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**HUMALOG<sup>®</sup> Mix75/25<sup>™</sup>**  
**75% INSULIN LISPRO PROTAMINE SUSPENSION AND**  
**25% INSULIN LISPRO INJECTION**  
**(rDNA ORIGIN)**  
**100 UNITS PER ML (U-100)**

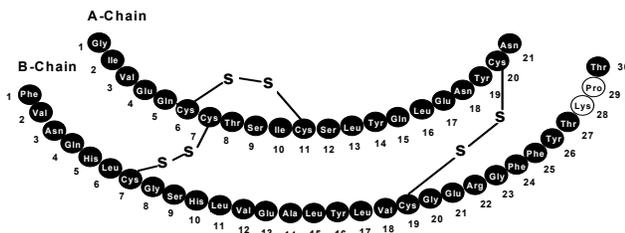
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**DESCRIPTION**

Humalog<sup>®</sup> Mix75/25<sup>™</sup> [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro 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. Insulin lispro 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. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:

**Figure 1**



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

20 Humalog Mix75/25 vials and disposable insulin delivery devices contain a sterile suspension  
 21 of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

22 Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 Units, 0.28 mg  
 23 protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg *m*-cresol, zinc  
 24 oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and water for injection.  
 25 Humalog Mix75/25 has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10%  
 26 may have been added to adjust pH.

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**CLINICAL PHARMACOLOGY**

**Antidiabetic Activity** — The primary activity of insulin, including Humalog Mix75/25, 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.

35 Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be  
 36 equipotent to regular human insulin on a molar basis. One unit of Humalog<sup>®</sup> has the same

37 glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of  
 38 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared to  
 39 Humulin<sup>®</sup> 70/30 on a unit for unit basis.

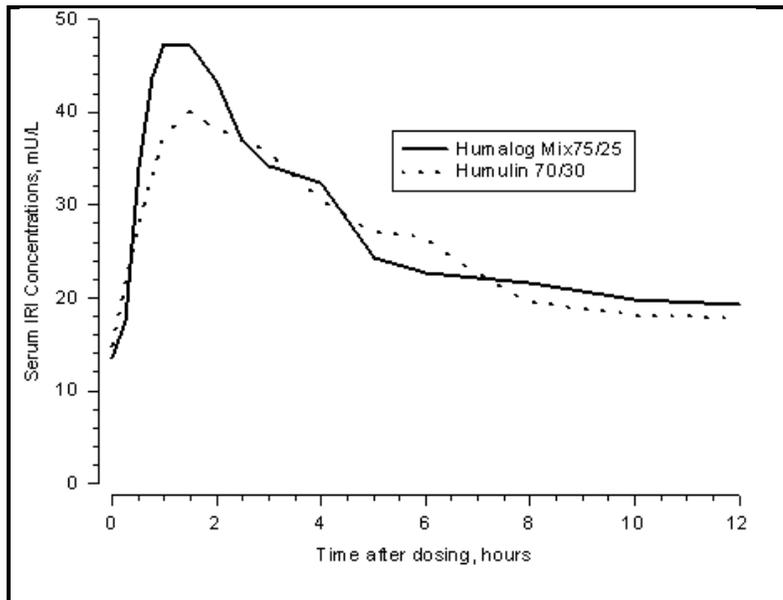
#### 40 **Pharmacokinetics**

41 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)  
 42 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix75/25, is  
 43 absorbed faster than regular human insulin (U-100). In nondiabetic subjects given subcutaneous  
 44 doses of Humalog ranging from 0.1-0.4 U/kg, peak serum concentrations were observed  
 45 30-90 minutes after dosing. When nondiabetic subjects received equivalent doses of regular  
 46 human insulin, peak insulin concentrations occurred 50-120 minutes after dosing. Similar results  
 47 were found in patients with type 1 diabetes.  
 48

**Figure 2**

**Serum immunoreactive insulin (IRI) concentrations, after subcutaneous injection of Humalog Mix75/25 or Humulin 70/30 in healthy nondiabetic subjects.**

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51 Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and  
 52 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin  
 53 lispro protamine suspension. In 30 nondiabetic subjects given subcutaneous doses (0.3 U/kg) of  
 54 Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes (median,  
 55 60 minutes) after dosing (Figure 2). Identical results were found in patients with type 1 diabetes.  
 56 The rapid absorption characteristics of Humalog are maintained with Humalog Mix75/25  
 57 (Figure 2).

