

# NovoLog<sup>®</sup>

## Insulin aspart (rDNA origin) Injection

### DESCRIPTION

NovoLog<sup>®</sup> (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  $C_{256}H_{381}N_{65}O_{79}S_6$  and a molecular weight of 5825.8.

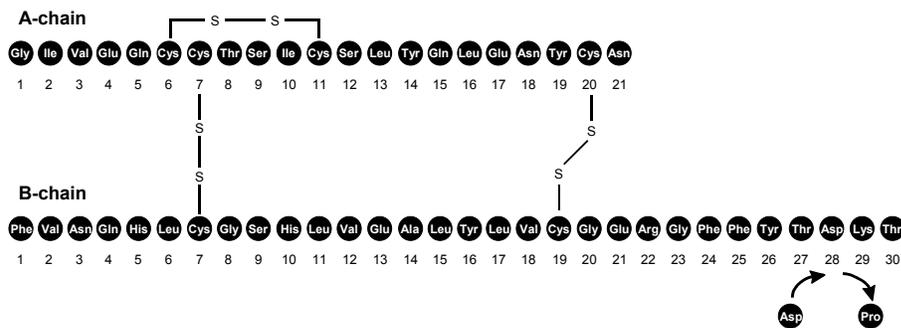


Figure 1. Structural formula of insulin aspart.

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  $\mu$ g/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

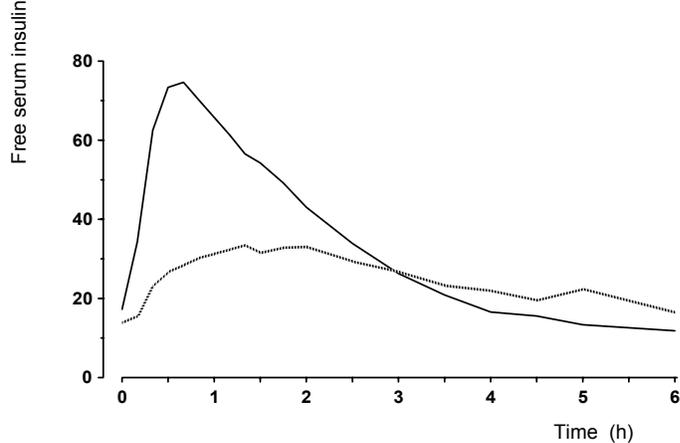
The primary activity of NovoLog is the regulation of glucose metabolism. Insulins, including NovoLog, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

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.

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 40 **Bioavailability and Absorption** - NovoLog has a faster absorption, a faster onset of action,  
 41 and 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.



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 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.

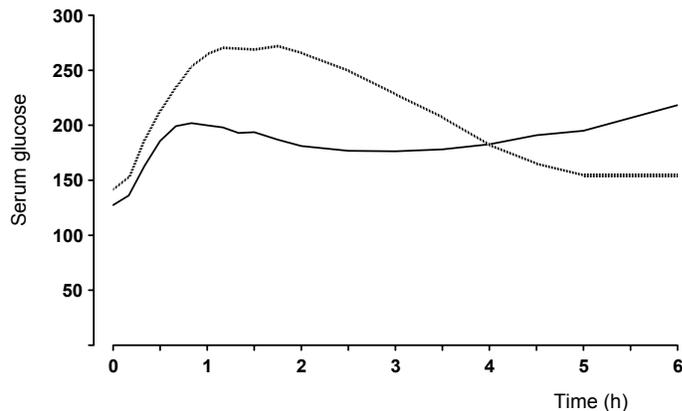
59 The intra-individual variability in time to maximum serum insulin concentration for healthy  
 60 male volunteers was significantly less for NovoLog than for regular human insulin. The  
 61 clinical significance of this observation has not been established.

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.

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 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 **Pharmacodynamics**

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 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.



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 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 **Special Populations**

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 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  $\geq 2$ ], 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.

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

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

**Obesity** - In a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m<sup>2</sup>), the pharmacokinetic parameters, AUC and C<sub>max</sub>, of NovoLog were generally unaffected by BMI. Clearance of NovoLog was reduced by 28% in patients with BMI >32 compared to patients with BMI <23 when a single dose of 0.1 U/kg NovoLog was administered. However, only 3 patients with BMI <23 were studied.

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

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

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

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

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

## **CLINICAL STUDIES**

To evaluate the safety and efficacy of NovoLog in patients with Type 1 diabetes, two six-month, open-label, active-control (NovoLog vs. Novolin<sup>®</sup> R) studies were conducted (see 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.

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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).

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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).

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Study	Treatment (n)	Mean HbA1c (%)		Hypoglycemia <sup>1</sup> (events / month / patient)	% of Patients Using Various Numbers of Insulin Injections / Day <sup>2</sup>				
		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 <sup>1</sup> Events requiring intervention from a third party during the last three months of treatment

174 <sup>2</sup> Percentages are rounded to the nearest whole number

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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<sup>®</sup> (buffered regular human insulin) in patients with Type 1 diabetes. Changes

179 in HbA1c and rates of hypoglycemia were comparable. Patients with Type 2 diabetes were  
180 also 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.)

