

NovoLog[®]**Insulin aspart (rDNA origin) Injection****DESCRIPTION**

NovoLog[®] (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. NovoLog 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 has the empirical formula C₂₅₆H₃₈₁N₆₅O₇₉S₆ and a molecular weight of 5825.8.

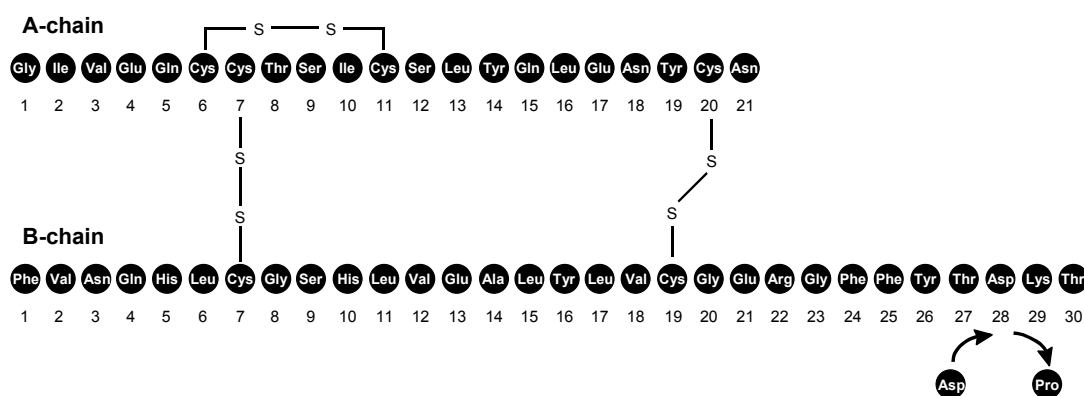


Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, and sodium chloride 0.58 mg/mL. NovoLog has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY**Mechanism of Action**

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

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see Figure 2 and Figure 3).

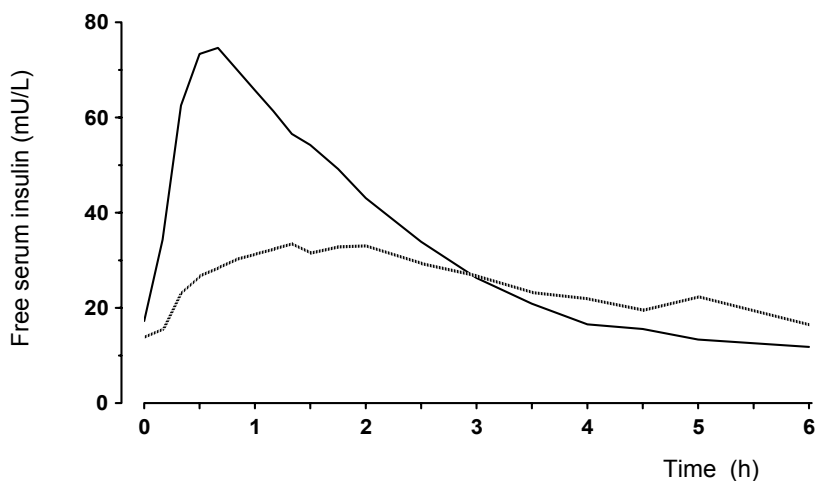
34 **Pharmacokinetics**

35 The single substitution of the amino acid proline with aspartic acid at position B28 in
36 NovoLog reduces the molecule's tendency to form hexamers as observed with regular human
37 insulin. NovoLog is, therefore, more rapidly absorbed after subcutaneous injection compared
38 to regular human insulin.

39

40 *Bioavailability and Absorption* - NovoLog has a faster absorption, a faster onset of action, and
41 a shorter duration of action than regular human insulin after subcutaneous injection (see
42 Figure 2 and Figure 3). The relative bioavailability of NovoLog compared to regular human
43 insulin indicates that the two insulins are absorbed to a similar extent.

44



45

46

47 Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a
48 single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve)
49 injected immediately before a meal in 22 patients with Type 1 diabetes.

50

51 In studies in healthy volunteers (total n=107) and patients with Type 1 diabetes (total n=40),
52 NovoLog consistently reached peak serum concentrations approximately twice as fast as
53 regular human insulin. The median time to maximum concentration in these trials was 40 to
54 50 minutes for NovoLog versus 80 to 120 minutes for regular human insulin. In a clinical trial
55 in patients with Type 1 diabetes, NovoLog and regular human insulin, both administered
56 subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of
57 82.1 and 35.9 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of
58 insulin aspart have not been established in patients with Type 2 diabetes.

59 The intra-individual variability in time to maximum serum insulin concentration for healthy
60 male volunteers was significantly less for NovoLog than for regular human insulin. The
61 clinical significance of this observation has not been established.

62 In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between
63 NovoLog and regular human insulin described above, were observed independent of the
64 injection site (abdomen, thigh, or upper arm). Differences in pharmacokinetics between
65 NovoLog® and regular human insulin are not associated with differences in overall glycemic
66 control.

67

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

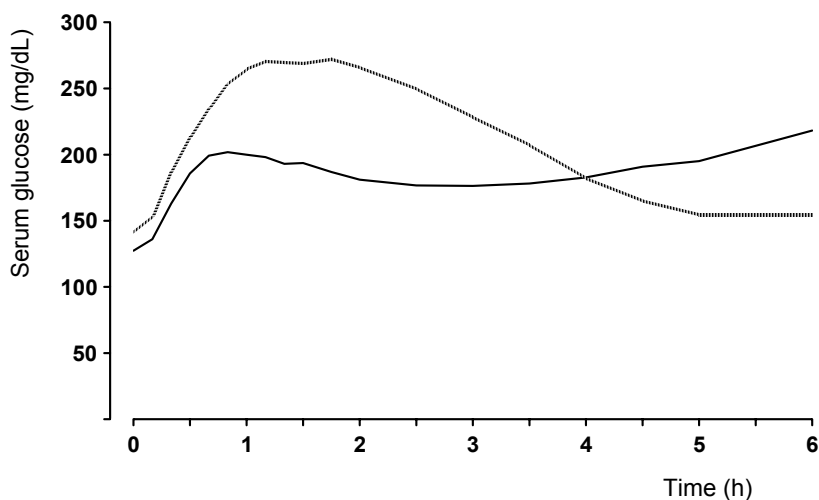
72

73 **Pharmacodynamics**

74 Studies in normal volunteers and patients with diabetes demonstrated that NovoLog has a
75 more rapid onset of action than regular human insulin.

76 In a 6-hour study in patients with Type 1 diabetes (n=22), the maximum glucose-lowering
77 effect of NovoLog occurred between 1 and 3 hours after subcutaneous injection (see Figure 3).
78 The duration of action for NovoLog is 3 to 5 hours compared to 5 to 8 hours for regular human
79 insulin. The time course of action of insulin and insulin analogs such as NovoLog may vary
80 considerably in different individuals or within the same individual. The parameters of
81 NovoLog activity (time of onset, peak time and duration) as designated in Figure 3 should be
82 considered only as general guidelines. The rate of insulin absorption and consequently the
83 onset of activity is known to be affected by the site of injection, exercise, and other variables
84 (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog® and
85 regular human insulin are not associated with differences in overall glycemic control.

86



87

88

89 Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose
90 of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately
91 before a meal in 22 patients with Type 1 diabetes.

