

NDA 20-563/S-024  
Page 1

A2.0 NL 3690 AMP <sup>1</sup>

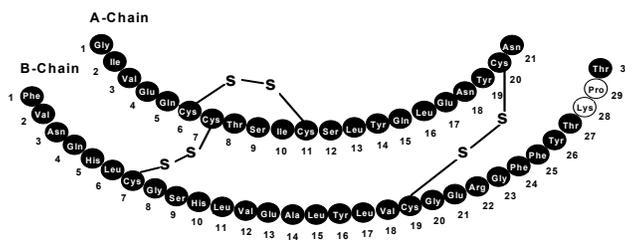
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12

**HUMALOG<sup>®</sup>**  
**INSULIN LISPRO INJECTION**  
**(rDNA ORIGIN)**  
**100 UNITS PER ML (U-100)**

**DESCRIPTION**

Humalog<sup>®</sup> (insulin lispro, rDNA origin) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for insulin lispro.

Humalog has the following primary structure:



13  
14  
15  
16  
17  
18  
19  
20  
21  
22

**Figure 1**

Insulin lispro has the empirical formula  $C_{257}H_{383}N_{65}O_{77}S_6$  and a molecular weight of 5808, both identical to that of human insulin.

The vials, cartridges, and Pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

Each milliliter of Humalog injection contains insulin lispro 100 Units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Mmetacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

**CLINICAL PHARMACOLOGY**

23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34

**Antidiabetic Activity**

The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of human regular insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and human regular insulin is comparable when administered to normal volunteers by the intravenous route.

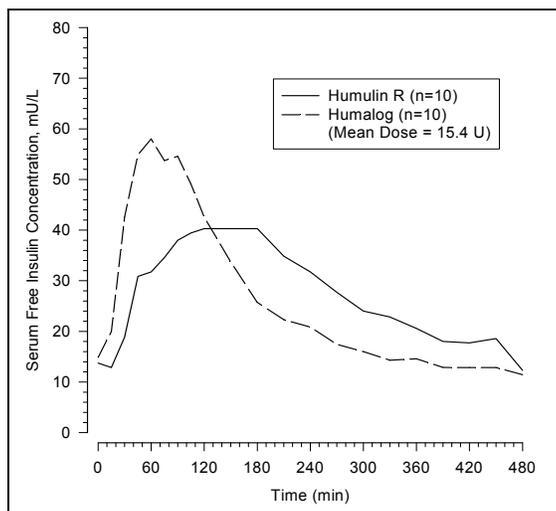
NDA 20-563/S-024  
Page 2

2

35 **Pharmacokinetics**

36 *Absorption and Bioavailability* — Humalog is as bioavailable as human regular insulin, with  
37 absolute bioavailability ranging between 55%-77% with doses between 0.1-0.2 U/kg, inclusive.  
38 Studies in normal volunteers and patients with type 1 (insulin-dependent) diabetes demonstrated  
39 that Humalog is absorbed faster than human regular insulin (U-100) (*see* Figure 2). In normal  
40 volunteers given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum levels  
41 were seen 30-90 minutes after dosing. When normal volunteers received equivalent doses of  
42 human regular insulin, peak insulin levels occurred between 50-120 minutes after dosing.  
43 Similar results were seen in patients with type 1 diabetes. The pharmacokinetic profiles of  
44 Humalog and human regular insulin are comparable to one another when administered to normal  
45 volunteers by the intravenous route. Humalog was absorbed at a consistently faster rate than  
46 human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin or  
47 Humalog at abdominal, deltoid, or femoral subcutaneous sites, the three sites often used by  
48 patients with diabetes. After abdominal administration of Humalog, serum drug levels are higher  
49 and the duration of action is slightly shorter than after deltoid or thigh administration (*see*  
50 **DOSAGE AND ADMINISTRATION**). Humalog has less intra- and inter-patient variability  
51 compared to human regular insulin.

52 **Figure 2**  
53 **Serum Humalog and insulin levels after subcutaneous injection of human regular insulin**  
54 **or Humalog (0.2 U/kg) immediately before a high carbohydrate meal in 10 patients with**  
55 **type 1 diabetes.\***



56 \*Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

57

58 *Distribution* — The volume of distribution for Humalog is identical to that of human regular  
59 insulin, with a range of 0.26-0.36 L/kg.

60 *Metabolism* — Human metabolism studies have not been conducted. However, animal studies  
61 indicate that the metabolism of Humalog is identical to that of human regular insulin.

62 *Elimination* — When Humalog is given subcutaneously, its  $t_{1/2}$  is shorter than that of human  
63 regular insulin (1 vs. 1.5 hours, respectively). When given intravenously, Humalog and human  
64 regular insulin show identical dose-dependent elimination, with a  $t_{1/2}$  of 26 and 52 minutes at  
65 0.1 U/kg and 0.2 U/kg, respectively.

NDA 20-563/S-024  
Page 3

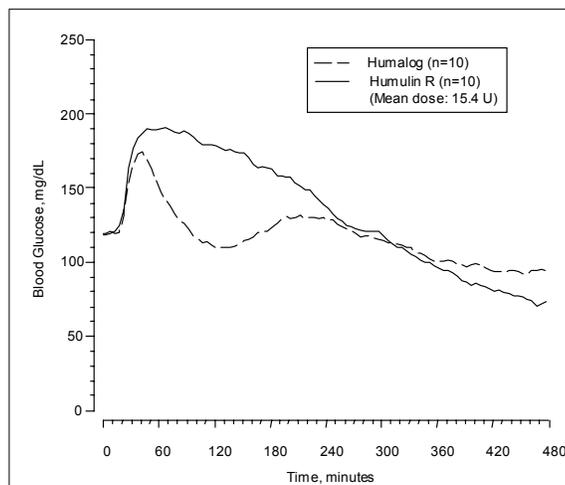
3

66 **Pharmacodynamics**

67 Studies in normal volunteers and patients with diabetes demonstrated that Humalog has a more  
68 rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter  
69 duration of glucose-lowering activity than human regular insulin (*see* Figure 3). The earlier onset  
70 of activity of Humalog is directly related to its more rapid rate of absorption. The time course of  
71 action of insulin and insulin analogs, such as Humalog, may vary considerably in different  
72 individuals or within the same individual. The parameters of Humalog activity (time of onset,  
73 peak time, and duration) as designated in Figure 3 should be considered only as general  
74 guidelines. The rate of insulin absorption and consequently the onset of activity is known to be  
75 affected by the site of injection, exercise, and other variables (*see* PRECAUTIONS, General).

76 **Figure 3**

77 **Blood glucose levels after subcutaneous injection of human regular insulin or**  
78 **Humalog (0.2 U/kg) immediately before a high carbohydrate meal in 10 patients with**  
79 **type 1 diabetes.\***



80 \*Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.  
81

82 **Special Populations**

83 *Age and Gender* — Information on the effect of age and gender on the pharmacokinetics of  
84 Humalog is unavailable. However, in large clinical trials, subgroup analysis based on age and  
85 gender did not indicate any difference in postprandial glucose parameters between Humalog and  
86 human regular insulin.

87 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of  
88 Humalog has not been studied.

89 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of  
90 Humalog has not been studied.

91 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics  
92 and pharmacodynamics of Humalog has not been studied. In large clinical trials, which included  
93 patients with Body Mass Index up to and including 35 kg/m<sup>2</sup>, no consistent differences were  
94 seen between Humalog and Humulin R with respect to postprandial glucose parameters.

95 *Renal Impairment* — Some studies with human insulin have shown increased circulating levels  
96 of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and a wide  
97 range of renal function, the pharmacokinetic differences between Humalog and human regular

NDA 20-563/S-024  
Page 4

4

98 insulin were generally maintained. However, the sensitivity of the patients to insulin did change,  
99 with an increased response to insulin as the renal function declined. Careful glucose monitoring  
100 and dose adjustments of insulin, including Humalog, may be necessary in patients with renal  
101 dysfunction.

102 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating  
103 levels of insulin in patients with hepatic failure. In a study of 22 patients with type 2 diabetes,  
104 impaired hepatic function did not affect the subcutaneous absorption or general disposition of  
105 Humalog when compared to patients with no history of hepatic dysfunction. In that study,  
106 Humalog maintained its more rapid absorption and elimination when compared to human regular  
107 insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog, may be  
108 necessary in patients with hepatic dysfunction.

