There may be local or state laws about how to throw away used needles and syringes.
12. Put the pen cap back on the insulin delivery device.

After the first use of the 3 mL PenFill[®] cartridge

1. If the 3 mL PenFill[®] cartridge is already in the insulin delivery device, turn it upside down between positions **a** and **b** (see Diagram 2 above), so that the glass ball moves from one end of the 3 mL PenFill[®] cartridge to the other. Do this until all of the insulin looks white and cloudy.
2. Before you inject, there must be at least 12 units of insulin left in the cartridge to make sure the remaining insulin is evenly mixed. If there are less than 12 units left, use a new 3 mL PenFill[®] cartridge.
3. An airshot should be done before each injection. Do the airshot as described in the device instruction manual.
4. Do not remove the 3 mL cartridge from the insulin delivery device.
5. Put the pen cap back on the insulin delivery device.

IMPORTANT NOTES

- Do not use if you need to do more than 6 airshots before the first use of each NovoLog[®] Mix 50/50 cartridge to get a drop of insulin at the needle tip. Contact Novo Nordisk at 1-800-727-6500.
- Remember to do an airshot before each injection. See the device instruction manual.
- Do not drop the NovoLog[®] Mix 50/50 cartridge and insulin delivery device.
- Keep the NovoLog[®] Mix 50/50 cartridge and insulin delivery device with you. Do not leave it in a car or other places where it can get too hot or too cold.
- NovoLog[®] Mix 50/50 cartridges are designed for use with NovoFine[®] disposable needles.

- Do not put a disposable needle on the NovoLog[®] Mix 50/50 cartridge and insulin delivery device until you are ready to use it. Remove the needle right after use. Do not recap the needle.
- **Throw away used needles safely, so other people will not be harmed.** Talk to your healthcare provider about how to safely throw away your used needles.
- Throw away the used NovoLog[®] Mix 50/50 cartridges without the needle attached.
- Always carry an extra NovoLog[®] Mix 50/50 cartridge with you in case the NovoLog[®] Mix 50/50 cartridge is damaged or lost. Always keep the NovoLog[®] Mix 50/50 cartridge in the outer carton when you are not using it in order to protect it from light.
- Keep your NovoLog[®] Mix 50/50 cartridge out of the reach of children. Use NovoLog[®] Mix 50/50 cartridges as directed to treat your diabetes. Do not share it with anyone else even if he or she also has diabetes.

Patient Instructions for Use

NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe

How to use the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe

NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe is a disposable insulin delivery system. NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe is to be used with NovoFine[®] single use needles. People who are blind or have severe vision problems should only use the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe with the help of a sighted person who is trained to use the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe the right way.

Please read these instructions completely before using this device.