92

93 **Special Populations**

94 *Children and Adolescents* - The pharmacokinetic and pharmacodynamic properties of
95 NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12
96 years, n=9) and adolescents (13-17 years [Tanner grade ≥ 2], n=9) with Type 1 diabetes. The
97 relative differences in pharmacokinetics and pharmacodynamics in children and adolescents
98 with Type 1 diabetes between NovoLog and regular human insulin were similar to those in
99 healthy adult subjects and adults with Type 1 diabetes.

100
101 *Geriatrics* - The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog
102 has not been studied.

103
104 *Gender* - In healthy volunteers, no difference in insulin aspart levels was seen between men
105 and women when body weight differences were taken into account. There was no significant
106 difference in efficacy noted (as assessed by HbA1c) between genders in a trial in patients with
107 Type 1 diabetes.

108
109 *Obesity* - In a study of 23 patients with type 1 diabetes and a wide range of body mass index
110 (BMI, 22-39 kg/m²), the pharmacokinetic parameters, AUC and C_{max}, of NovoLog® were
111 generally unaffected by BMI. Clearance of NovoLog® was reduced by 28% in patients with
112 BMI >32 compared to patients with BMI <23 when a single dose of 0.1 U/kg NovoLog® was
113 administered. However, only 3 patients with BMI <23 were studied.

114
115 *Ethnic Origin* - The effect of ethnic origin on the pharmacokinetics of NovoLog has not been
116 studied.

117
118 *Renal Impairment* - Some studies with human insulin have shown increased circulating levels
119 of insulin in patients with renal failure. A single subcutaneous dose of NovoLog® was
120 administered in a study of 18 patients with creatinine clearance values ranging from normal to
121 <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values
122 on AUC and C_{max} of NovoLog® was found. However, only 2 patients with severe renal
123 impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of
124 insulin, including NovoLog, may be necessary in patients with renal dysfunction (see
125 PRECAUTIONS, Renal Impairment).

126
127 *Hepatic Impairment* - Some studies with human insulin have shown increased circulating
128 levels of insulin in patients with liver failure. In an open-label, single-dose study of 24
129 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic
130 impairment), no correlation was found between the degree of hepatic failure and any
131 NovoLog® pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of
132 insulin, including NovoLog, may be necessary in patients with hepatic dysfunction (see
133 PRECAUTIONS, Hepatic Impairment).

134
135 *Pregnancy* - The effect of pregnancy on the pharmacokinetics and glucodynamics of
136 NovoLog has not been studied (see PRECAUTIONS, Pregnancy).

137
138 *Smoking* - The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog has
139 not been studied.

140 **CLINICAL STUDIES**

141
142 To evaluate the safety and efficacy of NovoLog in patients with Type 1 diabetes, two
143 six-month, open-label, active-control (NovoLog vs. Novolin® R) studies were conducted (see
144 Table 1). NovoLog was administered by subcutaneous injection immediately prior to meals

145 and regular human insulin was administered by subcutaneous injection 30 minutes before
 146 meals. NPH insulin was administered as the basal insulin in either single or divided daily
 147 doses. Changes in HbA1c, the rates of hypoglycemia (as determined from the number of
 148 events requiring intervention from a third party), and the incidence of ketosis were clinically
 149 comparable for the two treatment regimens. The mean total daily doses of insulin were greater
 150 (1-3 U/day) in the NovoLog-treated patients compared to patients who received regular human
 151 insulin. This difference was primarily due to basal insulin requirements. To achieve
 152 improved glycemic control, some patients required more than three doses of meal-related
 153 insulin and/or more than one dose of basal insulin (see Table 1). No serum glucose
 154 measurements were obtained in these studies.

155
 156 To evaluate the safety and efficacy of NovoLog in patients with Type 2 diabetes, one six-
 157 month, open-label, active-control (NovoLog vs. Novolin R) study was conducted (see Table
 158 1). NovoLog was administered by subcutaneous injection immediately prior to meals and
 159 regular human insulin was administered by subcutaneous injection 30 minutes before meals.
 160 NPH insulin was administered as the basal insulin in either single or divided daily doses.
 161 Changes in HbA1c and the rates of hypoglycemia (as determined from the number of events
 162 requiring intervention from a third party) were clinically comparable for the two treatment
 163 regimens. The mean total daily dose of insulin was greater (2 U/day) in the NovoLog-treated
 164 patients compared to patients who received regular human insulin. This difference was
 165 primarily due to basal insulin requirements. To achieve improved glycemic control, some
 166 patients required more than three doses of meal-related insulin and/or more than one dose of
 167 basal insulin (see Table 1).

168
 169 Table 1. Results of two six-month, active-control, open-label trials in patients with Type 1
 170 diabetes (Studies A and B) and one six-month, active-control, open-label trial in patients with
 171 Type 2 diabetes (Study C).

| Study | Treatment (n) | Mean HbA1c (%) | | Hypoglycemia ¹ (events / month / patient) | % of Patients Using Various Numbers of Insulin Injections / Day ² | | | | |
|-------|-------------------|----------------|---------|---|--|----|-------|-------|----|
| | | Baseline | Month 6 | | Rapid-acting | | | Basal | |
| | | | | | 1 - 2 | 3 | 4 - 5 | 1 | 2 |
| A | NovoLog (n=694) | 8.0 | 7.9 | 0.06 | 3 | 75 | 22 | 54 | 46 |
| | Novolin R (n=346) | 8.0 | 8.0 | 0.06 | 6 | 75 | 19 | 63 | 37 |
| B | NovoLog (n=573) | 7.9 | 7.8 | 0.08 | 4 | 90 | 6 | 94 | 6 |
| | Novolin R (n=272) | 8.0 | 7.9 | 0.06 | 4 | 91 | 4 | 93 | 7 |
| C | NovoLog (n=90) | 8.1 | 7.7 | 0.02 | 4 | 93 | 4 | 97 | 4 |
| | Novolin R (n=86) | 7.8 | 7.8 | 0.01 | 2 | 93 | 5 | 93 | 7 |

173 ¹ Events requiring intervention from a third party during the last three months of treatment

174 ² Percentages are rounded to the nearest whole number

175
 176 To evaluate the use of NovoLog by subcutaneous infusion with an external pump, two open-
 177 label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog

178 versus Velosulin (buffered regular human insulin) in patients with Type 1 diabetes. Changes in
179 HbA1c and rates of hypoglycemia were comparable. Patients with Type 2 diabetes were also
180 studied in an open-label, parallel design trial (16 weeks [n=127]) using NovoLog by
181 subcutaneous infusion compared to pre-prandial injection (in conjunction with basal NPH
182 injections). Reductions in HbA1c and rates of hypoglycemia were comparable. (See
183 INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, Mixing of Insulins,
184 Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED
185 STORAGE.)

186

187 **INDICATIONS AND USAGE**

188 NovoLog is indicated for the treatment of adult patients with diabetes mellitus, for the control
189 of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity
190 than human regular insulin, NovoLog given by injection should normally be used in regimens
191 with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by
192 external insulin pumps. (See WARNINGS, PRECAUTIONS [especially Usage in Pumps],
193 Information for Patients [especially For Patients Using Pumps], Mixing of Insulins, DOSAGE
194 AND ADMINISTRATION, RECOMMENDED STORAGE.)