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### 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.)

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### 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). Pump or infusion set malfunctions or**

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

233  
234 **PRECAUTIONS**

235 **General**

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

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

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

249  
250 *Hypoglycemia* - As with all insulin preparations, hypoglycemic reactions may be associated  
251 with the administration of NovoLog. Rapid changes in serum glucose levels may induce  
252 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early  
253 warning symptoms of hypoglycemia may be different or less pronounced under certain  
254 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such  
255 as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions).  
256 Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior  
257 to patients' awareness of hypoglycemia.

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

262  
263 *Hepatic Impairment* - As with other insulins, the dose requirements for NovoLog may be  
264 reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY,  
265 Pharmacokinetics).

266  
267 *Allergy - Local Allergy* - As with other insulin therapy, patients may experience redness,  
268 swelling, or itching at the site of injection. These minor reactions usually resolve in a few

269 days to a few weeks, but in some occasions, may require discontinuation of NovoLog. In  
270 some instances, these reactions may be related to factors other than insulin, such as irritants in  
271 a skin cleansing agent or poor injection technique.

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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 cresol as an  
278 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  
285 human 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 NovoLog is recommended for use in Disetronic H-TRON<sup>®</sup> plus V100 with Disetronic 3.15  
301 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, or 507 with  
302 MiniMed 3 mL syringes and Polyfin<sup>®</sup> or Sof-set<sup>®</sup> infusion sets.

303

304 In-vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation,  
305 may occur with the use of NovoLog for more than two days at 37°C (98.6°F) in infusion sets  
306 and reservoirs. NovoLog in clinical use should not be exposed to temperatures greater than  
307 37°C (98.6°F). **NovoLog should not be mixed with other insulins or with a diluent when it  
308 is used in the pump.** (See WARNINGS, PRECAUTIONS, Mixing of Insulins, Information  
309 for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

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#### 312 **Information for Patients**

313 ***For all patients:***

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

323

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

327

328 ***For patients using pumps:***

329 Patients using external pump infusion therapy should be trained in intensive insulin therapy  
330 with multiple injections and in the function of their pump and pump accessories. NovoLog is  
331 recommended for use with Disetronic H-TRON plus V100 with Disetronic 3.15 plastic  
332 cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, and 507 with  
333 MiniMed 3 mL syringes and Polyfin or Sof-set infusion sets. The use of NovoLog in quick-  
334 release infusion sets and cartridge adapters has not been assessed.

335

336 **To avoid insulin degradation, infusion set occlusion, and loss of the preservative (cresol),**  
337 **the infusion sets (reservoir syringe, tubing, and catheter) and the NovoLog in the**  
338 **reservoir should be replaced, and a new infusion site selected every 48 hours or less.**

339 **Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded.** The  
340 temperature of the insulin may exceed ambient temperature when the pump housing, cover,  
341 tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are  
342 erythematous, pruritic, or thickened should be reported to medical personnel, and a new site  
343 selected because continued infusion may increase the skin reaction and/or alter the absorption  
344 of NovoLog.

345

346 Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and  
347 ketosis in a short time because of the small subcutaneous depot of insulin. This is especially  
348 pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have  
349 shorter duration of action. These differences are particularly relevant when patients are  
350 switched from infused buffered regular insulin or multiple injection therapy. Prompt  
351 identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems  
352 include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and  
353 degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these  
354 problems cannot be promptly corrected, patients should resume therapy with subcutaneous  
355 insulin injection and contact their physician. (See WARNINGS, PRECAUTIONS, Mixing of  
356 Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

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358 **Laboratory Tests**

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

### 362 **Drug Interactions**

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

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

### 380 **Mixing of Insulins**

- 381 • A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog  
382 with NPH human insulin immediately before injection produced some attenuation in the  
383 peak concentration of NovoLog, but that the time to peak and the total bioavailability of  
384 NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin,  
385 NovoLog should be drawn into the syringe first. The injection should be made  
386 immediately after mixing. Because there are no data on the compatibility of NovoLog and  
387 crystalline zinc insulin preparations, NovoLog should not be mixed with these  
388 preparations.
- 389 • The effects of mixing NovoLog with insulins of animal source or insulin preparations  
390 produced by other manufacturers have not been studied (see WARNINGS).
- 391 • Mixtures should not be administered intravenously.
- 392 • When used in external subcutaneous infusion pumps for insulin, NovoLog should not be  
393 mixed with any other insulins or diluent.
- 394

### 395 **Carcinogenicity, Mutagenicity, Impairment of Fertility**

396 Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the  
397 carcinogenic potential of NovoLog. In 52-week studies, Sprague-Dawley rats were dosed  
398 subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times  
399 the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively).  
400 At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in  
401 females when compared to untreated controls. The incidence of mammary tumors for  
402 NovoLog was not significantly different than for regular human insulin. The relevance of  
403

404 these findings to humans is not known. NovoLog was not genotoxic in the following tests:  
405 Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood  
406 lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo*  
407 UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous  
408 doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on  
409 U/body surface area), no direct adverse effects on male and female fertility, or general  
410 reproductive performance of animals was observed.