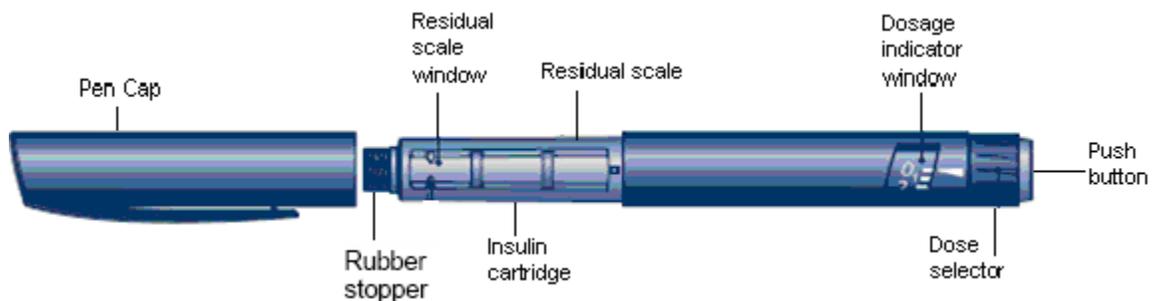


Figure 1 Diagram of a NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe

NovoFine[®] needle

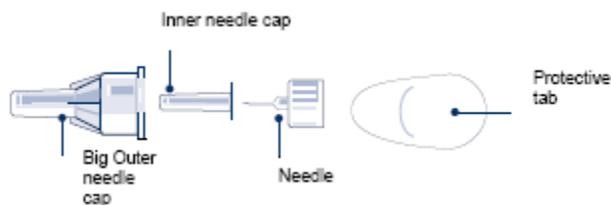
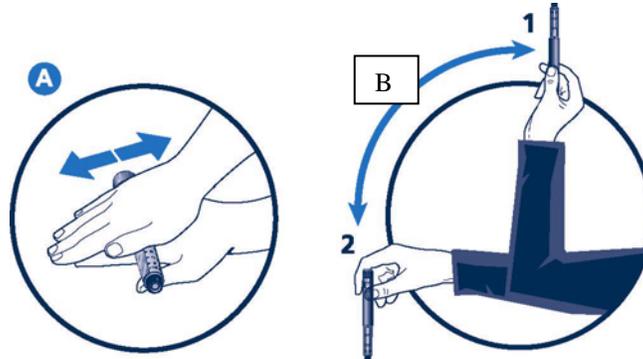


Figure 2 Diagram of a NovoFine[®] needle

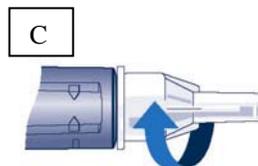
1. PREPARING THE NOVOLOG[®] MIX 50/50 FLEXPEN[®] PREFILLED SYRINGE

Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. NovoLog[®] Mix 50/50 should look white and cloudy (after being mixed). This is especially important if you use 2 types of insulin.

- Pull off the pen cap.
- Wipe the rubber stopper with an alcohol swab.

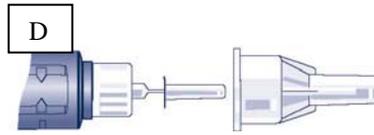


- Before using a new NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe for the first time, do the following to mix (resuspend) the insulin:
 - Hold the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe in a horizontal (flat) position between your palms (see diagram A above). Roll the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe between your palms 10 times.
 - Then, turn the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe up and down. Move the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe between position 1 and 2 so that the glass ball moves from one end of the insulin cartridge to the other (see diagram B above). Do this at least 10 times. Repeat the rolling and turning steps until all of the insulin looks white and cloudy. Mixing (resuspension) is easier when the insulin is at room temperature.
 - After mixing, continue to do the following steps right away. If there is a delay, the insulin will need to be mixed again.

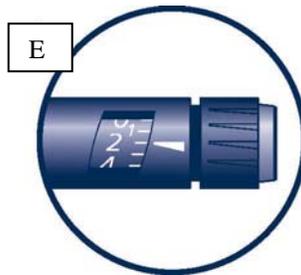


- Remove the protective tab from the disposable needle and screw the needle tightly onto the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe

(see diagram C above). Do not place a disposable needle on your NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe until you are ready to take your injection.



- Pull off the outer and inner needle caps (see diagram D above). Do not throw away the big outer needle cap.
- **Giving the airshot before each injection:**
Small amounts of air may collect in the needle and insulin cartridge during normal use. **To avoid injecting air and to make sure you take the right dose of insulin,** do the following:
 - **Dial 2 units by turning the dose selector so that the arrow lines up with the “2” in the dosage indicator window (see diagram E below).**
 - **Hold the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe with the needle pointing up. Tap the insulin cartridge gently with your finger a few times (see diagram F below).** A small air bubble may remain but it will not be injected. The NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe prevents the insulin cartridge from being completely emptied.



- Keep the needle pointing up and press the push button (on the end of the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe) all the way in (see diagram G below). You should see a drop of

insulin at the needle tip. If you don't see a drop of insulin, repeat the procedure (dial 2 units, tap the insulin cartridge and press the push button) until insulin appears. You may need to do this up to 6 times. If you don't see a drop of insulin after 6 times, do not use the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe and contact Novo Nordisk at 1-800-727-6500.