### 109 **Clinical Studies**

110 In open-label, cross-over studies of 1008 patients with type 1 diabetes and 722 patients with  
111 type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with  
112 human regular insulin (*see* Table 1). The clinical significance of improvement in postprandial  
113 hyperglycemia has not been established.  
114

Table 1

Comparison of Means of Glycemic Parameters at the End of Combined Treatment Periods. All Randomized Patients in Cross-Over Studies (3 months for each treatment)		
Type 1, N=1008		
Glycemic Parameter, (mg/dL)	Humalog <sup>a</sup>	Humulin <sup>®</sup> R <sup>a*</sup>
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA <sub>1c</sub> (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722		
Glycemic Parameter, (mg/dL)	Humalog <sup>a</sup>	Humulin R <sup>a</sup>
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA <sub>1c</sub> (%)	8.2 ± 1.3	8.2 ± 1.4

115 <sup>a</sup> Mean ± Standard Deviation

116 \* Humulin R (human insulin [rDNA origin] injection)

117

118 In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA<sub>1c</sub> did not differ  
119 between patients treated with human regular insulin and those treated with Humalog.

120 *Hypoglycemia* — While the overall rate of hypoglycemia did not differ between patients with  
121 type 1 and type 2 diabetes treated with Humalog compared with human regular insulin, patients  
122 with type 1 diabetes treated with Humalog had fewer hypoglycemic episodes between midnight  
123 and 6 a.m. The lower rate of hypoglycemia in the Humalog-treated group may have been related  
124 to higher nocturnal blood glucose levels, as reflected by a small increase in mean fasting blood  
125 glucose levels.

126 *Humalog in Combination with Sulfonylurea Agents* — In a two-month study in patients with  
127 fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were  
128 randomized to one of three treatment regimens; Humulin<sup>®</sup> NPH at bedtime plus SU, Humalog  
129 three times a day before meals plus SU, or Humalog three times a day before meals and  
130 Humulin NPH at bedtime. The combination of Humalog and SU resulted in an improvement in  
131 HbA<sub>1c</sub> accompanied by a weight gain (*see* Table 2).  
132

Table 2

Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone			
	Humulin N h.s. + SU	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA <sub>1c</sub> (%) at baseline	9.9	10.0	10.0
HbA <sub>1c</sub> (%) at 2-months	8.7	8.4	8.5
HbA <sub>1c</sub> (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia* (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

a.c.-three times a day before meals, h.s.-at bedtime, SU-oral sulfonylurea agent

\* blood glucose  $\leq$ 36mg/dL or needing assistance from third party

*Humalog in External Insulin Pumps* — To evaluate the administration of Humalog via external insulin pumps, two open-label cross-over design studies were performed in patients with type 1 diabetes. One study involved 39 patients treated for 24 weeks with Humalog or regular human insulin. After 12 weeks of treatment, the mean HbA<sub>1c</sub> values decreased from 7.8% to 7.2% in the Humalog-treated patients and from 7.8% to 7.5% in the regular insulin-treated patients. Another study involved 60 patients treated for 24 weeks with either Humalog or buffered regular human insulin. After 12 weeks of treatment, the mean HbA<sub>1c</sub> values decreased from 7.7% to 7.4% in the Humalog-treated patients and remained unchanged from 7.7% in the buffered regular insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in both studies. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes

#### INDICATIONS AND USAGE

Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump.

#### CONTRAINDICATIONS

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

#### WARNINGS

**This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump). Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.**

NDA 20-563/S-024  
Page 6

6

167 **Hypoglycemia is the most common adverse effect associated with insulins, including**  
168 **Humalog. As with all insulins, the timing of hypoglycemia may differ among various**  
169 **insulin formulations. Glucose monitoring is recommended for all patients with diabetes.**

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

174 **External Insulin Pumps: When used in an external insulin pump, Humalog should not be**  
175 **diluted or mixed with any other insulin. Patients should carefully read and follow the**  
176 **external insulin pump manufacturer's instructions and the "INFORMATION FOR THE**  
177 **PATIENT" insert before using Humalog.**

178 Physicians should carefully evaluate information on external insulin pump use in this Humalog  
179 physician package insert and in the external insulin pump manufacturer's instructions. If  
180 unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt  
181 identification and correction of the cause is necessary. The patient may require interim therapy  
182 with subcutaneous insulin injections (*see* PRECAUTIONS, *For Patients Using External*  
183 *Insulin Pumps*, and DOSAGE AND ADMINISTRATION).

## 184 PRECAUTIONS

### 185 General

186 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated  
187 with the use of all insulins. Because of differences in the action of Humalog and other insulins,  
188 care should be taken in patients in whom such potential side effects might be clinically relevant  
189 (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering  
190 drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and  
191 hypersensitivity are among other potential clinical adverse effects associated with the use of all  
192 insulins.

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

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

199 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated  
200 with the administration of Humalog. Rapid changes in serum glucose levels may induce  
201 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early  
202 warning symptoms of hypoglycemia may be different or less pronounced under certain  
203 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as  
204 beta-blockers, or intensified diabetes control.

205 **Renal Impairment** — The requirements for insulin may be reduced in patients with renal  
206 impairment.

207 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or  
208 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including  
209 Humalog, may be necessary.

210 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,  
211 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to  
212 a few weeks. In some instances, these reactions may be related to factors other than insulin, such  
213 as irritants in a skin cleansing agent or poor injection technique.

214 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to  
215 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,

216 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized  
217 allergy, including anaphylactic reaction, may be life threatening. In controlled clinical trials,  
218 pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and  
219 30 patients receiving Humalog (N=2944) (p=0.053). Localized reactions and generalized  
220 myalgias have been reported with the use of cresol as an injectable excipient.

221 **Antibody Production** — In large clinical trials, antibodies that cross-react with human insulin  
222 and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As  
223 expected, the largest increase in the antibody levels during the 12-month clinical trials was  
224 observed with patients new to insulin therapy.

225 **Usage in External Insulin Pumps** — **The infusion set (reservoir syringe, tubing, and**  
226 **catheter), Disetronic® D-TRON®<sup>2,4</sup> or D-TRON®<sup>2,4</sup> plus cartridge adapter, and Humalog**  
227 **in the external insulin pump reservoir should be replaced and a new infusion site selected**  
228 **every 48 hours or less. Humalog in the external insulin pump should not be exposed to**  
229 **temperatures above 37°C (98.6°F).**

230 In the D-TRON®<sup>2,4</sup> or D-TRON®<sup>2,4</sup> plus pump, Humalog 3 mL cartridges may be used for up  
231 to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and  
232 a new infusion site should be selected every 48 hours or less.

233 When used in an external insulin pump, Humalog should not be diluted or mixed with any  
234 other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients*  
235 *Using External Insulin Pumps, Mixing of Insulins*, DOSAGE AND ADMINISTRATION, and  
236 Storage).

### 237 **Information for Patients**

238 Patients should be informed of the potential risks and advantages of Humalog and alternative  
239 therapies. Patients should also be informed about the importance of proper insulin storage,  
240 injection technique, timing of dosage, adherence to meal planning, regular physical activity,  
241 regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and  
242 management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

243 Patients should be advised to inform their physician if they are pregnant or intend to become  
244 pregnant.

245 Refer patients to the "INFORMATION FOR THE PATIENT" insert for information on proper  
246 injection technique, timing of Humalog dosing (≤15 minutes before or immediately after a meal),  
247 storing and mixing insulin, and common adverse effects.

248 **Use of the Humalog Pen:** Patients should read the "INFORMATION FOR THE PATIENT"  
249 insert and the "Disposable Insulin Delivery Device User Manual" before starting therapy with a  
250 Humalog Pen and re-read them each time the prescription is renewed. Patients should be  
251 instructed on how to properly use the delivery device (refer to "Disposable Insulin Delivery  
252 Device User Manual"), prime the Pen, and properly dispose of needles. Patients should be  
253 advised not to share their Pens with others.

254 **For Patients Using External Insulin Pumps:** Patients using an external infusion pump should  
255 be trained in intensive insulin therapy and in the function of their external insulin pump and  
256 pump accessories. Humalog may be used with the MiniMed®<sup>1</sup> Models 506, 507, and 508  
257 insulin pumps using MiniMed®<sup>1</sup> Polyfin®<sup>1</sup> infusion sets. Humalog may also be used in  
258 Disetronic®<sup>2</sup> H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and  
259 the Disetronic D-TRON®<sup>2,4</sup> and D-TRON®<sup>2,4</sup> plus insulin pumps (with Humalog 3 mL  
260 cartridges) using Disetronic Rapid®<sup>2</sup> infusion sets.