58 Figure 2 represents serum insulin concentration versus time curves of Humalog Mix75/25 and  
 59 Humulin 70/30. Humalog Mix75/25 has a more rapid absorption than Humulin 70/30, which has  
 60 been confirmed in patients with type 1 diabetes.

61 *Distribution* — Radiolabeled distribution studies of Humalog Mix75/25 have not been  
62 conducted. However, the volume of distribution following injection of Humalog is identical to  
63 that of regular human insulin, with a range of 0.26-0.36 L/kg.

64 *Metabolism* — Human metabolism studies of Humalog Mix75/25 have not been conducted.  
65 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of  
66 Humalog Mix75/25, is identical to that of regular human insulin.

67 *Elimination* — Humalog Mix75/25 has two absorption phases, a rapid and a prolonged phase,  
68 representative of the insulin lispro and insulin lispro protamine suspension components of the  
69 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot  
70 be calculated after administration of Humalog Mix75/25 because of the prolonged insulin lispro  
71 protamine suspension absorption.

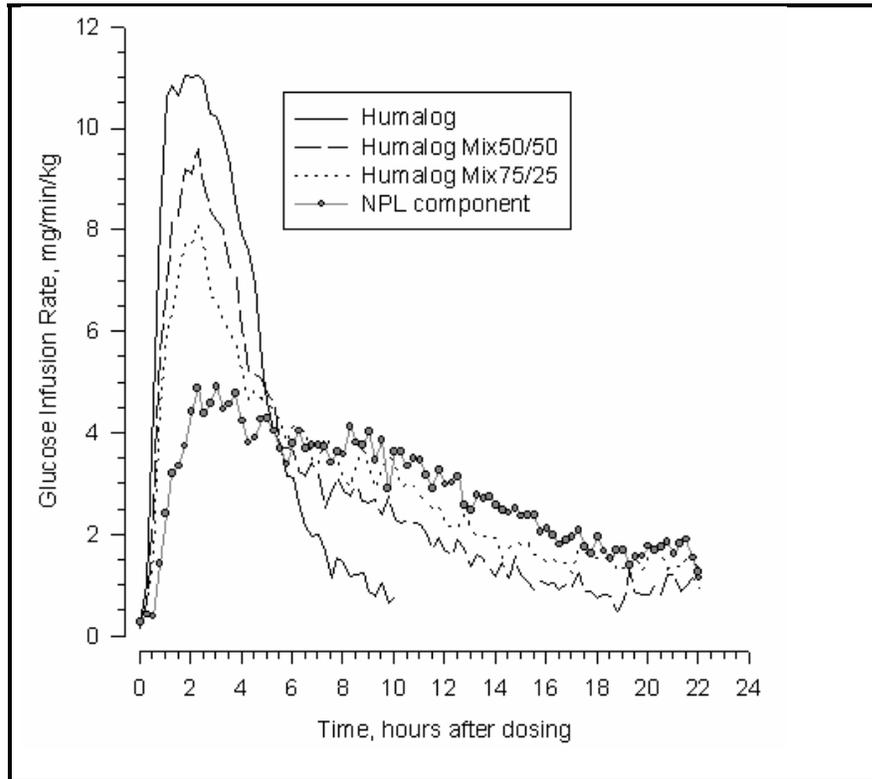
72 **Pharmacodynamics** — Studies in nondiabetic subjects and patients with diabetes  
73 demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak  
74 for glucose-lowering, and a shorter duration of glucose-lowering activity than regular human  
75 insulin. The early onset of activity of Humalog Mix75/25 is directly related to the rapid  
76 absorption of Humalog. The time course of action of insulin and insulin analogs such as  
77 Humalog (and hence Humalog Mix75/25) may vary considerably in different individuals or  
78 within the same individual. The parameters of Humalog Mix75/25 activity (time of onset, peak  
79 time, and duration) as presented in Figures 2, 3, and 4 should be considered only as general  
80 guidelines. The rate of insulin absorption and consequently the onset of activity is known to be  
81 affected by the site of injection, exercise, and other variables (*see General under*  
82 **PRECAUTIONS**).