195

196 **CONTRAINDICATIONS**

197 NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to
198 NovoLog or one of its excipients.

199

200 **WARNINGS**

201 **NovoLog differs from regular human insulin by a more rapid onset and a shorter**
202 **duration of activity. Because of the fast onset of action, the injection of NovoLog should**
203 **immediately be followed by a meal. Because of the short duration of action of NovoLog,**
204 **patients with diabetes also require a longer-acting insulin to maintain adequate glucose**
205 **control. Glucose monitoring is recommended for all patients with diabetes and is**
206 **particularly important for patients using external pump infusion therapy.**

207

208 **Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog.**
209 **As with all insulins, the timing of hypoglycemia may differ among various insulin**
210 **formulations.**

211

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

216

217 **Insulin Pumps: When used in an external insulin pump for subcutaneous infusion,**
218 **NovoLog should not be diluted or mixed with any other insulin. Physicians and patients**
219 **should carefully evaluate information on pump use in the NovoLog physician and patient**
220 **package inserts and in the pump manufacturer's manual (e.g. NovoLog-specific**
221 **information should be followed for in-use time, frequency of changing infusion sets, or**

222 **other details specific to NovoLog usage, because NovoLog-specific information may**
223 **differ from general pump manual instructions).**

224

225 **Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and**
226 **ketosis in a short time because of the small subcutaneous depot of insulin. This is**
227 **especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed**
228 **through skin and have shorter duration of action. These differences may be particularly**
229 **relevant when patients are switched from multiple injection therapy or infusion with**
230 **buffered regular insulin. Prompt identification and correction of the cause of**
231 **hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may**
232 **be required. (See PRECAUTIONS, Mixing of Insulins, Information for Patients,**
233 **DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)**

234

235 **PRECAUTIONS**

236 **General**

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

244 As with all insulin preparations, the time course of NovoLog action may vary in different
245 individuals or at different times in the same individual and is dependent on site of injection,
246 blood supply, temperature, and physical activity.

247 Adjustment of dosage of any insulin may be necessary if patients change their physical
248 activity or their usual meal plan. Insulin requirements may be altered during illness,
249 emotional disturbances, or other stresses.

250

251 *Hypoglycemia* - As with all insulin preparations, hypoglycemic reactions may be associated
252 with the administration of NovoLog. Rapid changes in serum glucose levels may induce
253 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early
254 warning symptoms of hypoglycemia may be different or less pronounced under certain
255 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such
256 as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions).
257 Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior
258 to patients' awareness of hypoglycemia.

259

260 *Renal Impairment* - As with other insulins, the dose requirements for NovoLog® may be
261 reduced in patients with renal impairment (see CLINICAL PHARMACOLOGY,
262 Pharmacokinetics).

263

264 *Hepatic Impairment* - As with other insulins, the dose requirements for NovoLog® may be
265 reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY,
266 Pharmacokinetics).

267

268 *Allergy - Local Allergy* - As with other insulin therapy, patients may experience redness,
269 swelling, or itching at the site of injection. These minor reactions usually resolve in a few
270 days to a few weeks, but in some occasions, may require discontinuation of NovoLog. In
271 some instances, these reactions may be related to factors other than insulin, such as irritants in
272 a skin cleansing agent or poor injection technique.

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

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

279 In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735
280 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who
281 received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog
282 were discontinued due to allergic reactions.

283

284 *Antibody Production* - Increases in levels of anti-insulin antibodies that react with both human
285 insulin and insulin aspart have been observed in patients treated with NovoLog®. The
286 number of patients treated with insulin aspart experiencing these increases is greater than the
287 number among those treated with human regular insulin. Data from a 12-month controlled
288 trial in patients with Type 1 diabetes suggest that the increase in these antibodies is transient.
289 The differences in antibody levels between the human regular insulin and insulin aspart
290 treatment groups observed at 3 and 6 months were no longer evident at 12 months. The
291 clinical significance of these antibodies is not known. They do not appear to cause
292 deterioration in HbA1c or to necessitate increases in insulin dose.

293

294 *Pregnancy and Lactation*

295 Female patients should be advised to tell their physician if they intend to become, or if they
296 become pregnant. Information is not available on the use of NovoLog during pregnancy or
297 lactation.

298

299 *Usage in Pumps*

300

301 **Pumps:**

302 NovoLog is recommended for use in Disetronic H-TRON series, MiniMed 500 series, and
303 other equivalent pumps.

304

305 **Reservoirs and infusion sets:**

306 NovoLog is recommended for use in any reservoir and infusion sets that are compatible with
307 insulin and the specific pump. In-vitro studies have shown that pump malfunction, loss of
308 metacresol, and insulin degradation, may occur when NovoLog is maintained in a pump
309 system for more than 48 hours. Reservoirs and infusion sets should be changed at least every
310 48 hours.

311

312 NovoLog in clinical use should not be exposed to temperatures greater than 37°C (98.6°F).

313 **NovoLog should not be mixed with other insulins or with a diluent when it is used in the**
314 **pump.** (See WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients,
315 DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

316

317 **Information for Patients**

318

319 *For all patients:*

320 Patients should be informed about potential risks and advantages of NovoLog therapy
321 including the possible side effects. Patients should also be offered continued education and
322 advice on insulin therapies, injection technique, life-style management, regular glucose
323 monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo-
324 and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of
325 dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage
326 of insulin. Patients should be informed that frequent, patient-performed blood glucose
327 measurements are needed to achieve optimal glycemic control and avoid both hyper- and
328 hypoglycemia.

329

330 Female patients should be advised to tell their physician if they intend to become, or if they
331 become pregnant. Information is not available on the use of NovoLog during pregnancy or
332 lactation (see PRECAUTIONS, Pregnancy).

333

334 *For patients using pumps*

335 Patients using external pump infusion therapy should be trained in intensive insulin therapy
336 with multiple injections and in the function of their pump and pump accessories.

337

338 **Pumps:**

339 NovoLog is recommended for use in Disetronic H-TRON series, MiniMed 500 series, and
340 other equivalent pumps

341

342 **Reservoirs and infusion sets:**

343 NovoLog is recommended for use in any reservoir and infusion sets that are compatible with
344 insulin and the specific pump. Please see recommended reservoir and infusion sets in the
345 pump manual.

346

347 **To avoid insulin degradation, infusion set occlusion, and loss of the preservative**
348 **(metacresol), reservoirs, infusion sets, and injection site should be changed at least every**
349 **48 hours.**

350

351

352 **Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded.** The
353 temperature of the insulin may exceed ambient temperature when the pump housing, cover,
354 tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are
355 erythematous, pruritic, or thickened should be reported to medical personnel, and a new site
356 selected because continued infusion may increase the skin reaction and/or alter the absorption
357 of NovoLog. Pump or infusion set malfunctions or insulin degradation can lead to
358 hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin.
359 This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed
360 through skin and have shorter duration of action. These differences are particularly relevant
361 when patients are switched from infused buffered regular insulin or multiple injection therapy.
362 Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary.
363 Problems include pump malfunction, infusion set occlusion, leakage, disconnection or
364 kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may
365 occur. If these problems cannot be promptly corrected, patients should resume therapy with
366 subcutaneous insulin injection and contact their physician. (See WARNINGS,
367 PRECAUTIONS, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and
368 RECOMMENDED STORAGE.)

369

370 **Laboratory Tests**

371 As with all insulin therapy, the therapeutic response to NovoLog should be monitored by
372 periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is
373 recommended for the monitoring of long-term glycemic control.

