

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])
Suspension for subcutaneous injection
Initial U.S. Approval: 2001**

-----RECENT MAJOR CHANGES-----

- Indications and Usage (1) 4/2010
- Dosage and Administration (2.1) 4/2010

-----INDICATIONS AND USAGE-----

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

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

-----DOSAGE AND ADMINISTRATION-----

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

-----DOSAGE FORMS AND STRENGTHS-----

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

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

-----CONTRAINDICATIONS-----

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

-----WARNINGS AND PRECAUTIONS-----

- NovoLog Mix 70/30 should not be mixed with any other insulin product (5.1)
- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision. (5.1, 5.2).

- Insulin, particularly when given in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3)
- Like all insulins, NovoLog Mix 70/30 requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5)
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog Mix 70/30 (5.6)

-----ADVERSE REACTIONS-----

Adverse reactions observed with insulin therapy include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

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

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

Revised: 4/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing
- 2.2 Resuspension

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Administration
- 5.2 Hypoglycemia
- 5.3 Hypokalemia
- 5.4 Renal Impairment
- 5.5 Hepatic Impairment
- 5.6 Hypersensitivity and Allergic Reactions
- 5.7 Antibody Production

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 NovoLog Mix 70/30 versus Novolin 70/30
- 14.2 Combination Therapy: Insulin and Oral Agents in Patients with Type 2 Diabetes

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Recommended Storage

17 PATIENT COUNSELING INFORMATION

- 17.1 Physician Instructions

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Important Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

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

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

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

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

2.2 Resuspension

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

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

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

54

55 **3 DOSAGE FORMS AND STRENGTHS**

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

- 58 • 10 mL vials
- 59 • 3 mL NovoLog Mix 70/30 FlexPen

60

61 **4 CONTRAINDICATIONS**

62 NovoLog Mix 70/30 is contraindicated

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

65

66 **5 WARNINGS AND PRECAUTIONS**

67 **5.1 Administration**

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

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

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

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

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

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

87 NovoLog Mix 70/30 FlexPen is for use by one person only.

88

89 **5.2 Hypoglycemia**

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

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

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

109 **5.3 Hypokalemia**

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

116 **5.4 Renal Impairment**

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

122 **5.5 Hepatic Impairment**

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

128 **5.6 Hypersensitivity and Allergic Reactions**

129 *Local Reactions-* As with other insulin therapy, patients may experience reactions such
130 as erythema, edema or pruritus at the site of NovoLog Mix 70/30 injection. These reactions
131 usually resolve in a few days to a few weeks, but in some occasions, may require
132 discontinuation of NovoLog Mix 70/30. In some instances, these reactions may be related to the
133 insulin molecule, other components in the insulin preparation including protamine and cresol,

134 components in skin cleansing agents, or injection techniques. Localized reactions and
135 generalized myalgias have been reported with the use of cresol as an injectable excipient.

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

140

141 **5.7 Antibody Production**

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

148

149 **6 ADVERSE REACTIONS**

150 *Clinical Trial Experience*

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

- 154 • Hypoglycemia
155 Hypoglycemia is the most commonly observed adverse reaction in patients using insulin,
156 including NovoLog Mix 70/30 [*see Warnings and Precautions (5.2)*]. NovoLog Mix
157 70/30 should not be used during episodes of hypoglycemia [*see Contraindications (4)*
158 *and Warnings and Precautions (5)*].
- 159 • Insulin initiation and glucose control intensification
160 Intensification or rapid improvement in glucose control has been associated with
161 transitory, reversible ophthalmologic refraction disorder, worsening of diabetic
162 retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic
163 control decreases the risk of diabetic retinopathy and neuropathy.
- 164 • Lipodystrophy
165 Long-term use of insulin, including NovoLog Mix 70/30, can cause lipodystrophy at the
166 site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of
167 adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin
168 absorption. Rotate insulin injection sites within the same region to reduce the risk of
169 lipodystrophy.
- 170 • Weight gain
171 Weight gain can occur with some insulin therapies, including NovoLog Mix 70/30, and
172 has been attributed to the anabolic effects of insulin and the decrease in glycosuria.
- 173 • Peripheral Edema
174 Insulin may cause sodium retention and edema, particularly if previously poor metabolic
175 control is improved by intensified insulin therapy.
- 176 • Frequencies of adverse drug reactions

177 The frequencies of adverse drug reactions during a clinical trial with NovoLog Mix 70/30
 178 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the
 179 tables below. The trial was a three-month, open-label trial in patients with Type 1 or
 180 Type 2 diabetes who were treated twice daily (before breakfast and before supper) with
 181 NovoLog Mix 70/30.
 182

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

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

185
 186 **Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 diabetes mellitus**
 187 **(Adverse events with frequency \geq 5% are included.)**

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

188
 189 **Postmarketing Data**

190 Additional adverse reactions have been identified during post-approval use of NovoLog
 191 Mix 70/30. Because these adverse reactions are reported voluntarily from a population of
 192 uncertain size, it is generally not possible to reliably estimate their frequency. They include
 193 medication errors in which other insulins have been accidentally substituted for NovoLog Mix
 194 70/30 [see *Patient Counseling Information* (17)].