261 **The infusion set (reservoir syringe, tubing, catheter), D-TRON®<sup>2,4</sup> or D-TRON®<sup>2,4</sup> plus**  
262 **cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced,**  
263 **and a new infusion site selected every 48 hours or less. Humalog in the external pump**  
264 **should not be exposed to temperatures above 37°C (98.6°F). A Humalog 3 mL cartridge used**

NDA 20-563/S-024  
Page 8

8

265 in the D-TRON®<sup>2,4</sup> or D-TRON®<sup>2,4</sup> plus pump should be discarded after 7 days, even if it still  
266 contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported  
267 to medical personnel, and a new site selected.

268 **Humalog should not be diluted or mixed with any other insulin when used in an external**  
269 **insulin pump.**

### 270 **Laboratory Tests**

271 As with all insulins, the therapeutic response to Humalog should be monitored by periodic  
272 blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the  
273 monitoring of long-term glycemic control.

### 274 **Drug Interactions**

275 Insulin requirements may be increased by medications with hyperglycemic activity such as  
276 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral  
277 contraceptives, phenothiazines, and thyroid replacement therapy (*see* CLINICAL  
278 PHARMACOLOGY).

279 Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity,  
280 such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and certain antidepressants  
281 (monoamine oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors,  
282 beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.  
283 Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

284 **Mixing of Insulins** — Care should be taken when mixing all insulins as a change in peak  
285 action may occur. The American Diabetes Association warns in its Position Statement on Insulin  
286 Administration, "On mixing, physiochemical changes in the mixture may occur (either  
287 immediately or over time). As a result, the physiological response to the insulin mixture may  
288 differ from that of the injection of the insulins separately." Mixing Humalog with Humulin N or  
289 Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given  
290 alone or mixed with Humulin N, Humalog results in a more rapid absorption and  
291 glucose-lowering effect compared with human regular insulin.

292 The effects of mixing Humalog with insulins of animal source or insulin preparations produced  
293 by other manufacturers have not been studied (*see* WARNINGS).

294 If Humalog is mixed with a longer-acting insulin, such as Humulin N or Humulin U, Humalog  
295 should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting  
296 insulin. Injection should be made immediately after mixing. Mixtures should not be administered  
297 intravenously.

298 Humalog should not be diluted or mixed with any other insulin when used in an external  
299 insulin pump.

### 300 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

301 Long-term studies in animals have not been performed to evaluate the carcinogenic potential  
302 of Humalog. Humalog was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity  
303 assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay,  
304 chromosomal aberration tests, and a micronucleus test). There is no evidence from animal  
305 studies of Humalog-induced impairment of fertility.

### 306 **Pregnancy**

307 **Teratogenic Effects — Pregnancy Category B** — Reproduction studies have been performed in  
308 pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average  
309 human dose (40 units/day) based on body surface area. The results have revealed no evidence of  
310 impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and  
311 well-controlled studies in pregnant women. Because animal reproduction studies are not always  
312 predictive of human response, this drug should be used during pregnancy only if clearly needed.

NDA 20-563/S-024  
Page 9

9

313 Although there are limited clinical studies of the use of Humalog in pregnancy, published  
314 studies with human insulins suggest that optimizing overall glycemic control, including  
315 postprandial control, before conception and during pregnancy improves fetal outcome. Although  
316 the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also  
317 has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first  
318 trimester and increase during the second and third trimesters. Careful monitoring of the patient is  
319 required throughout pregnancy. During the perinatal period, careful monitoring of infants born to  
320 mothers with diabetes is warranted.

### 321 **Nursing Mothers**

322 It is unknown whether Humalog is excreted in significant amounts in human milk. Many  
323 drugs, including human insulin, are excreted in human milk. For this reason, caution should be  
324 exercised when Humalog is administered to a nursing woman. Patients with diabetes who are  
325 lactating may require adjustments in Humalog dose, meal plan, or both.

### 326 **Pediatric Use**

327 In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years,  
328 comparable glycemic control as measured by HbA<sub>1c</sub> was achieved regardless of treatment group:  
329 human regular insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%,  
330 and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of  
331 adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA<sub>1c</sub>  
332 was achieved regardless of treatment group; human regular insulin 30 to 45 minutes before  
333 meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was  
334 similar for all three treatment regimens. Adjustment of basal insulin may be required. To  
335 improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added  
336 directly to the Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND  
337 ADMINISTRATION).

### 338 **Geriatric Use**

339 Of the total number of subjects (n=2834) in eight clinical studies of Humalog,  
340 twelve percent (n=338) were 65 years of age or over. The majority of these were type 2 patients.  
341 HbA<sub>1c</sub> values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic  
342 studies to assess the effect of age on the onset of Humalog action have not been performed.

## 343 **ADVERSE REACTIONS**

344 Clinical studies comparing Humalog with human regular insulin did not demonstrate a  
345 difference in frequency of adverse events between the two treatments.

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

347 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

348 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

349 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

## 350 **OVERDOSAGE**

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

## 357 **DOSAGE AND ADMINISTRATION**

358 Humalog is intended for subcutaneous administration, including use in select external  
359 insulin pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage

NDA 20-563/S-024  
Page 10

10

360 regimens of Humalog will vary among patients and should be determined by the Health Care  
361 Professional familiar with the patient's metabolic needs, eating habits, and other lifestyle  
362 variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to  
363 human regular insulin (i.e., one unit of Humalog has the same glucose-lowering capability as one  
364 unit of human regular insulin), but with more rapid activity. The quicker glucose-lowering effect  
365 of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment  
366 of dose or schedule of basal insulin may be needed when a patient changes from other insulins to  
367 Humalog, particularly to prevent pre-meal hyperglycemia.

368 When used as a meal-time insulin, Humalog should be given within 15 minutes before or  
369 immediately after a meal. Human regular insulin is best given 30-60 minutes before a meal. To  
370 achieve optimal glucose control, the amount of longer-acting insulin being given may need to be  
371 adjusted when using Humalog.

372 The rate of insulin absorption and consequently the onset of activity is known to be affected by  
373 the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster  
374 rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin  
375 or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients with  
376 diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid  
377 onset of action and has less variability in its onset of action among injection sites compared with  
378 human regular insulin (*see* PRECAUTIONS). After abdominal administration, Humalog  
379 concentrations are higher than those following deltoid or thigh injections. Also, the duration of  
380 action of Humalog is slightly shorter following abdominal injection, compared with deltoid and  
381 femoral injections. As with all insulin preparations, the time course of action of Humalog may  
382 vary considerably in different individuals or within the same individual. Patients must be  
383 educated to use proper injection techniques.

384 Humalog may be diluted with STERILE DILUENT for Humalog<sup>®</sup>, Humulin<sup>®</sup> N,  
385 Humulin<sup>®</sup> 50/50, Humulin<sup>®</sup> 70/30, and NPH Iletin<sup>®</sup> to a concentration of 1:10 (equivalent to  
386 U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when  
387 stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog when  
388 used in an external insulin pump.

389 Parenteral drug products should be inspected visually prior to administration whenever the  
390 solution and the container permit. If the solution is cloudy, contains particulate matter, is  
391 thickened, or is discolored, the contents must not be injected. Humalog should not be used after  
392 its expiration date.

393 *External Insulin Pumps* — Humalog may be used with MiniMed<sup>®</sup> 1 Models 506, 507, and 508  
394 insulin pumps using MiniMed<sup>®</sup> 1 Polyfin<sup>®</sup> 1 infusion sets. Humalog may also be used in the  
395 Disetronic<sup>®</sup> 2 H-TRONplus<sup>®</sup> V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the  
396 Disetronic D-TRON<sup>®</sup> 2,4 and D-TRON<sup>®</sup> 2,4 plus pumps (with Humalog 3 mL cartridges) using  
397 Disetronic Rapid<sup>®</sup> 2 infusion sets.