83 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-  
84 lowering activity of Humalog, Humalog Mix75/25, Humalog<sup>®</sup> Mix50/50<sup>™</sup> and insulin lispro  
85 protamine suspension were compared (Figure 3). Graphs of mean glucose infusion rate versus  
86 time showed a distinct insulin activity profile for each formulation. The rapid onset of glucose-  
87 lowering activity characteristic of Humalog was maintained in Humalog Mix75/25.

88 In separate glucose clamp studies performed in nondiabetic subjects, glucodynamics of  
89 Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 4.  
90 Humalog Mix75/25 has a duration of activity similar to that of Humulin 70/30.

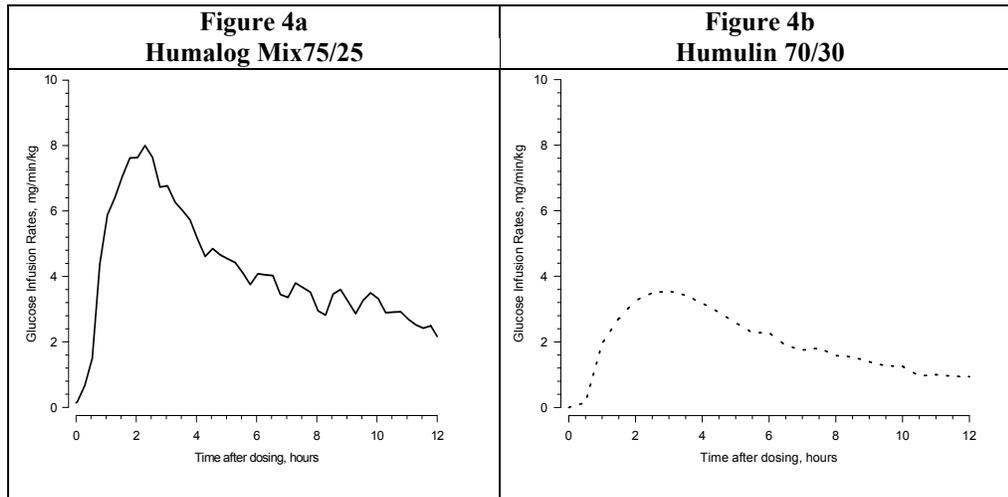
**Figure 3**  
**Insulin activity after injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or insulin lispro protamine suspension (NPL component) in 30 nondiabetic subjects.**

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**Figure 4**  
**Insulin activity after injection of Humalog Mix75/25 and Humulin 70/30 in nondiabetic subjects.**



93  
 94 Figures 3 and 4 represent insulin activity profiles as measured by glucose clamp studies in  
 95 healthy nondiabetic subjects.  
 96 Figure 3 shows the time activity profiles of Humalog, Humalog Mix75/25,  
 97 Humalog Mix50/50, and insulin lispro protamine suspension (NPL component).  
 98 Figure 4 is a comparison of the time activity profiles of Humalog Mix75/25 (Figure 4a) and of  
 99 Humulin 70/30 (Figure 4b) from two different studies.

#### 100 *Special Populations*

101 **Age and Gender** — Information on the effect of age on the pharmacokinetics of  
 102 Humalog Mix75/25 is unavailable. Pharmacokinetic and pharmacodynamic comparisons  
 103 between men and women administered Humalog Mix75/25 showed no gender differences. In  
 104 large Humalog clinical trials, subgroup analyses based upon age and gender demonstrated that  
 105 differences between Humalog and regular human insulin in postprandial glucose parameters are  
 106 maintained across sub-groups.

107 **Smoking** — The effect of smoking on the pharmacokinetics and glucodynamics of  
 108 Humalog Mix75/25 has not been studied.

109 **Pregnancy** — The effect of pregnancy on the pharmacokinetics and glucodynamics of  
 110 Humalog Mix75/25 has not been studied.

111 **Obesity** — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics  
 112 and glucodynamics of Humalog Mix75/25 has not been studied. In large clinical trials, which  
 113 included patients with Body-Mass-Index up to and including 35 kg/m<sup>2</sup>, no consistent differences  
 114 were observed between Humalog and Humulin R with respect to postprandial glucose  
 115 parameters.

116 **Renal Impairment** — The effect of renal impairment on the pharmacokinetics and  
 117 glucodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with type 2  
 118 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog  
 119 and human regular insulin were generally maintained. However, the sensitivity of the patients to

120 insulin did change, with an increased response to insulin as the renal function declined. Careful  
121 glucose monitoring and dose reductions of insulin, including Humalog Mix75/25, may be  
122 necessary in patients with renal dysfunction.