G



2. SETTING THE DOSE

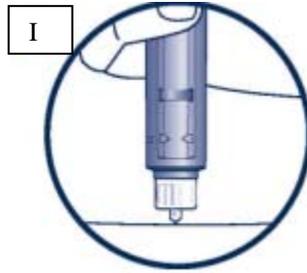
H



- Check and make sure that the dose selector is set at zero (0) (see diagram H above).
- Dial the number of units you need to inject by turning the dose selector so the arrow lines up with your dose.
- The dose can be corrected by turning the dose selector in either direction. When dialing back, be careful not to press the push button. Pressing the button will cause the insulin to come out. You cannot set a dose larger than the number of units left in the cartridge. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

3. GIVING THE INJECTION

Do the injection exactly as shown to you by your healthcare provider.



- Wipe the injection site with an alcohol swab and let the area dry.
- Pinch a fold of skin between 2 fingers, then push the needle into the pinched up skin (see diagram I above).
- Give the dose by pressing the push button all the way in (see diagram J below). Be careful to only press the push button when injecting.



- Keep the needle in the skin for at least 6 seconds, and keep the push button pressed all the way in until the needle has been pulled out from the skin. This will make sure that the full dose has been given. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**

After the injection

- Remove the needle from the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe after each injection. This helps to prevent contamination, infection, and leakage of insulin, and will help to make sure you inject the right dose of insulin. Put the needle in a sharps container, or some type of hard plastic or metal container that can be sealed such as a detergent bottle or coffee can. These containers should be sealed and thrown away safely. Ask your healthcare provider how to throw away a used sharps container. There may be local or state laws about how to throw away used needles and syringe.
- Put the pen cap back on the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe.

Healthcare providers, relatives, and other caregivers should follow general precautions for removing and disposing of needles to lessen the possible chance of needle stick injury.

4. FUTURE INJECTIONS

It is important that you use a new needle for each injection. Follow the directions in steps 1, 2, and 3 above.

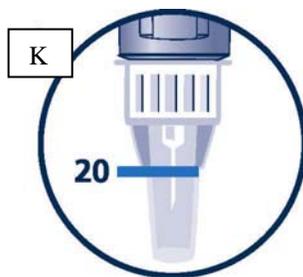
Before you inject, there must be at least 12 units of insulin left in the cartridge to make sure the remaining insulin is evenly mixed. If there are less than 12 units left, use a new NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe.

The numbers on the insulin cartridge can be used to estimate the amount of insulin left in the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe. Do not use these numbers to measure the insulin dose. You cannot set a dose more than the number of units remaining in the cartridge.

Mix (resuspend) the insulin before each injection:

- Turn the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe up and down between position **1** and **2** so that the glass ball moves from one end of the insulin cartridge to the other (see diagram B above). Do this at least 10 times. Repeat the procedure until all of the insulin looks white and cloudy.
- Continue to follow the directions as described in steps 1, 2, and 3 above. If there is a delay in any step, the insulin will need to be mixed (resuspended) again.

5. FUNCTION CHECK



If your NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe is not working the right way, follow this procedure:

- Screw on a new NovoFine[®] needle.
- Do an airshot as described in step 1.
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so that the arrow lines up with the 20 units in the dose indicator window.

- Hold the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe so the needle is pointing down.
- Press the push button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram K above). If the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe has released too much or too little insulin, do the function check again. If it happens again, do not use your NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe and contact Novo Nordisk at 1-800-727-6500.

6. IMPORTANT NOTES

- If you need to do more than 6 airshots before the first use of each NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe to get a drop of insulin at the needle tip, do not use the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe. Contact Novo Nordisk at 1-800-727-6500.
- Remember to perform an airshot before each injection. See diagrams E and F.
- Do not drop the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe.
- Keep the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe with you. Do not leave it in a car or other place where it can get too hot or too cold.
- NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe should be used with NovoFine[®] disposable needles.
- Do not put a disposable needle on the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe until you are ready to use it. Remove the needle right after use. Do not recap the needle.
- **Throw away used needles safely, so other people will not be harmed.** Talk to your healthcare provider about how to safely throw away your used needles.
- Throw away the used NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe without the needle attached.
- Always carry an extra NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe with you in case the NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe is damaged or lost.
- Keep your NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe out of the reach of children. Use NovoLog[®] Mix 50/50 FlexPen[®] Prefilled syringe as directed to treat your diabetes. Do not share it with anyone else even if he or she also has diabetes.