398 Humalog should not be diluted or mixed with any other insulin when used in an external  
399 insulin pump.

#### HOW SUPPLIED

400 Humalog (insulin lispro injection, rDNA origin) vials are available in the following package  
401 size:

402 100 units per mL (U-100)

403 10 mL vials

NDC 0002-7510-01 (VL-7510)

404 Humalog (insulin lispro injection, rDNA origin) cartridges are available in the following  
405 package sizes:

406 5 X 1.5 mL cartridges<sup>3</sup>

NDC 0002-7515-59 (VL-7515)

407 5 X 3 mL cartridges<sup>4</sup>

NDC 0002-7516-59 (VL-7516)

NDA 20-563/S-024  
Page 11

11

409 Humalog (insulin lispro injection, rDNA origin) Pen, disposable insulin delivery device, is  
410 available in the following package size:

411 5 X 3 mL disposable insulin delivery devices NDC 0002-8725-59 (HP-8725)

412

413 1 MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

414 2 Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

415 3 1.5 mL cartridges are for use in Becton Dickinson and Company's B-D® Pen and Novo Nordisk A/S's

416 NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices.

417 B-D® is a registered trademark of Becton Dickinson and Company. NovolinPen® and NovoPen® are registered  
418 trademarks of Novo Nordisk A/S.

419 4 3 mL cartridge is for use in Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device and Disetronic

420 D-TRON® and D-TRON®plus pumps. Autopen® is a registered trademark of Owen Mumford, Ltd.

421 Other product and company names may be the trademarks of their respective owners.

422

423 *Storage* — Unopened Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but  
424 not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F])  
425 vials, cartridges, and Pens must be used within 28 days or be discarded, even if they still contain  
426 Humalog. Protect from direct heat and light. See table below:

	Not in-use (unopened) Room Temperature below 86°F (30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room temperature, below 86°F (30°C)
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature
1.5 mL and 3 mL cartridge	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>
3 mL Pen	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>

427

428 *Use in an External Insulin Pump* — A Humalog 3 mL cartridge used in the D-TRON®<sup>2,4</sup> or  
429 D-TRON®<sup>2,4</sup>plus should be discarded after 7 days, even if it still contains Humalog. Infusion  
430 sets, D-TRON®<sup>2,4</sup> and D-TRON®<sup>2,4</sup>plus cartridge adapters, and Humalog in the external insulin  
431 pump reservoir should be discarded every 48 hours or less.

432 Literature revised XXX, 2004

433

434 A2.0 NL 3690 AMP

435

**Eli Lilly and Company, Indianapolis, IN 46285, USA**

PRINTED IN USA

Copyright © 1996, 2004, Eli Lilly and Company. All rights reserved.

NDA 20-563/S-024  
Final  
Page 1

1  
A2.0 NL 6603 AMP

2 **INFORMATION FOR THE PATIENT**  
3 **VIAL**

4 **HUMALOG<sup>®</sup>**  
5 **INSULIN LISPRO INJECTION**  
6 **(rDNA ORIGIN)**  
7 **100 UNITS PER ML (U-100)**

8 **WARNINGS**

9 **THIS LILLY HUMAN INSULIN ANALOG IS DIFFERENT FROM OTHER**  
10 **INSULINS BECAUSE IT HAS A RAPID ONSET AND SHORTER DURATION**  
11 **OF ACTION. THE RAPID ONSET OF ACTION MEANS THAT YOU SHOULD**  
12 **TAKE YOUR DOSE OF HUMALOG<sup>®</sup> (INSULIN LISPRO INJECTION, rDNA**  
13 **ORIGIN) WITHIN 15 MINUTES BEFORE OR IMMEDIATELY AFTER**  
14 **EATING. THE SHORT DURATION OF ACTION OF HUMALOG MEANS**  
15 **THAT IF YOU HAVE TYPE 1 DIABETES, YOU ALSO NEED TO USE A**  
16 **LONGER-ACTING INSULIN TO GIVE THE BEST GLUCOSE CONTROL**  
17 **(EXCEPT WHEN USING AN EXTERNAL INSULIN PUMP). IF YOU HAVE**  
18 **TYPE 2 DIABETES, HUMALOG MAY BE USED WITHOUT A**  
19 **LONGER-ACTING INSULIN WHEN USED IN COMBINATION THERAPY**  
20 **WITH SULFONYLUREA AGENTS.**

21 **ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY**  
22 **UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH,**  
23 **MANUFACTURER, TYPE (E.G., REGULAR, NPH, LENTE), SPECIES (BEEF,**  
24 **PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA**  
25 **VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A**  
26 **CHANGE IN THE TIMING OR DOSAGE OF HUMALOG OR THE**  
27 **LONGER-ACTING INSULIN, OR BOTH.**

28 **PATIENTS TAKING HUMALOG MAY REQUIRE A CHANGE IN DOSAGE**  
29 **FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS**  
30 **NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST**  
31 **SEVERAL WEEKS OR MONTHS.**

32 **EXTERNAL INSULIN PUMP: WHEN USED IN AN EXTERNAL INSULIN**  
33 **PUMP, HUMALOG SHOULD NOT BE DILUTED OR MIXED WITH ANY**  
34 **OTHER INSULIN. CAREFULLY READ AND FOLLOW THE EXTERNAL**  
35 **INSULIN PUMP MANUFACTURER'S INSTRUCTIONS AND THIS INSERT**  
36 **BEFORE USING HUMALOG (see INSTRUCTIONS FOR INSULIN VIAL USE**  
37 **section).**

38 **DIABETES**

39 Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This  
40 hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when  
41 the pancreas does not make enough insulin to meet your body's needs.

42 To control your diabetes, your doctor has prescribed injections of insulin products to keep your  
43 blood glucose at a near-normal level. You have been instructed to test your blood and/or your  
44 urine regularly for glucose. Studies have shown that some chronic complications of diabetes  
45 such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood  
46 sugar is maintained as close to normal as possible. The American Diabetes Association

NDA 20-563/S-024  
Final  
Page 2

2

47 recommends that if your pre-meal glucose levels are consistently above 130 mg/dL or your  
48 hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is more than 7%, consult your doctor. A change in your diabetes  
49 therapy may be needed. If your blood tests consistently show below-normal glucose levels, you  
50 should also let your doctor know. Proper control of your diabetes requires close and constant  
51 cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat  
52 a balanced diet, exercise regularly, and take your insulin injections as prescribed.

53 Always keep an extra supply of Humalog as well as a spare syringe and needle on hand.  
54 Always wear diabetic identification so that appropriate treatment can be given if complications  
55 occur away from home.

## HUMALOG

### Description

57 Humalog (insulin lispro [rDNA origin]) is made by a special non-disease-producing laboratory  
58 strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene  
59 for this human insulin analog. Humalog consists of zinc-insulin lispro crystals dissolved in a  
60 clear fluid. Humalog is a sterile solution and is for subcutaneous injection. It should not be used  
61 intramuscularly. The concentration of Humalog is 100 units/mL (U-100). Humalog starts  
62 lowering blood glucose more quickly and has a shorter duration of action compared to regular  
63 human insulin. This means that your dose of Humalog should be given within 15 minutes before  
64 or immediately after a meal (regular insulin works best when given 30 to 60 minutes before a  
65 meal). The short duration of action of Humalog means that if you have type 1 diabetes, you need  
66 to use a longer-acting insulin to give the best glucose control (except when using an external  
67 insulin pump). If you have type 2 diabetes, Humalog may be used without a longer-acting insulin  
68 when used in combination therapy with sulfonylurea agents. The time course of Humalog action,  
69 like that of other insulins, may vary in different individuals or at different times in the same  
70 individual, based on dose, site of injection, blood supply, temperature, and physical activity.

### Identification

72 Insulin lispro injection (rDNA origin), by Eli Lilly and Company, has the trademark Humalog.  
73 Your doctor has prescribed the type of insulin that he/she believes is best for you.

### **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.**

76 Always check the carton and bottle labels of the Humalog you receive from your pharmacy to  
77 make sure it is the same as that your doctor has prescribed.

78 Always examine the appearance of Humalog solution in your bottle before withdrawing each  
79 dose. Humalog is a clear and colorless liquid with a water-like appearance and consistency. Do  
80 not use if it appears cloudy, thickened, or slightly colored, or if solid particles are visible.  
81 Always check the appearance of Humalog solution in the bottle before use and if you note  
82 anything unusual in its appearance or notice your insulin requirements changing markedly,  
83 consult your doctor.  
84

### Storage

85 Humalog may be diluted with the appropriate sterile diluent only under the direction of a  
86 physician. **However, do not dilute Humalog when used in an external insulin pump.**

87 After withdrawal of the initial dose, diluted Humalog should be discarded 28 days after first  
88 use when refrigerated and 14 days after first use when stored at room temperature.