411

### 412 **Pregnancy - Teratogenic Effects - Pregnancy Category C**

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

416

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

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423 Subcutaneous reproduction and teratology studies have been performed with NovoLog and  
424 regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats  
425 before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis.  
426 The effects of NovoLog did not differ from those observed with subcutaneous regular human  
427 insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and  
428 visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the  
429 human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a  
430 dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0  
431 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal  
432 hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50  
433 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the  
434 human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose  
435 of 1.0 U/kg/day for rabbits, based on U/body surface area.

436

### 437 **Nursing Mothers**

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

441

### 442 **Pediatric Use**

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

444

445

**446 Geriatric Use**

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

455

456

**457 ADVERSE REACTIONS**

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

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

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

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

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

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

469

**470 OVERDOSAGE**

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

477

**478 DOSAGE AND ADMINISTRATION**

479 NovoLog should generally be given immediately before a meal (start of meal within 5-10  
480 minutes after injection) because of its fast onset of action. The dosage of  
481 NovoLog should be individualized and determined, based on the physician's advice, in  
482 accordance with the needs of the patient. The total daily individual insulin requirement is  
483 usually between 0.5-1.0 units/kg/day. When used in a meal-related subcutaneous injection  
484 treatment regimen, 50-70% of total insulin requirements may be provided by NovoLog and the  
485 remainder provided by an intermediate-acting or long-acting insulin. When used in external  
486 insulin infusion pumps, the initial programming of the pump is based on the total daily insulin  
487 dose of the previous regimen. Although there is significant interpatient variability,  
488 approximately 50% of the total dose is given as meal-related boluses of NovoLog and the  
489 remainder as basal infusion. Because of NovoLog's comparatively rapid onset and short  
490 duration of glucose lowering activity, some patients may require more basal insulin and more

491 total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human  
492 regular insulin. Additional basal insulin injections, or higher basal rates in external  
493 subcutaneous infusion pumps may be necessary. **Infusion sets and the insulin in the infusion**  
494 **sets must be changed every 48 hours or sooner to assure the activity of NovoLog and**  
495 **proper pump function.** (See WARNINGS, PRECAUTIONS, Information for Patients)  
496

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

502 Parenteral drug products should be inspected visually for particulate matter and discoloration  
503 prior to administration, whenever solution and container permit. Never use any NovoLog if it  
504 has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog  
505 should not be used after the printed expiration date.  
506

### 507 **HOW SUPPLIED**

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

510 10 mL vials NDC 0169-7501-11  
511 3 mL PenFill® cartridges\* NDC 0169-3303-12  
512 3 mL NovoLog FlexPen® Prefilled syringe NDC 0169-6339-10  
513

514 \* NovoLog PenFill cartridges are for use with NovoFine® disposable needles and the  
515 following 3 mL PenFill cartridge compatible delivery devices: NovoPen®3, NovoPen Junior,  
516 Innovo® and InDuo®.

517 NovoLog FlexPen Prefilled syringes are for use with NovoFine disposable needles.  
518

### 519 **RECOMMENDED STORAGE**

520 NovoLog in unopened vials, cartridges, and NovoLog FlexPen Prefilled syringes should be  
521 stored between 2° and 8°C (36° to 46°F). *Do not freeze. Do not use NovoLog if it has been*  
522 **frozen or exposed to temperatures that exceed 37°C (98.6°F).** After a vial or cartridge has  
523 been punctured, it may be kept at temperatures below 30°C (86°F) for up to 28 days, but  
524 should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated.  
525 Cartridges should not be refrigerated after insertion into the NovoPen 3. Infusion sets  
526 (reservoirs, tubing, and catheters) and the NovoLog in the reservoir should be discarded after  
527 no more than 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).  
528

529 Rx only  
530

531 Date of Issue: [date]  
532 8-XXXX-XX-XXX-X  
533

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

536

537 Manufactured By Novo Nordisk A/S

538 2880 Bagsvaerd, Denmark

539 [www.novonordisk-us.com](http://www.novonordisk-us.com)

540

541 NovoLog<sup>®</sup>, Novolin<sup>®</sup>, Velosulin<sup>®</sup>, PenFill<sup>®</sup>, FlexPen<sup>®</sup>, NovoFine<sup>®</sup>, NovoPen<sup>®</sup>, and Innovo<sup>®</sup>

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