195
 196 **7 DRUG INTERACTIONS**

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

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

215

216 **8 USE IN SPECIFIC POPULATIONS**

217 **8.1 Pregnancy**

218 Pregnancy Category B.

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

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

234 Animal reproduction studies have not been conducted with NovoLog Mix 70/30.
235 However, subcutaneous reproduction and teratology studies have been performed with
236 NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in
237 rats and rabbits. In these studies, NovoLog was given to female rats before mating, during
238 mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of
239 NovoLog did not differ from those observed with subcutaneous regular human insulin.
240 NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal
241 abnormalities in rats at a dose of 200 U/kg/day (approximately 32-times the human

242 subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of
243 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based
244 on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high
245 doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a
246 dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of
247 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits
248 based on U/body surface area.

249 Female patients should be advised to discuss with their physician if they intend to, or if
250 they become pregnant. There are no adequate and well-controlled studies of the use of
251 NovoLog Mix 70/30 in pregnant women.
252

253 **8.3 Nursing Mothers**

254 It is unknown whether insulin aspart is excreted in human milk as occurs with human
255 insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or
256 NovoLog in lactating women. Women with diabetes who are lactating may require adjustments
257 of their insulin doses.
258

259 **8.4 Pediatric Use**

260 Safety and effectiveness of NovoLog Mix 70/30 have not been established in pediatric
261 patients.
262

263 **8.5 Geriatric Use**

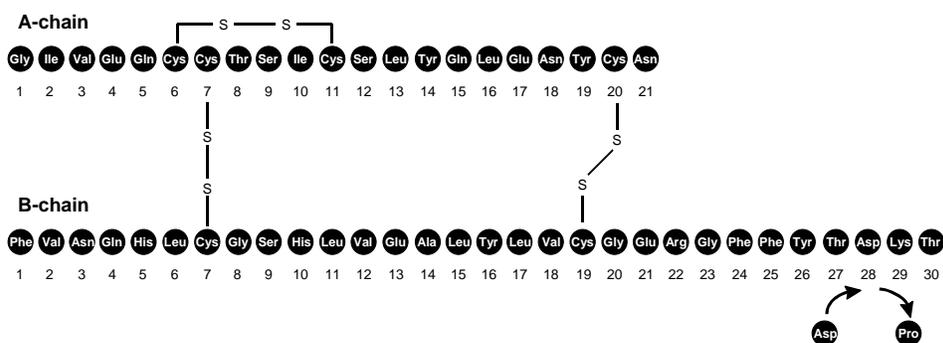
264 Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients
265 aged 65 and over to determine whether they respond differently than younger patients. In
266 general, dose selection for an elderly patient should be cautious, usually starting at the low end of
267 the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function,
268 and of concomitant disease or other drug therapy in this population.
269

270 **10 OVERDOSAGE**

271 Hypoglycemia may occur as a result of an excess of insulin relative to food intake,
272 energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral
273 glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe
274 episodes with coma, seizure, or neurologic impairment may be treated with
275 intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained
276 carbohydrate intake and observation may be necessary because hypoglycemia may recur after
277 apparent clinical recovery.
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279 **11 DESCRIPTION**

280 NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart
281 injection, [rDNA origin]) is a human insulin analog suspension containing 70% insulin aspart
282 protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a blood glucose-
283 lowering agent with an earlier onset and an intermediate duration of action. Insulin aspart is
284 homologous with regular human insulin with the exception of a single substitution of the amino
285 acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology
286 utilizing *Saccharomyces cerevisiae* (baker's yeast). Insulin aspart (NovoLog) has the empirical
287 formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 Da.
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289
290 **Figure 1. Structural formula of insulin aspart**

291
292 NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart
293 100 Units/mL.