89 **Not in-use (unopened):** Unopened Humalog bottles should be stored in a refrigerator but not  
90 in the freezer. Do not use Humalog if it has been frozen.

91 **In-use:** Humalog bottles should be refrigerated after first dose has been withdrawn. If  
92 refrigeration is not possible, the bottle of Humalog that you are currently using can be kept  
93 unrefrigerated, up to 28 days, as long as it is kept at room temperature (below 86°F [30°C]) and  
94 away from direct heat and light. Do not use Humalog if it has been frozen.  
95

NDA 20-563/S-024  
Final  
Page 3

3

96 Humalog in the external insulin pump reservoir and the complete infusion set should be  
97 replaced and a new infusion site selected every 48 hours or less. Humalog in an external insulin  
98 pump should not be exposed to temperatures above 98.6°F (37°C), such as in a sauna or hot tub,  
99 hot showers, direct sunlight, or radiant heater.

100

101 **Do not use Humalog after the expiration date stamped on the label or if it has been**  
102 **frozen.**

103

### INSTRUCTIONS FOR INSULIN VIAL USE

104

#### Use with Syringes

105

**NEVER SHARE NEEDLES AND SYRINGES.**

106

#### **Correct Syringe Type**

107

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL = 1 cc).  
108 With Humalog, it is important to use a syringe that is marked for U-100 insulin preparations. For  
109 this reason, you should always use a syringe marked for the strength of Humalog you are  
110 injecting. Failure to use the proper syringe can lead to a mistake in dosage, causing serious  
111 problems for you, such as a blood glucose level that is too low or too high.

112

#### **Syringe Use**

113

To help avoid contamination and possible infection, follow these instructions exactly.

114

Disposable plastic syringes and needles should be used only once and then discarded in a  
115 responsible manner. Place the used needle in a puncture-resistant disposable container and  
116 properly dispose of it as directed by your Health Care Professional.

117

Reusable glass syringes and needles must be sterilized before each injection. **Follow the**  
118 **package directions supplied with your syringe.** Described below are 2 methods of sterilizing.

119

#### **Boiling**

120

1. Put syringe, plunger, and needle in strainer, place in saucepan, and cover with water. Boil  
121 for 5 minutes.
- 122 2. Remove articles from water. When they have cooled, insert plunger into barrel, and fasten  
123 needle to syringe with a slight twist.
- 124 3. Push plunger in and out several times until water is completely removed.

125

#### **Isopropyl Alcohol**

126

If the syringe, plunger, and needle cannot be boiled, as when you are traveling, they may be  
127 sterilized by immersion for at least 5 minutes in Isopropyl Alcohol, 91%. Do not use bathing,  
128 rubbing, or medicated alcohol for this sterilization. If the syringe is sterilized with alcohol, it  
129 must be absolutely dry before use.

130

#### **Preparing the Dose**

131

1. Wash your hands.
- 132 2. Inspect the appearance of Humalog solution in the bottle. It should look clear and  
133 colorless. Do not use Humalog if it appears cloudy, thickened, or slightly colored, or if  
134 solid particles are visible.
- 135 3. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
- 136 4. Wipe the top of the bottle with an alcohol swab.
- 137 5. If you are mixing insulins, refer to the instructions for mixing that follow.
- 138 6. Draw air into the syringe equal to your Humalog dose. Put the needle through rubber top  
139 of the Humalog bottle and inject the air into the bottle.
- 140 7. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
- 141 8. Making sure the tip of the needle is in the Humalog, withdraw the correct dose into the  
142 syringe.
- 143 9. Before removing the needle from the bottle, check your syringe for air bubbles, which  
144 reduce the amount of Humalog. If bubbles are present, hold the syringe straight up and tap

NDA 20-563/S-024  
Final  
Page 4

4

145 its side until the bubbles float to the top. Push them out with the plunger and withdraw the  
146 correct dose.  
147 10. Remove the needle from the bottle and lay the syringe down so that the needle does not  
148 touch anything.

### 149 **Mixing Humalog with Longer-acting Human Insulins**

150 **Humalog should not be mixed with any other insulin when used in an external insulin**  
151 **pump.**

- 152 1. Humalog should be mixed with longer-acting human insulins only on the advice of your  
153 doctor.
- 154 2. Draw air into your syringe equal to the amount of longer-acting insulin you are taking.  
155 Insert the needle into the longer-acting insulin bottle and inject the air. Withdraw the  
156 needle.
- 157 3. Now inject air into your Humalog bottle in the same manner, but **do not** withdraw the  
158 needle.
- 159 4. Turn the bottle and syringe upside down.
- 160 5. Making sure the tip of the needle is in the Humalog solution, withdraw the correct dose of  
161 Humalog into the syringe.
- 162 6. Before removing the needle from the bottle of Humalog, check your syringe for air  
163 bubbles, which reduce the amount of Humalog in it. If bubbles are present, hold the  
164 syringe straight up and tap its side until the bubbles float to the top. Push them out with  
165 the plunger and withdraw the correct dose.
- 166 7. Remove the needle from the bottle of Humalog and insert it into the bottle of the  
167 longer-acting insulin. Turn the bottle and syringe upside down. Hold the bottle and  
168 syringe firmly in one hand and shake gently. Making sure the tip of the needle is in the  
169 insulin, withdraw your dose of longer-acting insulin.

170 8. Remove the needle and lay the syringe down so that the needle does not touch anything.

171 When you are mixing two types of insulin, always draw Humalog into the syringe first.

172 Always mix the insulin preparations in this same sequence in order to maintain purity of the  
173 Humalog vial. You should inject your insulins immediately after mixing.

174 Syringes from different manufacturers may vary in the amount of space between the bottom  
175 line and the needle. Because of this, do not change:

- 176 • the sequence of mixing, or
- 177 • the model and brand of syringe or needle that the doctor has prescribed.

### 178 **Injection**

179 Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to  
180 be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as  
181 instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply  
182 gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue  
183 damage, give the next injection at a site at least 1/2 inch from the previous injection site. The  
184 usual sites of injection are abdomen, thighs, and arms. Place the used needle in a puncture-  
185 resistant disposable container and properly dispose of it as directed by your Health Care  
186 Professional.

### 187 Use in an External Insulin Pump

188 Your doctor should train you on intensive insulin therapy. You should also be trained on the  
189 use of your external insulin pump and pump accessories.

190 Humalog may be used with the MiniMed®<sup>1</sup> Models 506, 507, and 508 insulin pumps using  
191 MiniMed®<sup>1</sup> Polyfin®<sup>1</sup> infusion sets. Humalog may also be used in the Disetronic®<sup>2</sup>  
192 H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), using the  
193 Disetronic®<sup>2</sup> Rapid®<sup>2</sup> infusion set.

NDA 20-563/S-024  
Final  
Page 5

5

194 Follow the external insulin pump manufacturer's instructions for use of Humalog in an  
195 external insulin pump. Humalog should not be diluted or mixed with any other insulin when used  
196 in an external insulin pump.

197 You should replace the infusion set (reservoir syringe, tubing, and catheter) and Humalog in  
198 the external insulin pump reservoir every 48 hours or less. You should also choose a new  
199 infusion site every 48 hours or less. Contact your doctor if your infusion sites are red, itching, or  
200 thickened, and then choose a new infusion site.

### 201 **DOSAGE**

202 Your doctor has told you which insulin to use, how much, and when and how often to inject it.  
203 Because each patient's case of diabetes is different, this schedule has been individualized for  
204 you. Your usual Humalog dose may be affected by changes in your food, activity, or work  
205 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things  
206 that may affect your Humalog dose are:

### 207 **Illness**

208 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.  
209 Even if you are not eating, you will still require insulin. You and your doctor should establish a  
210 sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine  
211 glucose and ketones frequently and call your doctor as instructed.

### 212 **Pregnancy**

213 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may  
214 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or  
215 are nursing a baby, consult your doctor. Humalog has not been tested in pregnant or nursing  
216 women.

### 217 **Geriatric Use**

218 Elderly patients using Humalog had HbA<sub>1c</sub> values and hypoglycemia rates similar to those  
219 observed in younger patients. The onset of action of Humalog may be different in elderly  
220 patients.