374

375 **Drug Interactions**

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

- 378 • The following are examples of substances that may increase the blood-glucose-lowering
379 effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors,
380 disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene,
381 salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- 382 • The following are examples of substances that may reduce the blood-glucose-lowering
383 effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g.,
384 epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin,
385 thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).
- 386 • Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the
387 blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which
388 may sometimes be followed by hyperglycemia.
- 389 • In addition, under the influence of sympatholytic medicinal products such as beta-
390 blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be
391 reduced or absent (see CLINICAL PHARMACOLOGY).

392

393 **Mixing of Insulins**

- 394 • A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog
395 with NPH human insulin immediately before injection produced some attenuation in the
396 peak concentration of NovoLog, but that the time to peak and the total bioavailability of
397 NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin,
398 NovoLog should be drawn into the syringe first. The injection should be made
399 immediately after mixing. Because there are no data on the compatibility of NovoLog and
400 crystalline zinc insulin preparations, NovoLog should not be mixed with these
401 preparations.
- 402 • The effects of mixing NovoLog with insulins of animal source or insulin preparations
403 produced by other manufacturers have not been studied (see WARNINGS).
 - 404 • Mixtures should not be administered intravenously.
 - 405 • When used in external subcutaneous infusion pumps for insulin, NovoLog should not be
406 mixed with any other insulins or diluent.
- 407

408 **Carcinogenicity, Mutagenicity, Impairment of Fertility**

409 Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the
410 carcinogenic potential of NovoLog. In 52-week studies, Sprague-Dawley rats were dosed
411 subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times
412 the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively).
413 At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in
414 females when compared to untreated controls. The incidence of mammary tumors for
415 NovoLog was not significantly different than for regular human insulin. The relevance of
416 these findings to humans is not known. NovoLog was not genotoxic in the following tests:
417 Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood
418 lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in *ex vivo*
419 UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous
420 doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on
421 U/body surface area), no direct adverse effects on male and female fertility, or general
422 reproductive performance of animals was observed.

423

424 **Pregnancy - Teratogenic Effects - Pregnancy Category C**

425 There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant
426 women. NovoLog should be used during pregnancy only if the potential benefit justifies the
427 potential risk to the fetus.

428

429 It is essential for patients with diabetes or history of gestational diabetes to maintain good
430 metabolic control before conception and throughout pregnancy. Insulin requirements may
431 decrease during the first trimester, generally increase during the second and third trimesters,
432 and rapidly decline after delivery. Careful monitoring of glucose control is essential in such
433 patients.

434

435 Subcutaneous reproduction and teratology studies have been performed with NovoLog and
436 regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats
437 before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis.
438 The effects of NovoLog did not differ from those observed with subcutaneous regular human

439 insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and
440 visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the
441 human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a
442 dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0
443 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal
444 hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50
445 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the
446 human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose
447 of 1.0 U/kg/day for rabbits, based on U/body surface area.

448

449 **Nursing Mothers**

450 It is unknown whether insulin aspart is excreted in human milk. Many drugs, including
451 human insulin, are excreted in human milk. For this reason, caution should be exercised when
452 NovoLog is administered to a nursing mother.

453

454 **Pediatric Use**

455 Safety and effectiveness of NovoLog in children have not been studied.

456

457 **Geriatric Use**

458 Of the total number of patients (n= 1,375) treated with NovoLog in 3 human insulin-controlled
459 clinical studies, 2.6% (n=36) were 65 years of age or over. Half of these patients had Type 1
460 diabetes (18/1285) and half had Type 2 (18/90) diabetes. The HbA1c response to NovoLog,
461 as compared to human insulin, did not differ by age, particularly in patients with Type 2
462 diabetes. Additional studies in larger populations of patients 65 years of age or over are
463 needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger
464 patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of
465 NovoLog action have not been performed.

466

467

468 **ADVERSE REACTIONS**

469 Clinical trials comparing NovoLog with regular human insulin did not demonstrate a
470 difference in frequency of adverse events between the two treatments.

471 Adverse events commonly associated with human insulin therapy include the following:

472 **Body as Whole** - *Allergic reactions* (see PRECAUTIONS, Allergy).

473 **Skin and Appendages** - *Injection site reaction, lipodystrophy, pruritus, rash* (see
474 PRECAUTIONS, Allergy; Information for Patients, Usage in Pumps).

475 **Other** – *Hypoglycemia, Hyperglycemia and ketosis* (see WARNINGS and PRECAUTIONS).

476 In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were
477 observed in some patients treated with NovoLog. The clinical significance of this finding is
478 unknown.

479

480 **OVERDOSAGE**

481 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
482 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
483 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes

484 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
485 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
486 may be necessary because hypoglycemia may recur after apparent clinical recovery.

487

488 **DOSAGE AND ADMINISTRATION**

489 NovoLog should generally be given immediately before a meal (start of meal within 5 to 10
490 minutes after injection) because of its fast onset of action. The dosage of
491 NovoLog should be individualized and determined, based on the physician's advice, in
492 accordance with the needs of the patient. The total daily individual insulin requirement is
493 usually between 0.5 to 1.0 units/kg/day. When used in a meal-related subcutaneous injection
494 treatment regimen, 50 to 70% of total insulin requirements may be provided by NovoLog and
495 the remainder provided by an intermediate-acting or long-acting insulin. When used in
496 external insulin infusion pumps, the initial programming of the pump is based on the total
497 daily insulin dose of the previous regimen. Although there is significant interpatient
498 variability, approximately 50% of the total dose is given as meal-related boluses of NovoLog
499 and the remainder as basal infusion. Because of NovoLog's comparatively rapid onset and
500 short duration of glucose lowering activity, some patients may require more basal insulin and
501 more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using
502 human regular insulin. Additional basal insulin injections, or higher basal rates in external
503 subcutaneous infusion pumps may be necessary. **NovoLog in the reservoir and infusion
504 sets, and the injection site must be changed at least every 48 hours.**

505 NovoLog should be administered by subcutaneous injection in the abdominal wall, the thigh,
506 or the upper arm, or by continuous subcutaneous infusion in the abdominal wall. Injection
507 sites and infusion sites should be rotated within the same region. As with all insulins, the
508 duration of action will vary according to the dose, injection site, blood flow, temperature, and
509 level of physical activity.

510 Parenteral drug products should be inspected visually for particulate matter and discoloration
511 prior to administration, whenever solution and container permit. Never use any NovoLog if it
512 has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog
513 should not be used after the printed expiration date.

514

515 **HOW SUPPLIED**

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

| | |
|---|------------------|
| 518 10 mL vials | NDC 0169-7501-11 |
| 519 3 mL PenFill [®] cartridges* | NDC 0169-3303-12 |
| 520 3 mL NovoLog FlexPen [®] Prefilled syringe | NDC 0169-6339-10 |
| 521 3 mL NovoLog InnoLet [®] Prefilled syringe | NDC 0169-xxxx-xx |

522

523 * NovoLog PenFill cartridges are for use with NovoFine[®] disposable needles and the
524 following Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices:
525 NovoPen[®] 3, NovoPen Junior, InnoLet[®], and InDuo[®].