123 **Hepatic Impairment** — Some studies with human insulin have shown increased circulating  
124 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the  
125 pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied. However, in a  
126 study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the  
127 subcutaneous absorption or general disposition of Humalog when compared to patients with no  
128 history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and  
129 elimination when compared to regular human insulin. Careful glucose monitoring and dose  
130 adjustments of insulin, including Humalog Mix75/25, may be necessary in patients with hepatic  
131 dysfunction.

### 132 **INDICATIONS AND USAGE**

133 Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin  
134 lispro, is indicated in the treatment of patients with diabetes mellitus for the control of  
135 hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering activity  
136 compared to Humulin 70/30 while having a similar duration of action. This profile is achieved by  
137 combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine  
138 suspension.

### 139 **CONTRAINDICATIONS**

140 Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients  
141 sensitive to insulin lispro or any of the excipients contained in the formulation.

### 142 **WARNINGS**

143 **Humalog differs from regular human insulin by its rapid onset of action as well as a**  
144 **shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given**  
145 **within 15 minutes before a meal.**

146 **Hypoglycemia is the most common adverse effect associated with the use of insulins,**  
147 **including Humalog Mix75/25. As with all insulins, the timing of hypoglycemia may differ**  
148 **among various insulin formulations. Glucose monitoring is recommended for all patients**  
149 **with diabetes.**

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

### 154 **PRECAUTIONS**

155 *General* — Hypoglycemia and hypokalemia are among the potential clinical adverse effects  
156 associated with the use of all insulins. Because of differences in the action of Humalog Mix75/25  
157 and other insulins, care should be taken in patients in whom such potential side effects might be  
158 clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using  
159 potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).  
160 Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated  
161 with the use of all insulins.

162 As with all insulin preparations, the time course of action of Humalog Mix75/25 may vary in  
163 different individuals or at different times in the same individual and is dependent on site of  
164 injection, blood supply, temperature, and physical activity.

165 Adjustment of dosage of any insulin may be necessary if patients change their physical activity  
166 or their usual meal plan. Insulin requirements may be altered during illness, emotional  
167 disturbances, or other stress.

168 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated  
169 with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations  
170 may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value.  
171 Early warning symptoms of hypoglycemia may be different or less pronounced under certain  
172 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as  
173 beta-blockers, or intensified diabetes control.

174 **Renal Impairment** — As with other insulins, the requirements for Humalog Mix75/25 may be  
175 reduced in patients with renal impairment.

176 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or  
177 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including  
178 Humalog Mix75/25, may be necessary.

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

183 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to  
184 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,  
185 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized  
186 allergy, including anaphylactic reaction, may be life threatening. Localized reactions and  
187 generalized myalgias have been reported with the use of cresol as an injectable excipient.

188 Antibody Production — In clinical trials, antibodies that cross react with human insulin and  
189 insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures  
190 treatment groups.

191 *Information for Patients* — Patients should be informed of the potential risks and advantages  
192 of Humalog Mix75/25 and alternative therapies. Patients should not mix Humalog Mix75/25  
193 with any other insulin. They should also be informed about the importance of proper insulin  
194 storage, injection technique, timing of dosage, adherence to meal planning, regular physical  
195 activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition  
196 and management of hypo- and hyperglycemia, and periodic assessment for diabetes  
197 complications.

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

200 Refer patients to the INFORMATION FOR THE PATIENT insert for information on normal  
201 appearance, proper resuspension and injection techniques, timing of dosing (within 15 minutes  
202 before a meal), storing, and common adverse effects.

203 *Use of the Humalog Mix75/25 Pen:* Patients should read the “INFORMATION FOR THE  
204 PATIENT” insert and the “Disposable Insulin Delivery Device User Manual” before starting  
205 therapy with a Humalog Mix75/25 Pen and re-read them each time the prescription is renewed.  
206 Patients should be instructed on how to properly use the delivery device (refer to “Disposable  
207 Insulin Delivery Device User Manual”), prime the Pen, and properly dispose of needles. Patients  
208 should be advised not to share their Pens with others.

209 *Laboratory Tests* — As with all insulins, the therapeutic response to Humalog Mix75/25  
210 should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated  
211 hemoglobin is recommended for the monitoring of long-term glycemic control.