### 221 **Medication**

222 Insulin requirements may be increased if you are taking other drugs with hyperglycemic  
223 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin  
224 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,  
225 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and  
226 certain antidepressants. Your Health Care Professional is aware of other medications that may  
227 affect your diabetes control. Therefore, always discuss any medications you are taking with your  
228 doctor.

### 229 **Exercise**

230 Exercise may lower your body's need for insulin products during and for some time after the  
231 physical activity. Exercise may also speed up the effect of a dose of Humalog, especially if the  
232 exercise involves the area of injection site. Discuss with your doctor how you should adjust your  
233 regimen to accommodate exercise.

### 234 **Travel**

235 Persons traveling across more than 2 time zones should consult their doctor concerning  
236 adjustments in their insulin schedule.

## 237 **COMMON PROBLEMS OF DIABETES**

### 238 **Hypoglycemia (Low Blood Sugar)**

239 Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events  
240 experienced by insulin users. It can be brought about by:

- 241 1. **Missing or delaying meals.**
- 242 2. Taking too much insulin.
- 243 3. Exercising or working more than usual.

NDA 20-563/S-024  
Final  
Page 6

6

- 244 4. An infection or illness (especially with diarrhea or vomiting).  
245 5. A change in the body's need for insulin.  
246 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver  
247 disease.  
248 7. Interactions with other drugs that lower blood glucose, such as oral antidiabetic agents,  
249 salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants.  
250 8. Consumption of alcoholic beverages.

251 Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- |  |                       |
|--|-----------------------|
| 252 • sweating                                     | • drowsiness          |
| 253 • dizziness                                    | • sleep disturbances  |
| 254 • palpitation                                  | • anxiety             |
| 255 • tremor                                       | • blurred vision      |
| 256 • hunger                                       | • slurred speech      |
| 257 • restlessness                                 | • depressed mood      |
| 258 • tingling in the hands, feet, lips, or tongue | • irritability        |
| 259 • lightheadedness                              | • abnormal behavior   |
| 260 • inability to concentrate                     | • unsteady movement   |
| 261 • headache                                     | • personality changes |

262 Signs of severe hypoglycemia can include:

- |                       |            |
|-----------------------|------------|
| 263 • disorientation  | • seizures |
| 264 • unconsciousness | • death    |

265 Therefore, it is important that assistance be obtained immediately.

266 Early warning symptoms of hypoglycemia may be different or less pronounced under certain  
267 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as  
268 beta-blockers, changing insulin preparations, or intensified control (3 or more injections per day)  
269 of diabetes. A few patients who have experienced hypoglycemic reactions after transfer from  
270 animal-source insulin to human insulin have reported that the early warning symptoms of  
271 hypoglycemia were less pronounced or different from those experienced with their previous  
272 insulin.

273 Without recognition of early warning symptoms, you may not be able to take steps to avoid  
274 more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate  
275 hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should  
276 monitor their blood glucose frequently, especially prior to activities such as driving. If the blood  
277 glucose is below your normal fasting glucose, you should consider eating or drinking  
278 sugar-containing foods to treat your hypoglycemia.

279 Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar.

280 Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.  
281 More severe hypoglycemia may require the assistance of another person. Patients who are unable  
282 to take sugar orally or who are unconscious require an injection of glucagon or should be treated  
283 with intravenous administration of glucose at a medical facility.

284 You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain  
285 about these symptoms, you should monitor your blood glucose frequently to help you learn to  
286 recognize the symptoms that you experience with hypoglycemia.

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

### 290 **Hyperglycemia and Diabetic Ketoacidosis (DKA)**

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

- 293 1. Omitting your insulin or taking less than the doctor has prescribed.

NDA 20-563/S-024  
Final  
Page 7

7

294 2. Eating significantly more than your meal plan suggests.

295 3. Developing a fever, infection, or other significant stressful situation.

296 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in  
297 DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days,  
298 and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath.  
299 With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid  
300 pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to  
301 nausea, vomiting, dehydration, loss of consciousness, or death. Therefore, it is important that  
302 you obtain medical assistance immediately.

### 303 **Lipodystrophy**

304 Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the  
305 skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these  
306 conditions, consult your doctor. A change in your injection technique may help alleviate the  
307 problem.

### 308 **Allergy**

309 *Local Allergy* — Patients occasionally experience redness, swelling, and itching at the site of  
310 injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In  
311 some instances, this condition may be related to factors other than insulin, such as irritants in the  
312 skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

313 *Systemic Allergy* — Less common, but potentially more serious, is generalized allergy to  
314 insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in  
315 blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life  
316 threatening. If you think you are having a generalized allergic reaction, notify a doctor  
317 immediately.

## 318 **ADDITIONAL INFORMATION**

319 Additional information about diabetes may be obtained from your diabetes educator.

320 **DIABETES FORECAST** is a magazine designed especially for people with diabetes and their  
321 families. It is available by subscription from the American Diabetes Association (ADA), P.O.  
322 Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383).

323 Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research  
324 Foundation International (JDRFI), 120 Wall Street 19th Floor, New York, NY 10005,  
325 1-800-533-CURE (1-800-533-2873).

326 Additional information about Humalog can be obtained by calling The Lilly Answers Center at  
327 1-800-LillyRx (1-800-545-5979).

328

329 <sup>1</sup> MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

330 <sup>2</sup> Disetronic®, H-TRONplus®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

331 Other product and company names may be the trademarks of their respective owners.

332 Literature revised XXX, 2004

333 **Eli Lilly and Company Indianapolis, IN 46285, USA**

334 A2.0 NL 6603 AMP

PRINTED IN USA

335 Copyright © 1996, 2004, Eli Lilly and Company. All rights reserved.

A2.0 NL 9085 FSAMP

1  
2  
3  
**INFORMATION FOR THE PATIENT  
CARTRIDGE**

4  
5  
6  
7  
8  
**HUMALOG<sup>®</sup>  
INSULIN LISPRO INJECTION  
(rDNA ORIGIN)  
100 UNITS PER ML (U-100)**

9  
**1.5 ML CARTRIDGE**

10 For use in Becton Dickinson and Company's B-D<sup>®1</sup> Pen and Novo Nordisk A/S's  
11 NovoPen<sup>®2</sup>, NovolinPen<sup>®2</sup>, and NovoPen<sup>®2</sup> 1.5 insulin delivery devices (reusable  
12 insulin Pens).

13  
**3 ML CARTRIDGE**

14 For use in Owen Mumford, Ltd.'s Autopen<sup>®3</sup> 3 mL insulin delivery device  
15 (reusable insulin Pen), Disetronic<sup>®4</sup> D-TRON<sup>®4</sup> or D-TRON<sup>®4</sup>plus insulin pumps.

16  
17  
**WARNINGS**

18 **THIS LILLY HUMAN INSULIN ANALOG IS DIFFERENT FROM OTHER**  
19 **INSULINS BECAUSE IT HAS A RAPID ONSET AND SHORTER DURATION**  
20 **OF ACTION. THE RAPID ONSET OF ACTION MEANS THAT YOU SHOULD**  
21 **TAKE YOUR DOSE OF HUMALOG<sup>®</sup> (INSULIN LISPRO INJECTION, rDNA**  
22 **ORIGIN) WITHIN 15 MINUTES BEFORE OR IMMEDIATELY AFTER**  
23 **EATING. THE SHORT DURATION OF ACTION OF HUMALOG MEANS**  
24 **THAT IF YOU HAVE TYPE 1 DIABETES, YOU ALSO NEED TO USE A**  
25 **LONGER-ACTING INSULIN TO GIVE THE BEST GLUCOSE CONTROL**  
26 **(EXCEPT WHEN USING AN EXTERNAL INSULIN PUMP). IF YOU HAVE**  
27 **TYPE 2 DIABETES, HUMALOG MAY BE USED WITHOUT A**  
28 **LONGER-ACTING INSULIN WHEN USED IN COMBINATION THERAPY**  
29 **WITH SULFONYLUREA AGENTS.**

30 **ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY**  
31 **UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH,**  
32 **MANUFACTURER, TYPE (E.G., REGULAR, NPH, LENTE), SPECIES (BEEF,**  
33 **PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA**  
34 **VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A**  
35 **CHANGE IN THE TIMING OR DOSAGE OF HUMALOG OR THE**  
36 **LONGER-ACTING INSULIN, OR BOTH.**