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

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

302
303 **12 CLINICAL PHARMACOLOGY**

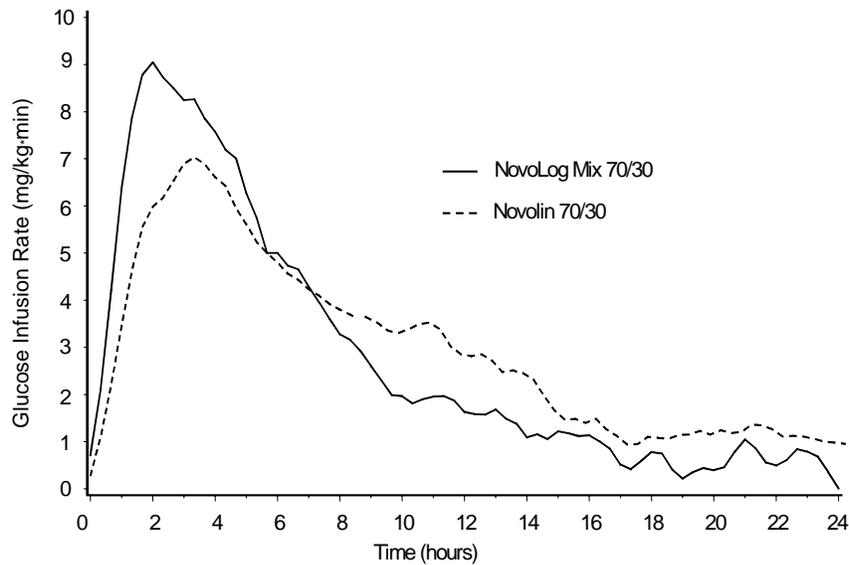
304 **12.1 Mechanism of Action**

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

309
310 **12.2 Pharmacodynamics**

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

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

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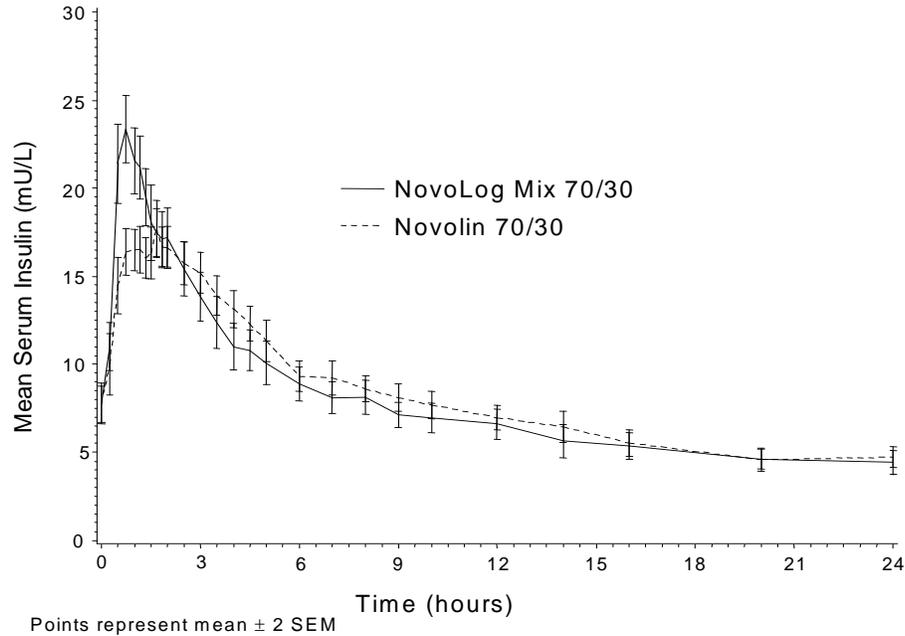
323 **12.3 Pharmacokinetics**

324 The single substitution of the amino acid proline with aspartic acid at position B28 in
 325 insulin aspart (NovoLog) reduces the molecule's tendency to form hexamers as observed with
 326 regular human insulin. The rapid absorption characteristics of NovoLog are maintained by
 327 NovoLog Mix 70/30. The insulin aspart in the soluble component of NovoLog Mix 70/30 is
 328 absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining
 329 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile
 330 after subcutaneous injection.

331 *Bioavailability and Absorption-* The relative bioavailability of NovoLog Mix 70/30
 332 compared to NovoLog and Novolin 70/30 indicates that the insulins are absorbed to similar
 333 extent. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with NovoLog
 334 Mix 70/30 (0.2 U/kg), a mean maximum serum concentration (C_{max}) of 23.4 ± 5.3 mU/L was
 335 reached after 60 minutes. The mean half-life ($t_{1/2}$) of NovoLog Mix 70/30 was about 8 to 9
 336 hours. Serum insulin levels returned to baseline 15 to 18 hours after a subcutaneous dose of
 337 NovoLog Mix 70/30. Similar data were seen in a separate euglycemic clamp study in healthy
 338 volunteers (n=24) after dosing with NovoLog Mix 70/30 (0.3 U/kg). A C_{max} of 61.3 ± 20.1
 339 mU/L was reached after 85 minutes. Serum insulin levels returned to baseline 12 hours after a
 340 subcutaneous dose.

341 The C_{max} and the area under the insulin concentration-time curve (AUC) after
 342 administration of NovoLog Mix 70/30 was approximately 20% greater than those after
 343 administration of Novolin 70/30, (see Fig. 3 for pharmacokinetic profiles).

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

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

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

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13 NONCLINICAL TOXICOLOGY

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370

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

371 NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward
 372 gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo*
 373 micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes.
 374

375 In fertility studies in male and female rats, NovoLog at subcutaneous doses up to 200 U/kg/day
 376 (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no
 377 direct adverse effects on male and female fertility, or on general reproductive performance of
 378 animals.
 379

380 **13.2 Animal Toxicology and/or Pharmacology**

381 In standard biological assays in mice and rabbits, one unit of NovoLog has the same
 382 glucose-lowering effect as one unit of regular human insulin. However, the effect of NovoLog
 383 Mix 70/30 is more rapid in onset compared to Novolin (human insulin) 70/30 due to its faster
 384 absorption after subcutaneous injection.
 385

386 **14 CLINICAL STUDIES**

387 **14.1 NovoLog Mix 70/30 versus Novolin 70/30**

388 In a three-month, open-label trial, patients with Type 1 (n=104) or Type 2 (n=187)
 389 diabetes were treated twice daily (before breakfast and before supper) with NovoLog Mix 70/30
 390 or Novolin 70/30. Patients had received insulin for at least 24 months before the study. Oral
 391 hypoglycemic agents were not allowed within 1 month prior to the study or during the study.
 392 The small changes in HbA_{1c} were comparable across the treatment groups (see Table 3).
 393
 394
 395

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

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

396
 397 The significance, with respect to the long-term clinical sequelae of diabetes, of the
 398 differences in postprandial hyperglycemia between treatment groups has not been established.