526 NovoLog FlexPen Prefilled syringes are for use with NovoFine disposable needles.

527 **RECOMMENDED STORAGE**

528 NovoLog in unopened vials, cartridges, NovoLog FlexPen, and NovoLog InnoLet Prefilled
 529 syringes should be stored between 2° and 8°C (36° to 46°F). *Do not freeze. Do not use*
 530 **NovoLog if it has been frozen or exposed to temperatures that exceed 37°C (98.6°F)**. After
 531 a vial, cartridge, or Prefilled syringe has been punctured, it may be kept at temperatures below
 532 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened
 533 vials may be refrigerated. Cartridges should not be refrigerated after insertion into the Novo
 534 Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices. The infusion set (tubing
 535 and needle) should be changed at least every 48 hours.

536

537 NovoLog in the reservoir should be discarded after at least every 48 hours of use or after
 538 exposure to temperatures that exceed 37°C (98.6°F).

539

| | Not in-use (unopened) Room Temperature (below 30° C) | Not in-use (unopened) Refrigerated | In-use (opened) Room Temperature (below 30° C) |
|----------------------------|--|---------------------------------------|---|
| 10 mL vial | 28 days | Until expiration date | 28 days (refrigerated/room temperature) |
| 3 mL PenFill cartridges | 28 days | Until expiration date | 28 days (Do not refrigerate) |
| 3 mL NovoLog FlexPen | 28 days | Until expiration date | 28 days (Do not refrigerate) |
| 3 mL NovoLog InnoLet | 28 days | Until expiration date | 28 days (Do not refrigerate) |

540

541

542 Rx only

543

544 Date of Issue: XX xx, 2004

545 8-XXXX-XX-XXX-X

546

547 Manufactured For Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey 08540

548 Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

549

550

551 www.novonordisk-us.com

552

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 554 are trademarks of Novo Nordisk A/S

555 InDuo® is a trademark of LifeScan, Inc., a Johnson & Johnson company.

556 H-TRON™ is a trademark of Disetronic Medical Systems, Inc.

557

1
2
3 **Information For The Patient**
4 **NovoLog[®] (Insulin aspart [rDNA origin] Injection)**
5 **3 mL PenFill[®] Disposable Cartridge (300 units per cartridge)**
6 **10 mL Vial (1000 units per vial)**
7 **100 units/mL (U-100)**

- 8 • What is the most important information I should know about NovoLog?
9 • For all NovoLog users
10 • For pump users
11 • What is NovoLog?
12 • Who should not use NovoLog?
13 • What should I know about using insulin?
14 • What should I know about using NovoLog?
15 • What should I avoid when using NovoLog?
16 • What are the possible side effects of NovoLog?
17 • How should I store NovoLog?
18 • General advice
19 • Injection and pump infusion instructions
20 • How should I inject NovoLog?
21 • Using Vials
22 • Using Cartridges
23 • How should I infuse NovoLog with an external subcutaneous insulin infusion
24 pump?
25 • How should I mix insulins?

26
27 Read this information carefully before you begin treatment. Read the information you
28 get whenever you get more medicine. There may be new information. This information
29 does not take the place of talking with your doctor about your medical condition or your
30 treatment. If you have any questions about NovoLog[®] (NO-voe-log), ask your doctor.
31 Only your doctor can determine if NovoLog[®] is right for you.
32

33 **What is the most important information I should know about NovoLog?**

34
35 *For All NovoLog Users*

- 36 • NovoLog (NO-voe-log) is different from regular human insulin and buffered regular
37 human insulin (Velosulin). It works faster (rapid onset of action) and will not work as
38 long (shorter duration of action) as regular human insulin or buffered regular human
39 insulin (Velosulin).
40
41 • Because the onset of action is fast, you should eat a meal 5 to 10 minutes after a
42 NovoLog injection or NovoLog bolus infusion dose given by an external pump. (A
43 bolus is a large dose.) Eating right after the dose will reduce the risk of low blood
44 sugar (hypoglycemia).
45

- 46 • The shorter duration of NovoLog's action means that you may need to use an
47 intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog
48 insulin infusion in the pump. This will give the best glucose control and will help you
49 avoid hyperglycemia (high blood sugar) and ketoacidosis (too much acid [low pH] in
50 your body).
- 51
- 52 • Glucose monitoring is recommended for all patients who use insulin.
- 53

54 If you use NovoLog by injection, you may need to increase some or all of the following:

- 55 • your total dose of insulin
- 56 • your dose of intermediate or long-acting insulin (for example, NPH)
- 57 • the number of injections of basal insulin
- 58

59 If you infuse NovoLog into the skin (subcutaneous tissue) by pump, you may need to
60 increase some or all of the following:

- 61 • your total insulin dose
- 62 • the basal infusion dose
- 63 • the proportion of total insulin given as a basal infusion
- 64

65 Age and exposure to heat affect the stability of NovoLog and its preservative. Also,
66 NovoLog does not work well after it has been frozen. Therefore, do not use old insulin or
67 insulin that has been exposed to temperature extremes. Hyperglycemia may be a sign that
68 the insulin is no longer working and needs to be replaced.

69

70 **Do not mix NovoLog:**

- 71 • with any other insulins when used in a pump
 - 72 • with Lantus[®] (insulin glargine [rDNA origin] injection) when used with injections
73 by syringe
- 74 (You may, however, mix NovoLog with NPH when used with injections by syringe.
75 See: How should I mix insulins?)
- 76

77 *For Pump Users*

- 78 • Glucose monitoring is very important for patients using external pump subcutaneous
79 infusion therapy. You should be aware that pump or infusion set malfunctions that
80 result in inadequate insulin infusion can quickly lead to hyperglycemia and ketosis.
81 Accordingly, problems with the infusion pump, the flow of insulin, or the quality of
82 the insulin should be identified and corrected as quickly as possible. There is only a
83 small amount of insulin infused into the skin with a pump. The faster absorption
84 through the skin of rapid-acting insulin analogs and shorter duration of action may
85 give you less time to identify and correct the problem than with buffered regular
86 insulin.
- 87
- 88 • Therefore, you should dose with insulin from a new vial of NovoLog if unexplained
89 hyperglycemia or pump alarms do not respond to all of the following:
 - 90 • a repeat dose (injection or bolus) of NovoLog

- 91 • a change in the infusion set, including the NovoLog in the reservoir
- 92 • a change in the infusion site

93

94 If these measures do not work, you may need to resume skin (subcutaneous)
95 injections with syringes or insulin pens. Continue to monitor your glucose and
96 ketones. If problems continue, you must contact your doctor.

97

- 98 • When NovoLog is used in an external subcutaneous insulin infusion pump, you
99 should use only recommended pumps. Reservoirs, infusion sets, and injection site
100 should be changed at least every 48 hours. In addition, the reservoir, the infusion set,
101 and infusion site should be changed:
 - 102 • with unexpected hyperglycemia or ketosis
 - 103 • when the alarm sounds, as specified by your pump manual
 - 104 • if the insulin or pump has been exposed to temperatures over 98.6°F (37°C), such
105 as in a sauna, with long showers, or on a hot day
 - 106 • if the insulin or pump could have absorbed radiant heat, for example from
107 sunlight, that would heat the insulin to over 98.6°F (37°C). Dark colored pump
108 cases or sport covers can increase this type of heat. The location where the pump
109 is worn may also affect the temperature

110

111 Patients who develop “pump bumps” (skin reactions at the infusion site) may need to
112 change infusion sites more often than every 48 hours.