212 *Drug Interactions* — Insulin requirements may be increased by medications with  
213 hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs  
214 (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

215 Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity,  
216 such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine

217 oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors, beta-adrenergic blockers,  
 218 inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may  
 219 mask the symptoms of hypoglycemia in some patients.

220 *Carcinogenesis, Mutagenesis, Impairment of Fertility* — Long-term studies in animals have  
 221 not been performed to evaluate the carcinogenic potential of Humalog or Humalog Mix75/25.  
 222 Insulin lispro was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays  
 223 (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal  
 224 aberration tests, and a micronucleus test). There is no evidence from animal studies of  
 225 impairment of fertility induced by insulin lispro.

226 *Pregnancy — Teratogenic Effects — Pregnancy Category B* — Reproduction studies with  
 227 insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and  
 228 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The  
 229 results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro.  
 230 There are, however, no adequate and well-controlled studies with Humalog or  
 231 Humalog Mix75/25 in pregnant women. Because animal reproduction studies are not always  
 232 predictive of human response, this drug should be used during pregnancy only if clearly needed.

233 *Nursing Mothers* — It is unknown whether insulin lispro is excreted in significant amounts in  
 234 human milk. Many drugs, including human insulin, are excreted in human milk. For this reason,  
 235 caution should be exercised when Humalog Mix75/25 is administered to a nursing woman.  
 236 Patients with diabetes who are lactating may require adjustments in Humalog Mix75/25 dose,  
 237 meal plan, or both.

238 *Pediatric Use* — Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years  
 239 of age have not been established.

240 *Geriatric Use* — Clinical studies of Humalog Mix75/25 did not include sufficient numbers of  
 241 patients aged 65 and over to determine whether they respond differently than younger patients.  
 242 In general, dose selection for an elderly patient should take into consideration the greater  
 243 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other  
 244 drug therapy in this population.

#### 245 **ADVERSE REACTIONS**

246 Clinical studies comparing Humalog Mix75/25 with human insulin mixtures did not  
 247 demonstrate a difference in frequency of adverse events between the two treatments.

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

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

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

251 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS)

#### 252 **OVERDOSAGE**

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

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260**DOSAGE AND ADMINISTRATION****Table 1\*****Summary of glucodynamic properties of insulin products (pooled cross-study comparison)**

Insulin Products	Dose, U/kg	Time of peak activity, hours after dosing	Percent of total activity occurring in the first 4 hours
Humalog	0.3	2.4 (0.8 – 4.3)	70% (49 – 89%)
Humulin R	0.32 (0.26 – 0.37)	4.4 (4.0 – 5.5)	54% (38 – 65%)
Humalog Mix75/25	0.3	2.6 (1.0 – 6.5)	35% (21 – 56%)
Humulin 70/30	0.3	4.4 (1.5 – 16)	32% (14 – 60%)
Humalog Mix50/50	0.3	2.3 (0.8 – 4.8)	45% (27 – 69%)
Humulin 50/50	0.3	3.3 (2.0 – 5.5)	44% (21 – 60%)
NPH	0.32 (0.27 – 0.40)	5.5 (3.5 – 9.5)	14% (3.0 – 48%)
NPL component	0.3	5.8 (1.3 – 18.3)	22% (6.3 – 40%)

261 \*The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the  
 262 total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp  
 263 studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.  
 264

265 Humalog Mix75/25 is intended only for subcutaneous administration. Humalog Mix75/25  
 266 should not be administered intravenously. Dosage regimens of Humalog Mix75/25 will vary  
 267 among patients and should be determined by the health care professional familiar with the  
 268 patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown  
 269 to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same  
 270 glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of  
 271 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared to  
 272 Humulin 70/30 on a unit for unit basis. The quicker glucose-lowering effect of Humalog is  
 273 related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

274 Humalog Mix75/25 starts lowering blood glucose more quickly than regular human insulin,  
 275 allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast,  
 276 mixtures containing regular human insulin should be given 30-60 minutes before a meal.

277 The rate of insulin absorption and consequently the onset of activity are known to be affected  
 278 by the site of injection, exercise, and other variables. As with all insulin preparations, the time  
 279 course of action of Humalog Mix75/25 may vary considerably in different individuals or within  
 280 the same individual. Patients must be educated to use proper injection techniques.