37 **PATIENTS TAKING HUMALOG MAY REQUIRE A CHANGE IN DOSAGE**  
38 **FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS**  
39 **NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST**  
40 **SEVERAL WEEKS OR MONTHS.**

41 **USE IN REUSABLE INSULIN PEN: TO OBTAIN AN ACCURATE DOSE,**  
42 **CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE**  
43 **MANUFACTURER'S INSTRUCTIONS AND THIS "INFORMATION FOR THE**  
44 **PATIENT" INSERT BEFORE USING THIS PRODUCT IN AN INSULIN PEN**  
45 **(see INSTRUCTIONS FOR USE section).**

46 | **USE IN AN EXTERNAL INSULIN PUMP: CAREFULLY READ AND**  
47 **FOLLOW THE EXTERNAL INSULIN PUMP MANUFACTURER'S**  
48 **INSTRUCTIONS AND THIS "INFORMATION FOR THE PATIENT" INSERT**  
49 **BEFORE USING THIS PRODUCT IN AN EXTERNAL INSULIN PUMP (see**  
50 **INSTRUCTIONS FOR USE section).**

51 **DIABETES**

52 Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This  
53 hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when  
54 the pancreas does not make enough insulin to meet your body's needs.

55 To control your diabetes, your doctor has prescribed injections of insulin products to keep your  
56 blood glucose at a near-normal level. You have been instructed to test your blood and/or your  
57 urine regularly for glucose. Studies have shown that some chronic complications of diabetes  
58 such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood  
59 sugar is maintained as close to normal as possible. The American Diabetes Association  
60 recommends that if your pre-meal glucose levels are consistently above 130 mg/dL or your  
61 hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is more than 7%, consult your doctor. A change in your diabetes  
62 | therapy may be needed. If your blood tests consistently show below-normal glucose levels, you  
63 should also let your doctor know. Proper control of your diabetes requires close and constant  
64 cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat  
65 a balanced diet, exercise regularly, and take your insulin injections as prescribed.

66 Always keep an extra supply of Humalog as well as a spare syringe and needle on hand.  
67 Always wear diabetic identification so that appropriate treatment can be given if complications  
68 occur away from home.

69 **HUMALOG**

70 **Description**

71 Humalog (insulin lispro [rDNA origin]) is made by a special non-disease-producing laboratory  
72 strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene  
73 for this human insulin analog. Humalog consists of zinc-insulin lispro crystals dissolved in a  
74 clear fluid. Humalog is a sterile solution and is for subcutaneous injection. It should not be used  
75 intramuscularly. The concentration of Humalog is 100 units/mL (U-100). Humalog starts  
76 lowering blood glucose more quickly and has a shorter duration of action compared to regular  
77 human insulin. This means that your dose of Humalog should be given within 15 minutes before  
78 or immediately after a meal (regular insulin works best when given 30 to 60 minutes before a  
79 meal). The short duration of action of Humalog means that if you have type 1 diabetes, you need  
80 to use a longer-acting insulin to give the best glucose control (except when using an external  
81 insulin pump). If you have type 2 diabetes, Humalog may be used without a longer-acting insulin  
82 when used in combination therapy with sulfonylurea agents. The time course of Humalog action,  
83 like that of other insulins, may vary in different individuals or at different times in the same  
84 individual, based on dose, site of injection, blood supply, temperature, and physical activity.

85 **Identification**

86 Cartridges of insulin lispro injection (rDNA origin), by Eli Lilly and Company, have the  
87 trademark Humalog. Your doctor has prescribed the type of insulin that he/she believes is best  
88 for you.

89 **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND**  
90 **DIRECTION.**

91 **Cartridges of Humalog, 1.5 mL and 3 mL, are available in boxes of 5.**

92 **1.5 mL Cartridge**

93 **Humalog<sup>®</sup> 1.5 mL cartridges are for use in Becton Dickinson and Company's B-D<sup>®</sup> Pen**  
94 **and Novo Nordisk A/S's NovoPen<sup>®</sup>, NovolinPen<sup>®</sup>, and NovoPen<sup>®</sup> 1.5 insulin delivery**  
95 **devices ([reusable insulin Pens](#)).**

96 **3 mL Cartridge**

97 **Humalog<sup>®</sup> 3 mL cartridges are for use in Owen Mumford, Ltd.'s Autopen<sup>®</sup> 3 mL insulin**  
98 **delivery device (reusable insulin Pen) and in Disetronic D-TRON<sup>®4</sup> or D-TRON<sup>®4</sup>plus**  
99 **insulin pumps using Disetronic Rapid<sup>®4</sup> infusion sets.**

100 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the  
101 cartridge or for the cartridge to be reused.

102 Always examine the appearance of Humalog solution in a cartridge before administering a  
103 dose. When using a Humalog cartridge in an external insulin pump, inspect the cartridge before  
104 inserting it in the external insulin pump and periodically during use. Humalog is a clear and  
105 colorless liquid with a water-like appearance and consistency. Do not use if it appears cloudy,  
106 thickened, or slightly colored, or if solid particles are visible. If you note anything unusual in its  
107 appearance or notice your insulin requirements changing markedly, consult your doctor.

108 **Storage**

109 **When used in Reusable Insulin Pen**

110 **Not in-use (unopened):** Unopened Humalog cartridges should be stored in a refrigerator but  
111 not in the freezer. Do not use a Humalog cartridge if it has been frozen.

112 **In-use:** Humalog cartridges in-use should **NOT** be refrigerated but should be kept at room  
113 temperature (below 86°F [30°C]) away from direct heat and light. Humalog cartridge that you  
114 are using must be discarded **28 days after the first use.**

115 Do not use Humalog after the expiration date stamped on the label.

116 **When used in an External Insulin Pump**

117 **Infusion sets (tubing and catheters) and D-TRON<sup>®4</sup> or D-TRON<sup>®4</sup>plus cartridge**  
118 **adapter should be discarded every 48 hours or less. Humalog in an external insulin pump**  
119 **should not be exposed to temperatures above 98.6°F (37°C) such as in sauna or hot tub, hot**  
120 **showers, direct sunlight, or radiant heater. A Humalog 3 mL cartridge used in the**  
121 **D-TRON<sup>®4</sup> or D-TRON<sup>®4</sup>plus pump should be discarded after 7 days, even if it still**  
122 **contains Humalog.**

123 **INSTRUCTIONS FOR USE**

124 **Reusable insulin Pens and external insulin pumps differ in their operation. It is**  
125 **important to read, understand, and follow the instructions for use of the reusable insulin**  
126 **Pen or external insulin pump you are using.**

127 **NEVER SHARE INSULIN PENS, EXTERNAL INSULIN PUMPS, INFUSION SETS,**  
128 **CARTRIDGES, OR NEEDLES.**

129 **PREPARING FOR AN INJECTION USING REUSABLE INSULIN PEN OR EXTERNAL**  
130 **INSULIN PUMP**

- 131 1. Inspect the appearance of Humalog solution before you insert the cartridge into the  
132 reusable insulin Pen or external insulin pump. Humalog should look clear and colorless.  
133 Do not use Humalog if it appears cloudy, thickened, slightly colored, or if solid particles  
134 are visible. Once the cartridge is in use, inspect the insulin in the insulin Pen before each  
135 injection. When using a Humalog cartridge in an external insulin pump, inspect the  
136 cartridge before inserting it in the external insulin pump and periodically during use.
- 137 2. *Use in Reusable Insulin Pen* — Follow the reusable insulin Pen manufacturer's  
138 instructions carefully for loading the cartridge into the insulin Pen and for use of the  
139 insulin Pen.
- 140 a. Use an alcohol swab to wipe the exposed rubber surface on the metal cap end of the  
141 cartridge.
- 142 b. Follow the insulin needle manufacturer's instructions for attaching and changing the  
143 needle.
- 144 3. *Use in an External Insulin Pump* — Follow the external insulin pump manufacturer's  
145 instructions carefully for use of Humalog 3 mL cartridges in the D-TRON<sup>®4</sup> or  
146 D-TRON<sup>®4</sup>plus insulin pump.