399 Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were
 400 monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial
 401

402 **14.2 Combination Therapy: Insulin and Oral Agents in Patients with Type 2 Diabetes**

403 **Trial 1:**

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

414
 415 **Table 4: Combination Therapy with Oral Agents and Insulin in Patients with Type 2**
 416 **Diabetes Mellitus [Mean (SD)]**

Treatment duration 24-weeks	NovoLog Mix 70/30 + Metformin + Pioglitazone	Metformin + Pioglitazone
HbA _{1c}		
Baseline mean \pm SD (n)	8.1 ± 1.0 (102)	8.1 ± 1.0 (98)
End-of-study mean \pm SD (n) - LOCF	6.6 ± 1.0 (93)	7.8 ± 1.2 (87)
Adjusted Mean change from baseline \pm SE (n)*	-1.6 ± 0.1 (93)	-0.3 ± 0.1 (87)
Treatment difference mean \pm SE* 95% CI*	-1.3 ± 0.1 (-1.6, -1.0)	
Percentage of subjects reaching HbA _{1c} <7.0%	76%	24%
Percentage of subjects reaching HbA _{1c} ≤6.5%	59%	12%
Fasting Blood Glucose (mg/dL)		
Baseline Mean \pm SD (n)	173 ± 39.8 (93)	163 ± 35.4 (88)
End of Study Mean \pm SD (n) – LOCF	130 ± 50.0 (90)	162 ± 40.8 (84)
Adjusted Mean change from baseline \pm SE (n)*	-43.0 ± 5.3 (90)	-3.9 ± 5.3 (84)
End-of-Study Blood Glucose (Plasma) (mg/dL)		
2 Hour Post Breakfast	138 ± 42.8 (86)	188 ± 57.7 (74)
2 Hour Post Lunch	150 ± 41.5 (86)	176 ± 56.5 (74)
2 Hour Post Dinner	141 ± 57.8 (86)	195 ± 60.1 (74)
% of patients with severe hypoglycemia**	3	0
% of patients with minor hypoglycemia**	52	3
Weight gain at end of study (kg)**	4.6 ± 4.3 (92)	0.8 ± 3.2 (86)

417 *Adjusted mean per group, treatment difference, and 95% CI were obtained based on an ANCOVA model with
 418 treatment, FPG stratum, and secretagogue stratum as fixed factors and baseline HbA_{1c} as the covariate.

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

421
 422
 423 **Trial 2:**

424 In a 28-week, open-label trial, insulin-naïve patients with type 2 diabetes with fasting
 425 plasma glucose above 140 mg/dL currently treated with metformin \pm thiazolidinedione therapy
 426 were randomized to receive either NovoLog Mix 70/30 twice daily [before breakfast and before
 427 supper] or insulin glargine once daily¹ (see Table 5). NovoLog Mix 70/30 was started at an
 428 average dose of 5-6 IU (0.07 ± 0.03 IU/kg) twice daily (before breakfast and before supper), and
 429 bedtime insulin glargine was started at 10-12 IU (0.13 ± 0.03 IU/kg). Insulin doses were titrated
 430 weekly by decrements or increments of -2 to +6 units per injection to a pre-meal glucose goal of

431 80-110 mg/dL. The metformin dose was adjusted to 2550 mg/day. Approximately one-third of
 432 the patients in each group were also treated with pioglitazone (30 mg/day). Insulin
 433 secretagogues were discontinued in order to reduce the risk of hypoglycemia. Most patients
 434 were Caucasian (53%), and the mean initial weight was 90 kg.

435
 436 **Table 5: Combination Therapy with Oral Agents and Two Types of Insulin in Patients**
 437 **with Type 2 Diabetes Mellitus [Mean (SD)]**

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

438
 439 **15 REFERENCES**

- 440 1. Raskin R, Allen E, Hollander P, et al. Initiating insulin therapy in type 2
 441 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*.
 442 2005; 28:260-265.

443
 444 **16 HOW SUPPLIED/STORAGE HANDLING**

445 **16.1 How Supplied**

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

- 448
 449 10 mL vials NDC 0169-3685-12
 450 3 mL NovoLog Mix 70/30 FlexPen NDC 0169-3696-19

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

452
 453 **16.2 Recommended Storage**

454 Unused NovoLog Mix 70/30 should be stored in a refrigerator between 2°C and 8°C
 455 (36°F to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling
 456 element. **Do not freeze NovoLog Mix 70/30 or use NovoLog Mix 70/30 if it has been frozen.**

457 **Vials:** After initial use, a vial may be kept at temperatures below 30°C (86°F) for up to
 458 28 days, but should not be exposed to excessive heat or sunlight. Open vials may be refrigerated.

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

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

469 These storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30° C[86° F])	Not in-use (unopened) Refrigerated (2° C - 8° C [36° F- 46° F])	In-use (opened) Room Temperature (below 30° C[86° F])
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3ml NovoLog Mix 70/30 FlexPen	14 days	Until expiration date	14 days (Do not refrigerate)

470

471

472 17 PATIENT COUNSELING INFORMATION

473 *[see FDA-Approved Patient Labeling]*

474

475 17.1 Physician Instructions

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

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

492 Accidental substitutions between NovoLog Mix 70/30 and other insulin products have
 493 been reported. Patients should be instructed to always carefully check that they are
 494 administering the appropriate insulin to avoid medication errors between NovoLog Mix 70/30
 495 and any other insulin. **The prescription for NovoLog Mix 70/30 should be written clearly in
 496 order to avoid confusion with other insulin products, for example, NovoLog or Novolin
 497 70/30.** In addition, the written prescription should clearly indicate the presentation, for example
 498 FlexPen or vial.