113

114 **For your safety, read the section “What are the possible side effects of NovoLog?” to**
115 **review the symptoms of low blood sugar (hypoglycemia) and high blood sugar**
116 **(hyperglycemia).**

117

118 **What is NovoLog?**

119 NovoLog is a clear, colorless, sterile solution for injection or infusion under the skin
120 (subcutaneously). NovoLog is a human-made form of insulin to lower your blood sugar
121 faster than human regular insulin. Because the insulin is human-made by recombinant
122 DNA technology (rDNA) and is chemically different from the insulin made by the human
123 body, it is called an insulin analog. The active ingredient in NovoLog is insulin aspart.
124 The concentration of insulin aspart is 100 units per milliliter, or U100. NovoLog also
125 contains: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate,
126 and sodium chloride. Hydrochloric acid and/or sodium hydroxide may be added to adjust
127 the pH. These ingredients help to preserve or stabilize NovoLog insulin. The pH
128 (balance between acid and alkaline conditions) is important to the stability of NovoLog.
129 Increases in temperature can affect the stability of NovoLog, so it may not work well.

130

131 **Who should not use NovoLog?**

132 Do not use NovoLog if:

- 133 • your blood sugar (glucose) is too low (hypoglycemia)
- 134 • you do not plan to eat right after your injection or infusion

- 135 • you are allergic to insulin aspart or any of the ingredients contained in NovoLog
136 (check with your doctor if you are not sure)

137

138 The effects of NovoLog on an unborn child or on a nursing baby are unknown.
139 Therefore, tell your doctor if you plan to become pregnant or breast feed, or if you
140 become pregnant. You may need to use another medicine.

141

142 Tell your doctor about all medicines and supplements that you are using. Some
143 medicines, including non-prescription medicines and dietary supplements, may affect
144 your diabetes.

145

146 **What should I know about using insulin?**

- 147 • Make any change of insulin cautiously and only under medical supervision. Changes
148 in the strength, manufacturer, type (for example: Regular, NPH, Lente[®]), species
149 (beef, pork, beef-pork, human) or method of manufacture (recombinant [rDNA] or
150 animal source insulin) may cause a need for a change in the timing or dose of the new
151 insulin.
- 152 • Glucose monitoring will help you and your health care provider adjust dosages.
- 153 • Always carry a quick source of sugar, such as candy or glucose tablets, to treat low
154 blood sugars (hypoglycemia).
- 155 • Always carry identification that states that you have diabetes.

156

157 **What should I know about using NovoLog?**

158 *See the end of this Patient Information for instructions for using NovoLog in*
159 *injections and pumps.*

160

- 161 • NovoLog starts working 10 to 20 minutes after injection or infusion. The greatest
162 blood sugar lowering effect is between 1 and 3 hours after injection or infusion. This
163 blood sugar lowering lasts for 3 to 5 hours. (The time periods are only general
164 guidelines.)
- 165
- 166 • Because the onset of action is rapid, you should eat a meal within 5 to 10 minutes after
167 a NovoLog injection or a NovoLog bolus dose from an external pump to avoid low
168 blood sugar (hypoglycemia).
- 169
- 170 • The shorter duration of NovoLog's action means that you may need to use an
171 intermediate or longer-acting insulin (basal insulin) or higher basal rates of NovoLog
172 insulin infusion in the pump. This will help you avoid hyperglycemia and
173 ketoacidosis.
- 174
- 175 • Do not inject or infuse in skin that has become reddened or bumpy or thickened after
176 infusion or injection. Insulin absorption in these areas may not be the same as that in
177 normal skin, and may change the onset and duration of insulin action.

178

- 179 • Use NovoLog only if it appears clear and colorless. Do not use NovoLog if it appears
180 cloudy, thickened, or colored, or if it contains solid particles.

181

182 **What should I avoid while using NovoLog?**

- 183 • Drinking alcohol may lead to hypoglycemia.
184 • Do not miss meals after injections of NovoLog or bolus infusions of NovoLog.

185

186 **What are the possible side effects of NovoLog?**

187 Insulins can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar),
188 allergy, and skin reactions.

189

190 **Hypoglycemia** (low blood sugar). This is the most common side effect. It occurs when
191 there is a conflict between the amount of carbohydrates (source of glucose) from your
192 food, the amount of glucose used by your body, and the amount and timing of insulin
193 dosing. Therefore, **hypoglycemia can occur with:**

- 194 • **The wrong insulin dose.** This can happen with any of the following:
195 • too much insulin is injected
196 • the bolus dose of insulin infusion is set too high
197 • the basal infusion dose is set too high
198 • the pump does not work right, delivering too much insulin
199 • **Medicines that directly lower glucose or increase sensitivity to insulin.** This can
200 happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for
201 infections), ACE inhibitors (for blood pressure and heart failure), salicylates,
202 including aspirin and NSAIDS (for pain), some antidepressants, and with other
203 medicines.
204 • **Medical conditions that limit the body's glucose reserve, lengthen the time**
205 **insulin stays in the body, or that increase sensitivity to insulin.** These conditions
206 include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and
207 the kidney.
208 • **Not enough carbohydrate (sugar or starch) intake.** This can happen if:
209 • a meal or snack is missed or delayed
210 • you have vomiting or diarrhea that decreases the amount of glucose absorbed by
211 your body
212 • alcohol interferes with carbohydrate metabolism
213 • **Too much glucose use by the body.** This can happen from:
214 • too much exercise
215 • higher than normal metabolism rates due to fever or an overactive thyroid

216

217 Hypoglycemia can be mild or severe. Its onset may be rapid. Patients with very good
218 (tight) glucose control, patients with diabetic neuropathy (nerve problems), or patients
219 using some Beta-blockers (used for high blood pressure and heart conditions) may have
220 few warning symptoms before severe hypoglycemia develops. Hypoglycemia may reduce
221 your ability to drive a car or use mechanical equipment without risk of injury to yourself
222 or others. Severe hypoglycemia can cause temporary or permanent harm to your heart or

223 brain. **It may cause unconsciousness, seizures, or death.** Symptoms of hypoglycemia
224 include:

- 225 • anxiety, irritability, restlessness, trouble concentrating, personality changes, mood
226 changes, or other abnormal behavior
- 227 • tingling in your hands, feet, lips, or tongue
- 228 • dizziness, light-headedness, or drowsiness
- 229 • nightmares or trouble sleeping
- 230 • headache
- 231 • blurred vision or slurred speech
- 232 • palpitations (rapid heart beat)
- 233 • sweating
- 234 • tremor (shaking) or unsteady gait (walking)

235

236 Mild to moderate hypoglycemia can be treated by eating or drinking carbohydrates (milk,
237 orange juice, sugar candies, or glucose tablets). More severe or continuing hypoglycemia
238 may require the help of another person or emergency medical personnel. Patients who are
239 unable to take sugar by mouth or who are unconscious may need treatment with a
240 glucagon injection or glucose given intravenously (in the vein).

241

242 Talk with your doctor about severe, continuing, or frequent hypoglycemia, and
243 hypoglycemia for which you had few warning symptoms.