147 **GENERAL INSTRUCTIONS**

148 For use in Reusable Insulin Pen

- 149 1. Wash your hands.
- 150 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
- 151 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 152 3. Cleanse the skin with alcohol where the injection is to be made.
- 153 4. With one hand, stabilize the skin by spreading it or pinching up a large area.
- 154 5. Inject the dose as instructed by your doctor. Hold the needle under the skin for at least 5
- 155 seconds after injecting.
- 156 6. After dispensing a dose, pull the needle out and apply gentle pressure over the injection
- 157 site for several seconds. **Do not rub the area.**
- 158 7. Immediately after an injection, remove the needle from the insulin Pen. Doing so will
- 159 guard against contamination, and prevent leakage of Humalog, reentry of air, and needle
- 160 clogs. **Do not reuse needles.** Place the used needle in a puncture-resistant disposable
- 161 container and properly dispose of it as directed by your Health Care Professional.
- 162 8. 1.5 mL cartridge — Once the cartridge is in use, do not continue to use it if the leading
- 163 edge of the plunger is beyond the black band on the cartridge. If a dose is started when the
- 164 leading edge of the plunger is beyond the black band, an appropriate dose may not be
- 165 delivered. Use the gauge on the side of the cartridge to help you judge how much
- 166 Humalog remains. The distance between each mark on the 1.5 mL cartridge is about
- 167 10 units.
- 168 3 mL cartridge — Use the gauge on the side of the cartridge to help you judge how much
- 169 insulin remains. The distance between each mark on the 3 mL cartridge is about 20 units.

170 For use in an External Insulin Pump

171 Your doctor should train you on intensive insulin therapy including sterile techniques. You

172 should also be trained on the use of your external insulin pump and pump accessories.

173 **You should replace the infusion set (tubing and catheter) and D-TRON®<sup>4</sup> or**

174 **D-TRON®<sup>4</sup>plus cartridge adapter every 48 hours or less.** You should also choose a new

175 infusion site every 48 hours or less. A Humalog 3 mL cartridge used in the pump should be

176 discarded after 7 days, even if it still contains Humalog. Contact your doctor if your infusion

177 sites are red, itching, or thickened, and then choose a new infusion site.

178 Follow the external insulin pump manufacturer's instructions carefully for use of Humalog

179 3 mL cartridges in Disetronic D-TRON®<sup>4</sup> or D-TRON®<sup>4</sup>plus insulin pump.

180 **DOSAGE**

181 Your doctor has told you which insulin to use, how much, and when and how often to inject it.

182 Because each patient's case of diabetes is different, this schedule has been individualized for

183 you. Your usual Humalog dose may be affected by changes in your food, activity, or work

184 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things

185 that may affect your Humalog dose are:

186 **Illness**

187 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.

188 Even if you are not eating, you will still require insulin. You and your doctor should establish a

189 sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine

190 glucose and ketones frequently and call your doctor as instructed.

191 **Pregnancy**

192 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may

193 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or

194 are nursing a baby, consult your doctor. Humalog has not been tested in pregnant or nursing

195 women.

196 **Geriatric Use**

197 Elderly patients using Humalog had HbA<sub>1c</sub> values and hypoglycemia rates similar to those  
198 observed in younger patients. The onset of action of Humalog may be different in elderly  
199 patients.

200 **Medication**

201 Insulin requirements may be increased if you are taking other drugs with hyperglycemic  
202 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin  
203 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,  
204 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and  
205 certain antidepressants. Your Health Care Professional is aware of other medications that may  
206 affect your diabetes control. Therefore, always discuss any medications you are taking with your  
207 doctor.

208 **Exercise**

209 Exercise may lower your body's need for insulin products during and for some time after the  
210 physical activity. Exercise may also speed up the effect of a dose of Humalog, especially if the  
211 exercise involves the area of injection site. Discuss with your doctor how you should adjust your  
212 regimen to accommodate exercise.

213 **Travel**

214 Persons traveling across more than 2 time zones should consult their doctor concerning  
215 adjustments in their insulin schedule.

216 **COMMON PROBLEMS OF DIABETES**

217 **Hypoglycemia (Low Blood Sugar)**

218 Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events  
219 experienced by insulin users. It can be brought about by:

- 220 1. **Missing or delaying meals.**  
221 2. Taking too much insulin.  
222 3. Exercising or working more than usual.  
223 4. An infection or illness (especially with diarrhea or vomiting).  
224 5. A change in the body's need for insulin.  
225 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver  
226 disease.  
227 7. Interactions with other drugs that lower blood glucose, such as oral antidiabetic agents,  
228 salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants.  
229 8. Consumption of alcoholic beverages.

230 Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- 231 • sweating  
232 • dizziness  
233 • palpitation  
234 • tremor  
235 • hunger  
236 • restlessness  
237 • tingling in the hands, feet, lips, or tongue  
238 • lightheadedness  
239 • inability to concentrate  
240 • headache
- drowsiness  
• sleep disturbances  
• anxiety  
• blurred vision  
• slurred speech  
• depressed mood  
• irritability  
• abnormal behavior  
• unsteady movement  
• personality changes

241 Signs of severe hypoglycemia can include:

- 242 • disorientation  
243 • unconsciousness
- seizures  
• death

244 Therefore, it is important that assistance be obtained immediately.

245 Early warning symptoms of hypoglycemia may be different or less pronounced under certain  
246 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as  
247 beta-blockers, changing insulin preparations, or intensified control (3 or more injections per day)  
248 of diabetes. A few patients who have experienced hypoglycemic reactions after transfer from  
249 animal-source insulin to human insulin have reported that the early warning symptoms of  
250 hypoglycemia were less pronounced or different from those experienced with their previous  
251 insulin.

252 Without recognition of early warning symptoms, you may not be able to take steps to avoid  
253 more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate  
254 hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should  
255 monitor their blood glucose frequently, especially prior to activities such as driving. If the blood  
256 glucose is below your normal fasting glucose, you should consider eating or drinking sugar-  
257 containing foods to treat your hypoglycemia.

258 Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar.  
259 Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.  
260 More severe hypoglycemia may require the assistance of another person. Patients who are unable  
261 to take sugar orally or who are unconscious require an injection of glucagon or should be treated  
262 with intravenous administration of glucose at a medical facility.

263 You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain  
264 about these symptoms, you should monitor your blood glucose frequently to help you learn to  
265 recognize the symptoms that you experience with hypoglycemia.

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

### 269 **Hyperglycemia and Diabetic Ketoacidosis (DKA)**

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

- 272 1. Omitting your insulin or taking less than the doctor has prescribed.
- 273 2. Eating significantly more than your meal plan suggests.
- 274 3. Developing a fever, infection, or other significant stressful situation.

275 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in  
276 DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days,  
277 and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath.  
278 With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid  
279 pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to  
280 nausea, vomiting, dehydration, loss of consciousness, or death. Therefore, it is important that  
281 you obtain medical assistance immediately.

### 282 **Lipodystrophy**

283 Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the  
284 skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these  
285 conditions, consult your doctor. A change in your injection technique may help alleviate the  
286 problem.

### 287 **Allergy**

288 *Local Allergy* — Patients occasionally experience redness, swelling, and itching at the site of  
289 injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In  
290 some instances, this condition may be related to factors other than insulin, such as irritants in the  
291 skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

292 *Systemic Allergy* — Less common, but potentially more serious, is generalized allergy to  
293 insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in  
294 blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life  
295 threatening. If you think you are having a generalized allergic reaction, notify a doctor  
296 immediately.

297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318

**ADDITIONAL INFORMATION**

Additional information about diabetes may be obtained from your diabetes educator.  
**DIABETES FORECAST** is a magazine designed especially for people with diabetes and their families. It is available by subscription from the American Diabetes Association (ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383).  
Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRFI), 120 Wall Street 19th Floor, New York, NY 10005, 1-800-533-CURE (1-800-533-2873).  
Additional information about Humalog can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979).

Literature revised XXX, 2004

Manufactured by Lilly France S.A.S.  
F-67640 Fegersheim, France  
for Eli Lilly and Company  
Indianapolis, IN 46285, USA

<sup>1</sup> B-D® is a registered trademark of Becton Dickinson and Company.  
<sup>2</sup> NovoPen® and NovolinPen®, are registered trademarks of Novo Nordisk A/S.  
<sup>3</sup> Autopen® is a registered trademark of Owen Mumford, Ltd.  
<sup>4</sup> Disetronic®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.  
Other product and company names may be the trademarks of their respective owners.