499

500

501 **Rx only**

502

503 Date of Issue:

504

505 Version:

506

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

509

510 NovoLog[®] Mix 70/30 is covered by US Patent Nos 5,547,930, 5,618,913, 5,834,422, 5,840,680,
511 5,866,538 and other patents pending.

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

514

515 © 2002 – 2010 Novo Nordisk A/S

516

517 Manufactured by:

518 Novo Nordisk A/S

519 DK-2880 Bagsvaerd, Denmark

520

521 For information about NovoLog Mix 70/30 contact:

522 Novo Nordisk Inc.

523 Princeton, New Jersey 08540

524 1-800-727-6500

525

526 www.novonordisk-us.com

Patient Information

NovoLog[®] Mix 70/30

(NŌ-vŏ-log-MIX-SEV-en-tee-THIR-tee)

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

Read the Patient Information leaflet that comes with NovoLog[®] Mix 70/30 before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog[®] Mix 70/30?

NovoLog[®] Mix 70/30 is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.

It is not known if NovoLog[®] Mix 70/30 is safe or effective in children.

Who should not use NovoLog[®] Mix 70/30?

Do not take NovoLog[®] Mix 70/30 if:

- Your blood sugar is too low (hypoglycemia)
- You are allergic to any of the ingredients in NovoLog[®] Mix 70/30. See the end of this leaflet for a complete list of ingredients in NovoLog[®] Mix 70/30. Check with your healthcare provider if you are not sure.

What should I tell my healthcare provider before taking NovoLog[®] Mix 70/30?

Before you use NovoLog[®] Mix 70/30, tell your healthcare provider if you:

- have kidney or liver problems
- **have any other medical conditions.** Medical conditions can affect your insulin needs and your dose of NovoLog[®] Mix 70/30.
- **are pregnant or plan to become pregnant.** It is not known if NovoLog[®] Mix 70/30 will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. You and your healthcare provider should decide about the best way to manage your diabetes while you are pregnant.
- **are breastfeeding or plan to breastfeed.** It is not known if NovoLog[®] Mix 70/30 passes into your breast milk. You and your healthcare provider should decide if you will take NovoLog[®] Mix 70/30 while you breastfeed.

Tell your healthcare provider about all medicines you take, including prescriptions and non-prescription medicines, vitamins and herbal supplements.

NovoLog[®] Mix 70/30 may affect the way other medicines work, and other medicines may affect how NovoLog[®] Mix 70/30 works. Your NovoLog[®] Mix 70/30 dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers and pharmacist when you get a new medicine.

How should I take NovoLog[®] Mix 70/30?

- Take NovoLog[®] Mix 70/30 exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much NovoLog[®] Mix 70/30 to take and when to take it.
- Do not make any changes to your dose or type of insulin unless your healthcare provider tells you to.
- **NovoLog Mix 70/30 starts acting fast. If you have Type 1 diabetes, inject it up to 15 minutes before you eat a meal.** Do not inject NovoLog[®] Mix 70/30 if you are not planning to eat within 15 minutes.
- **If you have Type 2 diabetes, you may inject NovoLog[®] Mix 70/30 up to 15 minutes before or after starting your meal.**
- **Do Not mix** NovoLog[®] Mix 70/30 with other insulin products.
- **Do Not** use NovoLog[®] Mix 70/30 in an insulin pump.
- **Inject NovoLog[®] Mix 70/30 under the skin (subcutaneously) of your stomach area, upper arms, buttocks or upper legs.** NovoLog[®] Mix 70/30 may affect your blood sugar levels faster if you inject it under the skin of your stomach area. Never inject NovoLog[®] Mix 70/30 into a vein or into a muscle.
- **Change (rotate) injection sites** within the area you choose with each dose. **Do not** inject into the exact same spot for each injection.
- **Read the instructions for use that come with your NovoLog[®] Mix 70/30.** Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog[®] Mix 70/30 before you start using it.

- NovoLog® Mix 70/30 comes in:
 - 10 mL vials for use with a syringe
 - 3 mL NovoLog® Mix 70/30 FlexPen®
- **If you take too much NovoLog® Mix 70/30, your blood sugar may fall too 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 (loss of consciousness).
- **If you forget to take your dose of NovoLog® Mix 70/30, your blood sugar may go too high (hyperglycemia).** If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like passing out (loss of consciousness), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:
 - increased thirst
 - frequent urination
 - drowsiness
 - loss of appetite
 - a hard time breathing
 - fruity smell on the breath
 - high amounts of sugar and ketones in your urine
 - nausea, vomiting (throwing up) or stomach pain
- Do not share needles, insulin pens or syringes with others.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise

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

What should I consider while using NovoLog® Mix 70/30?

- **Alcohol.** Drinking alcohol may affect your blood sugar when you take NovoLog® Mix 70/30.
- **Driving and operating machinery.** You may have trouble paying attention or reacting if you have low blood sugar

(hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you often have:

- low blood sugar
- decreased or no warning signs of low blood sugar

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

NovoLog® Mix 70/30 may cause serious side effects, including:

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

Very low blood sugar can cause you to pass out (loss of consciousness), seizures, and death. Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking NovoLog® Mix 70/30. 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. Your dose of NovoLog® Mix 70/30 may need to be changed.