281 Humalog Mix75/25 should be inspected visually before use. Humalog Mix75/25 should be  
 282 used only if it appears uniformly cloudy after mixing. Humalog Mix75/25 should not be used  
 283 after its expiration date.

Lilly's submission date: 2/25/04

**HOW SUPPLIED**

284  
 285 Humalog Mix75/25 vials are available in the following package size:  
 286 100 units per mL (U-100)  
 287 10 mL vials  
 288 NDC 0002-7511-01 (VL-7511)  
 289 Humalog Mix75/25 Pen, a disposable insulin delivery device, is available in the following  
 290 package size:  
 291 5 x 3 mL disposable insulin delivery devices  
 292 NDC 0002-8794-59 (HP-8794)  
 293

294 *Storage* — Humalog Mix75/25 should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but  
 295 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated (below  
 296 86°F [30°C]) vials must be used within 28 days or be discarded, even if they still contain  
 297 Humalog Mix75/25. Unrefrigerated (below 86°F [30°C]) Pens must be used within 10 days or be  
 298 discarded, even if they still contain Humalog Mix75/25. Protect [Humalog Mix75/25 vials or](#)  
 299 [Pens](#) from direct heat and light. See table below:  
 300

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

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 302 Literature issued XXXX 2003  
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**INFORMATION FOR THE PATIENT  
VIAL**

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**HUMALOG<sup>®</sup> Mix75/25<sup>™</sup>  
75% INSULIN LISPRO PROTAMINE SUSPENSION AND  
25% INSULIN LISPRO INJECTION  
(rDNA ORIGIN)  
100 Units per mL (U-100)**

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**WARNINGS**

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**THIS LILLY HUMAN INSULIN ANALOG MIXTURE IS DIFFERENT FROM OTHER INSULIN MIXTURES IN THAT ITS ONSET OF ACTION IS VERY QUICK. THE QUICK ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF HUMALOG<sup>®</sup> Mix75/25<sup>™</sup> (75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION, [rDNA ORIGIN]) WITHIN 15 MINUTES BEFORE YOU EAT.**

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**ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG Mix75/25.**

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**PATIENTS TAKING HUMALOG Mix75/25 MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.**

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**DIABETES**

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

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To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. The American Diabetes Association recommends that if your pre-meal glucose levels are consistently above 130 mg/dL, bedtime glucose levels are consistently above 160 mg/dL or hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is more than 7%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-targeted glucose levels, you should also let your doctor know. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed.

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Always keep an extra supply of Humalog Mix75/25 as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

## HUMALOG Mix75/25

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### Description

Humalog (insulin lispro [rDNA origin]) is made by a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for this human insulin analog. Humalog Mix75/25 is a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro, (rDNA origin). It is a longer-acting insulin combined with the more rapid onset of action of Humalog. The duration of activity is similar to that of Humulin 70/30 and may last up to 24 hours following injection. The time course of Humalog Mix75/25 action, like that of other insulins, may vary in different individuals or at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity. Humalog Mix75/25 is a sterile suspension and is for subcutaneous injection. It should not be used intravenously. The concentration of Humalog Mix75/25 is 100 units/mL (U-100).

Humalog Mix75/25 starts lowering blood glucose more quickly than regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing regular human insulin should be given 30-to 60 minutes before a meal.

### Identification

Insulin lispro injection (rDNA origin), manufactured by Eli Lilly and Company, has the trademark Humalog. Humalog products are available in two formulations—Humalog and Humalog Mix75/25. 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. YOU SHOULD NOT MIX HUMALOG Mix75/25 WITH ANOTHER INSULIN.**

Always check the carton and bottle labels of the Humalog Mix75/25 you receive from your pharmacy to make sure it is the same as that your doctor has prescribed.

Always examine the appearance of your bottle of Humalog Mix75/25 suspension before withdrawing each dose. A bottle of Humalog Mix75/25 must be carefully shaken or rotated several times to completely mix the insulin. Humalog Mix75/25 should look uniformly cloudy or milky after mixing. If not, repeat the above step until contents are mixed. Do not use if the insulin substance (the white material) remains at the bottom of the vial after mixing. Do not use a bottle of Humalog Mix75/25 if there are clumps in the insulin after mixing. Do not use a bottle of Humalog Mix75/25 if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance. Always check the appearance of your bottle of Humalog Mix75/25 suspension before using. If you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

### Storage

Humalog Mix75/25 should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of Humalog Mix75/25 that you are currently using can be kept unrefrigerated at room temperature (below 86°F [30°C]), **up to 28 days**, as long as it is kept as cool as possible and away from direct heat and light. Do not use Humalog Mix75/25 if it has been frozen. Do not use a bottle of Humalog Mix75/25 after the expiration date stamped on the label.