244

245 **Hyperglycemia** (high blood sugar) is another common side effect. It also occurs when
246 there is a conflict between the amount of carbohydrates (source of glucose) from your
247 food, the amount of glucose used by your body, and the amount and timing of insulin
248 dosing. Therefore, **hyperglycemia can occur with:**

- 249 • **The wrong insulin dose.** This can happen from any of the following:
 - 250 • too little or no insulin is injected
 - 251 • the bolus dose of insulin infusion is set too low
 - 252 • the basal infusion dose is set too low
 - 253 • the pump or catheter system does not work right, delivering too little insulin
 - 254 • the insulin's ability to lower glucose is changed by incorrect storage (freezing,
255 excessive heat), or usage after the expiration date
- 256 • **Medicines that directly increase glucose or decrease sensitivity to insulin.** This
257 can happen, for example, with thiazide water pills (used for blood pressure),
258 corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- 259 • **Medical conditions that increase the body's production of glucose or decrease
260 sensitivity to insulin.** These medical conditions include fevers, infections, heart
261 attacks, and stress.
- 262 • **Too much carbohydrate intake.** This can happen if you
 - 263 • eat larger meals
 - 264 • eat more often
 - 265 • increase the proportion of carbohydrate in your meals

266

267 Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA)**
268 **or very high glucose levels (hyperosmolar coma) and result in unconsciousness and**
269 **death.** Although DKA occurs most often in patients with Type 1 diabetes, it can occur in
270 patients with Type 2 diabetes who become severely ill. Urine or blood tests will show
271 acetone, ketones, and high levels of glucose. Hyperosmolar coma occurs most often in
272 patients with Type 2 diabetes. Urine and blood tests will show very high levels of
273 glucose.

274 Glucose monitoring is very important for patients using external pump infusion therapy.
275 You should be aware that pump or infusion set malfunctions that result in inadequate
276 insulin infusion can quickly lead to hyperglycemia and ketosis. Accordingly, problems
277 with the infusion pump, the flow of insulin, or the quality of the insulin should be
278 identified and corrected as quickly as possible. The faster absorption of rapid-acting
279 insulin analogs through the skin and shorter duration of action may give you less time to
280 identify and correct the problem.

281 Because some patients experience few symptoms of hyperglycemia and ketosis, it is
282 important to monitor your glucose several times a day. Symptoms of hyperglycemia
283 include:

- 284 • confusion or drowsiness
- 285 • fruity smelling breath
- 286 • rapid, deep breathing
- 287 • increased thirst
- 288 • decreased appetite, nausea, or vomiting
- 289 • abdominal (stomach area) pain
- 290 • rapid heart rate
- 291 • increased urination and dehydration (too little fluid in your body)

292
293 Mild hyperglycemia can be treated by extra doses of insulin and drinking fluids
294 (rehydration). Patients using pumps should check pump function and replace the insulin
295 in the reservoir-syringe, as well as change the tubing and catheter and the infusion site.
296 **Patients using pumps may need to resume insulin injections with syringes or**
297 **injection pens.** Glucose and acetone-ketone levels should be monitored more often until
298 they return to normal. **More severe or continuing hyperglycemia requires prompt**
299 **evaluation and treatment by your health care provider.**

300
301 **Allergy can be serious.** Generalized allergy is an uncommon, but possibly life-
302 threatening, reaction to insulin products. Symptoms include:

- 303 • itchy rash over the entire body
- 304 • shortness of breath or wheezing
- 305 • confusion
- 306 • low blood pressure
- 307 • rapid heart beat
- 308 • sweating

309 **If you think you are having a generalized allergic reaction, get emergency medical**
310 **help right away.**

311

312 Allergic reactions at the injection site (itching, redness, hardness, or swelling) are more
313 common than generalized allergy. They may need several days or weeks to clear up.
314 Pump patients with site reactions may need to change their infusion sites more often than
315 every 48 hours. Patients should avoid injection or infusion of insulin into skin areas that
316 have reactions. Tell your doctor about such reactions, because they can become more
317 severe, or they may change the absorption of insulin.

318
319 **Lipodystrophy** is a common change in the fat below the injection site. These changes
320 include loss of fat (depressions in the skin called lipoatrophy) or thickening of the tissue
321 under the skin (lipohypertrophy). Pump patients with lipodystrophy may need to change
322 their infusion sites more often than every 48 hours. Patients should avoid injection or
323 infusion of insulin into skin areas that have these reactions. Tell your doctor about such
324 reactions because they can become more severe, or they may change the absorption of
325 insulin.

326 327 **How should I store NovoLog?**

- 328 • **NovoLog can be damaged by high temperatures.** Therefore, be sure to protect it
329 from high air temperatures, heat from the sun, saunas, long showers, and other heat
330 sources. This is especially important if you use a pump or an insulin pen, because
331 you carry these devices with you and they may be exposed to different temperatures
332 as you go about your daily activities. **Throw NovoLog away if it has been in**
333 **temperatures greater than 98.6°F (37°C).**
- 334
335 • **Unopened NovoLog** should be stored in a refrigerator but not in the freezer and
336 protected from light. Even if it has been refrigerated and protected from sunlight and
337 unopened, it should not be used after the expiration date on the label and the carton.
338 Unopened vials and cartridges can be stored unrefrigerated at temperatures below
339 86°F (30°C) and protected from light for up to 28 days.
- 340
341 • **Punctured vials and cartridges** can be stored unrefrigerated at temperatures below
342 86°F (30°C) and protected from light for up to 28 days. Punctured vials may be
343 stored in the refrigerator. Cartridges inserted into their NovoPen[®] 3 device should not
344 be stored in the refrigerator.
- 345
346 • **The NovoLog in the pump reservoir and the complete infusion set** (reservoir,
347 tubing, catheter-needle) should be replaced **at least every 48 hours**. Replacement
348 should be more often than every 48 hours if you have hyperglycemia, the pump alarm
349 sounds, or the insulin flow is blocked (occlusion).
- 350
351 • Never use NovoLog if it has been stored improperly.

352 353 **General advice**

354 This leaflet summarizes the most important information about NovoLog. If you would
355 like more information, talk with your doctor. You can ask your pharmacist or doctor for
356 information about NovoLog that is written for health professionals.

357

358 **Injection and pump infusion instructions**

- 359 • NovoLog comes in 10 mL (milliliter) vials or in 3 mL cartridges. NovoLog can be
360 withdrawn from vials with syringes for injection or for insertion into the reservoirs of
361 external subcutaneous infusion pumps (Disetronic H-TRON[®] series, MiniMed 500
362 series, or other pumps recommended by your doctor.)
- 363 • Doses of insulin are measured in units. NovoLog is available as a U-100 insulin.
364 One milliliter (mL) of U-100 contains 100 units of insulin aspart (1 mL=1 cc). Only
365 U-100 type syringes should be used for injection to ensure proper dosing.
- 366 • Disposable syringes and needles are sterile if the package is sealed. They should be
367 used only once and thrown away properly, to protect others from harm.
- 368 • NovoLog PenFill[®] cartridges are for use with NovoFine[®] disposable needles and the
369 following Novo Nordisk 3 mL PenFill[®] compatible insulin delivery devices:
370 NovoPen[®] 3, NovoPen[®] Junior, Innovo[®], and InDuo[®]. Never share needles.