- **Low potassium in your blood (hypokalemia)**
- **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 talk to your healthcare provider.
- **Serious allergic reaction (whole body reaction). Get medical help right away, if you have any of these symptoms of an allergic reaction:**
 - a rash over your whole body
 - have trouble breathing
 - a fast heartbeat
 - sweating
 - feel faint

The most common side effects of NovoLog[®] Mix 70/30 include:

- **Skin thickening or pits at the injection site (lipodystrophy).** Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.
- **Weight gain**
- **Swelling of your hands and feet**
- **Vision changes**

These are not all of the possible side effects from NovoLog[®] Mix 70/30. Ask your healthcare provider or pharmacist for more information.

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

How should I store NovoLog[®] Mix 70/30?

All Unopened NovoLog[®] Mix 70/30:

- Keep all unopened NovoLog[®] Mix 70/30 in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not freeze or store next to the refrigerator cooling element.** Do not use NovoLog[®] Mix 70/30 if it has been frozen.
- Keep unopened NovoLog[®] Mix 70/30 in the carton to protect from light.
- Unopened vials can be used until the expiration date on the NovoLog[®] Mix 70/30 label, if the medicine has been stored in a refrigerator.
- Unused NovoLog[®] Mix 70/30 FlexPen[®] can be used until the expiration date on the NovoLog[®] Mix 70/30 FlexPen[®] label, if the medicine has been stored in a refrigerator.

After NovoLog[®] Mix 70/30 has been opened:

- **Vials**
 - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
 - Keep vials away from direct heat or light.
 - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
- **NovoLog[®] Mix 70/30 FlexPen[®]**
 - Keep at room temperature below 86°F (30°C) for up to 14 days.

- **Do not** store a NovoLog[®] Mix 70/30 FlexPen[®] that you are using in the refrigerator.
- Keep NovoLog[®] Mix 70/30 FlexPen[®] away from direct heat or light.
- Throw away a used NovoLog[®] Mix 70/30 FlexPen[®] after 14 days, even if there is insulin left in the syringe.

Never use insulin after the expiration date that is printed on the label and carton.

Keep NovoLog[®] Mix 70/30 and all medicines out of the reach of children.

General advice about NovoLog[®] Mix 70/30

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog[®] Mix 70/30 for a condition for which it was not prescribed. Do not give NovoLog[®] Mix 70/30 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 70/30. If you would like more information about NovoLog[®] Mix 70/30 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog[®] Mix 70/30 that is written for healthcare professionals. For more information call 1-800-727-6500 or go to www.novonordisk-us.com.

What are the ingredients in NovoLog[®] Mix 70/30?

- **Active Ingredients NovoLog[®] Mix 70/30 FlexPen[®] and Vial:** 70% Insulin aspart protamine suspension and 30% insulin aspart injection (rDNA origin).
- **Inactive Ingredients NovoLog[®] Mix 70/30 FlexPen[®]:** glycerol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, protamine sulfate, water for injection, hydrochloric acid or sodium hydroxide.
- **Inactive Ingredients NovoLog[®] Mix 70/30 Vial:** mannitol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, protamine sulfate, water for injection, hydrochloric acid or sodium hydroxide.

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

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 2311 and is available at www.diabetes.org.

Date of Issue:

Version:

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

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

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

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Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about NovoLog Mix 70/30[®] contact:

Novo Nordisk Inc.

100 College Road West,

Princeton, New Jersey 08540

Patient Instructions for Use

NovoLog[®] Mix 70/30 FlexPen[®]

Read the following instructions carefully before you start using your NovoLog[®] Mix 70/30 FlexPen[®] and each time you get a refill. There may be new information. You should read the instructions even if you have used NovoLog[®] Mix 70/30 FlexPen[®] before.

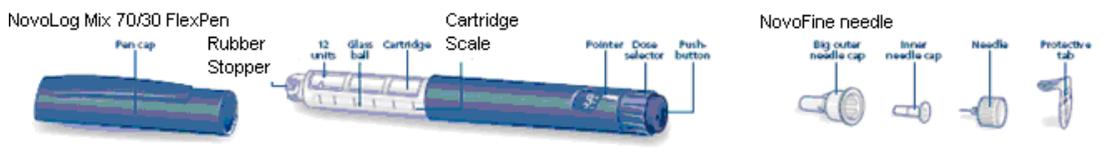
NovoLog[®] Mix 70/30 FlexPen[®] is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. NovoLog[®] Mix 70/30 FlexPen[®] is designed to be used with NovoFine[®] needles.

NovoLog Mix[®] 70/30 FlexPen[®] should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog[®] Mix 70/30 FlexPen[®] the right way.

Getting ready

Make sure you have the following items:

- NovoLog[®] Mix 70/30 FlexPen[®]
- New NovoFine[®] needle
- Alcohol swab



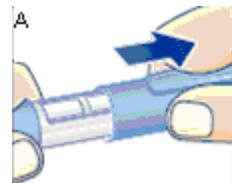
PREPARING YOUR NOVOLOG[®] MIX 70/30 FLEXPEN[®]

- Wash your hands with soap and water.
- Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog[®] Mix 70/30 should look cloudy after mixing.

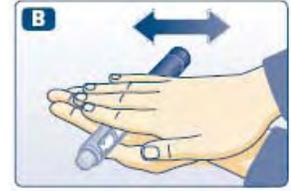
Before your first injection with a new NovoLog[®] Mix 70/30 FlexPen[®] you must mix the insulin:

- A. Let the insulin reach room temperature before you use it. This makes it easier to mix.

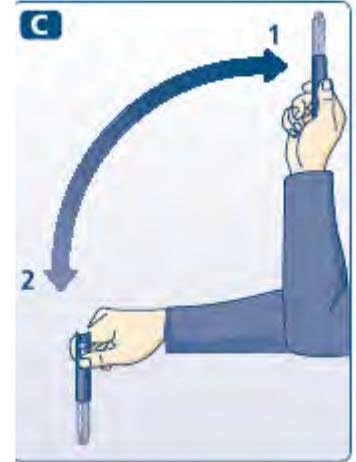
Pull off the pen cap (see diagram A).



B. Roll the pen between your palms 10 times – it is important that the pen is kept horizontal (see diagram B).



C. Then gently move the pen up and down ten times between position **1** and **2** as shown, so the glass ball moves from one end of the cartridge to the other (see diagram C).



Repeat rolling and moving the pen until the liquid appears white and cloudy.

For every following injection move the pen up and down between positions 1 and 2 at least ten times until the liquid appears white and cloudy.

After mixing, complete all the following steps of the injection right away. If there is a delay, the insulin will need to be mixed again.

Wipe the rubber stopper with an alcohol swab.

⚠ 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 70/30 FlexPen[®].

Attaching the needle

D. Remove the protective tab from a disposable needle.



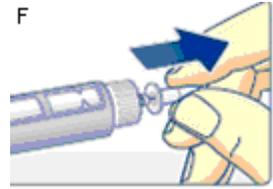
Screw the needle tightly onto your NovoLog[®] Mix 70/30 FlexPen[®]. It is important that the needle is put on straight (see diagram D).

Never place a disposable needle on your NovoLog[®] Mix 70/30 FlexPen[®] until you are ready to take your injection.

E. Pull off the big outer needle cap (see diagram E).



F. Pull off the inner needle cap and dispose of it (see diagram F).



- ⚠ Always use a new needle for each injection to help ensure sterility and prevent blocked needles.
- ⚠ Be careful not to bend or damage the needle before use.
- ⚠ To reduce the risk of a needle stick, **never put the inner needle cap back on the needle.**

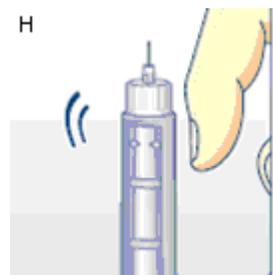
Giving the airshot before each injection:

Before each injection small amounts of air may collect in the cartridge during normal use. **To avoid injecting air and to make sure you take the right dose of insulin:**

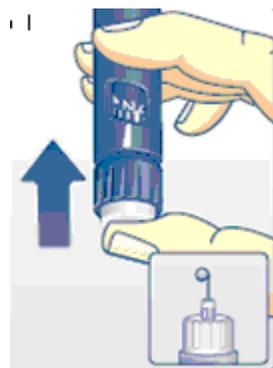
G. Turn the dose selector to select 2 units (see diagram G).



H. Hold your NovoLog® Mix 70/30 FlexPen® with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram H).



I. Keep the needle pointing upwards, press the push-button all the way in (see diagram I). The dose selector returns to 0.



A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If you do not see a drop of insulin after 6 times, do not use the NovoLog Mix® 70/30 FlexPen® and contact Novo Nordisk at 1-800-727-6500.

A small air bubble may remain at the needle tip, but it will not be injected.

SELECTING YOUR DOSE

Check and make sure that the dose selector is set at 0.

- J. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram J). When turning the dose selector, be careful not to press the push-button as insulin will come out.

You cannot select 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.

- ⚠ Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.



GIVING THE INJECTION

Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting. Wipe the skin with an alcohol swab and let the area dry.

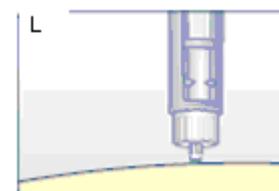
- K. Insert the needle into your skin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram K). Be careful only to push the button when injecting.

Turning the dose selector will not inject insulin.



- L. 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 (see diagram L). This will make sure that the full dose has been given.



You may see a drop of NovoLog® Mix 70/30 at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with an alcohol swab. **Do not rub the area.**

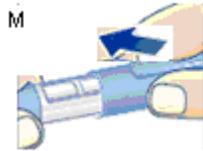
After the injection

Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog[®] Mix 70/30 FlexPen[®] after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

▲ Put the needle and any empty NovoLog[®] Mix 70/30 FlexPen[®] or any used NovoLog[®] Mix 70/30 FlexPen[®] still containing insulin in a sharps container or some type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

The NovoLog[®] Mix 70/30 FlexPen[®] prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

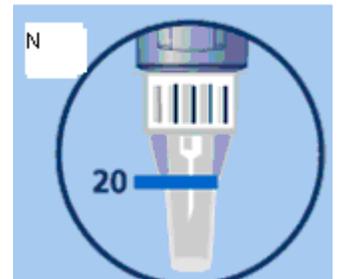
M. Put the pen cap on the NovoLog[®] Mix 70/30 FlexPen[®] and store the NovoLog[®] Mix 70/30 FlexPen[®] without the needle attached (see diagram M).