371

372 *How should I inject NovoLog?*

373

374 *Using Vials*

- 375 1. The vial and the insulin should be inspected. The insulin should be clear and colorless.
376 The tamper-resistant cap should be in place to be removed by you. If the cap had been
377 removed before your first use of the vial, or if the insulin is cloudy or colored, you
378 should return the vial to the pharmacy. Do not use it.
- 379 2. Both the injection site and your hands should be cleaned with soap and water or with
380 alcohol. The injection site should be dry before you inject.
- 381 3. The rubber stopper should be wiped with an alcohol wipe.
- 382 4. The plunger of the syringe should be pulled back until the black tip is at the level for
383 the number of units to be injected.
- 384 5. Insert the needle of the syringe through the rubber stopper of the vial. Push in the
385 syringe plunger completely to put air into the vial.
- 386 6. Turn the vial upside-down with the needle-syringe still attached, and pull the plunger
387 back a few units past the correct dose.
- 388 7. Remove any air bubbles by flicking the syringe and squirting air bubbles out the
389 needle. Continue pushing the plunger until you have the correct dose.
- 390 8. Lift the vial off the syringe.
- 391 9. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or
392 blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold
393 between your fingers and push the needle straight into the pinched skin. Because
394 insulin absorption and activity can be affected by the site you choose, you should
395 discuss the injection site with your doctor.
- 396 10. Release the pinched skin and push the plunger in completely. Keep the needle in the
397 skin for a few seconds before withdrawing the syringe.
- 398 11. Press the injection site for a few seconds to reduce bleeding. **Do not rub.**
- 399 12. To avoid needle sticks, throw away the syringe and needle without recapping. Discuss
400 sterile technique and proper disposal of your used insulin supplies with your doctor.

401

402 *Using Cartridges*

- 403 1. The cartridge and the insulin should be inspected. The insulin should be clear and
404 colorless. The tamper-resistant foil should be in place to be removed by you. If the
405 foil had been punctured or removed before your first use of the cartridge or if the
406 insulin is cloudy or colored, you should return the cartridge to the pharmacy. Do not
407 use it.
- 408 2. Both the injection site and your hands should be cleaned with soap and water or with
409 alcohol. The injection site should be dry before you inject. Do not use skin that is
410 reddened, itchy, or thickened as an infusion site.
- 411 3. Insert a 3 mL cartridge in the pen-device barrel. Attach a new needle to the end of the
412 cartridge and turn the pen device upside-down so that any air bubbles can be
413 eliminated by flicking the pen device and squirting air bubbles out the needle. (This
414 should eliminate extra air for all future doses from that cartridge. However, the needle
415 will need to be changed for each dose.)
- 416 4. Set the dose to be delivered by twisting the top of the pen-device until the correct
417 number appears in the window.
- 418 5. Inject NovoLog into the subcutaneous (under the skin) tissue (not into muscle or
419 blood vessels) in the abdomen, thighs, upper arms, or buttocks. Pinch the skin fold
420 between your fingers and push the needle straight into the pinched skin. Because
421 insulin absorption and activity can be affected by the site you choose, you should
422 discuss the injection site with your doctor.
- 423 6. Release the pinched skin. Inject the dose by pressing the flat plunger button on the
424 top of the pen-device. Keep the needle in the skin for a few seconds before
425 withdrawing the pen-device.
- 426 7. Press the injection site for a few seconds to reduce bleeding. **Do not rub.**
- 427 8. Throw away the disposable needle without recapping to avoid needle sticks. Discuss
428 sterile technique and proper disposal of your used insulin supplies with your doctor.

429

430 **How should I infuse NovoLog with an external subcutaneous insulin infusion pump?**

431

432 NovoLog is recommended for use with the Disetronic H-TRON[®] series, MiniMed 500
433 series, or other pumps recommended by your doctor.

434

- 435 1. Inspect your insulin as you would for an injection. The insulin should be clear and
436 colorless and without particles. The tamper-resistant cap should be in place to be
437 removed by you. If the cap had been removed before your first use of the vial or if the
438 insulin is cloudy or colored, you should return the vial to the pharmacy. Do not use it.
- 439 2. Both the infusion site and your hands should be cleaned with soap and water or with
440 alcohol. The infusion site should be dry before you insert the catheter-needle and
441 tubing. Do not use skin that is reddened, itchy, bumpy or thickened as an infusion site
442 because the onset and duration of NovoLog action may not be the same as that in
443 normal skin.
- 444 3. Fill the reservoir-syringe with 2 days worth of NovoLog plus about 25 extra units to
445 prime the pump and fill up the dead space of the infusion tubing.

- 446 4. Remove air bubbles from the reservoir according to the pump manufacturers'
447 instructions.
- 448 5. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the
449 infusion set until you see a drop of insulin coming out of the infusion needle-catheter.
450 Flick the tubing to remove air bubbles. Follow the pump manufacturers' instructions
451 for additional priming.
- 452 6. Prime the needle-catheter and insert the infusion set into the skin according to the
453 pump manufacturer.
- 454 7. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin
455 infusion according to instructions from your doctor and the manufacturer of your
456 pump equipment.
- 457 8. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the
458 insulin every 48 hours or less, even if you have not used all of the insulin. This will
459 help ensure that NovoLog and the pump works well. (See "What is the most
460 important information I should know about NovoLog?")
- 461 9. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the
462 insulin if you experience a pump alarm, catheter blockage, hyperglycemia, or if your
463 pump insulin has been exposed to heat greater than 98.6°F (37°C). (See "What is the
464 most important information I should know about NovoLog?") Hyperglycemia
465 identified with glucose monitoring may be the first indication of a problem with the
466 pump, infusion set, or NovoLog. Hyperglycemia in the absence of an alarm still
467 requires you to investigate because pump alarms are designed to detect back-pressure
468 and occlusion. The alarms may not detect all the changes to NovoLog that could
469 result in hyperglycemia. You may need to resume subcutaneous insulin injections if
470 the cause of the problem cannot be promptly identified or fixed. (See
471 "Hyperglycemia" under "What are the possible side effects of NovoLog?")
472 Remember that long stretches of tubing increase the risk for kinking and expose the
473 insulin in the tubing to more variations in temperature.
474

475 **These instructions give you specific information for use of NovoLog in external**
476 **subcutaneous infusion pumps, but are not a substitute for pump education.**
477

478 *How should I mix insulins?*
479

480 **NovoLog should be mixed only when syringe injections are used.** NovoLog can be
481 mixed with NPH human insulin immediately before use. The NovoLog should be drawn
482 into the syringe before the NPH. Mixing with other insulins has not been studied.

483 **NovoLog should not be mixed with Lantus® (insulin glargine [rDNA origin]**
484 **injection). Mixed insulins should NEVER be used in a pump or for intravenous**
485 **infusion.**
486

- 487 1. Add together the doses of NPH and NovoLog. The total dose will determine the final
488 volume in the syringe after drawing up both insulins into the syringe.
- 489 2. Roll the NPH vial between your hands until the liquid is equally cloudy throughout.
- 490 3. Draw into the syringe the same amount of air as the NPH dose. Inject this air into the
491 NPH vial and then remove the needle without withdrawing or touching any of the

- 492 NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog
493 vial and may change how quickly it works.)
494 4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into
495 the NovoLog vial. With the needle in place, turn the vial upside-down and withdraw
496 the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the
497 full dose and not an air dose.
498 5. Insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe-
499 needle still in it. Withdraw the correct dose of NPH.
500 6. Inject immediately to reduce changes in how quickly the insulin works.

501
502

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

505

506 For information contact:
507 Novo Nordisk Pharmaceuticals Inc.,
508 100 College Road West
509 Princeton, New Jersey 08540
510 1-800-727-6500
511 www.novonordisk-us.com

512

513 Manufactured by
514 Novo Nordisk A/S
515 2880 Bagsvaerd, Denmark

516

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