FUNCTION CHECK

If your NovoLog[®] Mix 70/30 FlexPen[®] is not working the right way, follow the steps below:

- Screw on a new NovoFine[®] needle
- Remove the big outer needle cap and the inner needle cap
- Do an airshot as described in "Giving the airshot before each injection".
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the NovoLog[®] Mix 70/30 FlexPen[®] 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 N). If NovoLog[®] Mix 70/30 FlexPen[®] has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog[®] Mix 70/30 FlexPen[®] and contact Novo Nordisk at 1-800-727-6500.

Maintenance

Your NovoLog[®] Mix 70/30 FlexPen[®] is designed to work accurately and safely. It must be handled with care. Avoid dropping your NovoLog[®] Mix 70/30 FlexPen[®] as it may damage it. If you are concerned that your NovoLog[®] Mix 70/30 FlexPen[®] is damaged, use a new one. You can clean the outside of your NovoLog[®] Mix 70/30 FlexPen[®] by wiping it with a damp cloth. Do not soak or wash your NovoLog[®] Mix 70/30 FlexPen[®] as it may damage it. Do not refill your NovoLog[®] Mix 70/30 FlexPen[®].

- ▲ Remove the needle from the NovoLog[®] Mix 70/30 FlexPen[®] after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.
- ▲ Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.
- ▲ Keep your NovoLog[®] Mix 70/30 FlexPen[®] and needles out of the reach of children.
- ▲ Use NovoLog[®] Mix 70/30 FlexPen[®] as directed to treat your diabetes. Do not share it with anyone else even if they also have diabetes.
- ▲ Always use a new needle for each injection.
- ▲ Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.
- ▲ As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog[®] Mix 70/30 FlexPen[®] is lost or damaged.
- ▲ Remember to keep the disposable NovoLog[®] Mix 70/30 FlexPen[®] with you. Do not leave it in a car or other location where it can get too hot or too cold.

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

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

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

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Princeton, New Jersey 08540

Patient Instructions for Use

NovoLog[®] Mix 70/30 10ml vial (100 Units/mL, U-100)

Read the following Patient Instructions for Use carefully before you start using your NovoLog[®] Mix 70/30 10ml vial and each time you get a refill. There may be new information. You should read the instructions even if you have used NovoLog[®] Mix 70/30 10ml vials before.

Before starting, gather all of the supplies that you will need to use for preparing and giving your insulin injection.

Never re-use syringes and needles.

How should I prepare and deliver the injection using the NovoLog[®] Mix 70/30 10 ml vial?

1. Check to make sure you have the correct type of insulin. This is especially important if you use different types of insulin.
2. Look at the vial and the insulin. The insulin should be white and cloudy after mixing. The tamper-resistant cap should be on the vial before the first use. If the cap has already been removed before your first use of the vial, or if the insulin looks clear or contains any particles, do not use it and return it to your pharmacy.
3. Wash your hands with soap and water. Clean your injection site with an alcohol swab and let the injection site dry before you inject. Talk with your healthcare provider about how to rotate injection sites and how to give an injection.
4. If you are using a new vial, pull off the tamper-resistant cap. Wipe the rubber stopper with an alcohol swab.
5. Roll the vial gently 10 times in your hands to mix it. This should be done with the vial in a horizontal (flat) position between your palms. **Do not** shake the vial. Shaking right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin. The insulin should be used only if it looks white and cloudy.
6. Pull back the plunger on the syringe until the black tip reaches the marking for the number of units you will inject.
7. Push the needle through the rubber stopper into the vial, and push the plunger all the way in to force air into the vial.
8. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose needed.
9. If there are air bubbles in the syringe, tap the syringe gently with your finger to raise the air bubbles to the top. Slowly push the plunger to the marking for your dose. This should move any air bubbles in the syringe back into the vial.
10. Check to make sure you have the right dose of NovoLog[®] Mix 70/30 in the syringe.

11. Pull the syringe out of the vial's rubber stopper.
12. If there is a delay after you rolled the vial, you will have to roll it again to remix the insulin and redraw your medicine. Your healthcare provider should tell you if you need to pinch the skin before inserting the needle. This can be different from person to person so it is important to ask your doctor if you did not receive instructions on pinching the skin. Insert the needle into the skin right away. Push the plunger to inject the insulin under your skin. Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin. When you are finished injecting the insulin, pull the needle out of your skin.
13. You may see a drop of NovoLog[®] Mix 70/30 at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you pull the needle from your skin, press the injection site lightly with an alcohol swab. **Do not** rub the area. **Do not** recap the needle.
14. **After the injection, dispose of the needle and syringe in a puncture-resistant container.** Place used syringes, needles, and insulin vials in a disposable puncture-resistant sharps container, or some type of hard plastic or metal container with a screw on cap such as a detergent bottle or coffee can.
15. Ask your healthcare provider about the right way to throw away used syringes and needles. There may be state or local laws about the right way to throw away used syringes and needles. **Do not** throw away used needles and syringes in household trash or recycling bins.

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

Date of Issue:

Version:

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