## INJECTION PROCEDURES

### NEVER SHARE NEEDLES AND SYRINGES

#### Correct Syringe Type

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL = 1 cc). With Humalog Mix75/25, it is important to use a syringe that is marked for U-100 insulin preparations.

#### Syringe Use

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

95 Disposable plastic syringes and needles should be used only once and then discarded in a  
96 responsible manner.

### 97 **Preparing the Dose**

- 98 1. Wash your hands.
- 99 2. Carefully shake or rotate the insulin bottle several times to completely mix the insulin.
- 100 3. Inspect the insulin. Humalog Mix75/25 suspension should look uniformly cloudy or  
101 milky. Do not use it if you notice anything unusual in its appearance (*see* Identification  
102 above).
- 103 4. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
- 104 5. Wipe the top of the bottle with an alcohol swab.
- 105 6. Draw air into the syringe equal to your Humalog Mix75/25 dose. Put the needle through  
106 rubber top of the Humalog Mix75/25 bottle and inject the air into the bottle.
- 107 7. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
- 108 8. Making sure the tip of the needle is in the Humalog Mix75/25, withdraw the correct dose  
109 into the syringe.
- 110 9. Before removing the needle from the bottle, check your syringe for air bubbles, which  
111 reduce the amount of Humalog Mix75/25. If bubbles are present, hold the syringe straight  
112 up and tap its side until the bubbles float to the top. Push them out with the plunger and  
113 withdraw the correct dose.
- 114 10. Remove the needle from the bottle and lay the syringe down so that the needle does not  
115 touch anything.

### 116 **Injection Instructions**

- 117 1. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the  
118 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 119 2. Cleanse the skin with alcohol where the injection is to be made.
- 120 3. With one hand, stabilize the skin by spreading it or pinching up a large area.
- 121 4. Insert the needle as instructed by your doctor.
- 122 5. Push the plunger in as far as it will go.
- 123 6. Pull the needle out and apply gentle pressure over the injection site for several seconds.  
124 **Do not rub the area.** Place the used needle in a puncture-resistant disposable container  
125 and properly dispose of it as directed by your Health Care Professional.

### 126 **DOSAGE**

127 Your doctor has told you which insulin to use, how much, and when and how often to inject it.  
128 Because each patient's case of diabetes is different, this schedule has been individualized for you.  
129 Your usual Humalog Mix75/25 dose may be affected by changes in your food, activity, or work  
130 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that  
131 may affect your Humalog Mix75/25 dose are:

#### 132 **Illness**

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

#### 137 **Pregnancy**

138 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may  
139 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or  
140 are nursing a baby, consult your doctor. Humalog Mix75/25 has not been tested in pregnant or  
141 nursing women.

#### 142 **Medication**

143 Insulin requirements may be increased if you are taking other drugs with hyperglycemic  
144 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin  
145 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,

146 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and  
 147 certain antidepressants. Your **hHealth eCare pProfessional** is aware of these and other  
 148 medications that may affect your diabetes control. Therefore, always discuss any medications  
 149 you are taking with your doctor.

#### 150 **Exercise**

151 Exercise may lower your body's need for insulin products during and for some time after the  
 152 physical activity. Exercise may also speed up the effect of a Humalog Mix75/25 dose, especially  
 153 if the exercise involves the area of your injection site. Discuss with your doctor how you should  
 154 adjust your regimen to accommodate exercise.

#### 155 **Travel**

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

158

### 159 **COMMON PROBLEMS OF DIABETES**

#### 160 **Hypoglycemia (Insulin Reaction Low blood sugar)**

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

- 163 1. **Missing or delaying meals**
- 164 2. Taking too much insulin
- 165 3. Exercising or working more than usual
- 166 4. An infection or illness (especially with diarrhea or vomiting)
- 167 5. A change in the body's need for insulin
- 168 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver  
 169 disease
- 170 7. Interactions with other drugs that lower blood glucose, such as oral antidiabetic agents,  
 171 salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants
- 172 8. Consumption of alcoholic beverages

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

- |  |                       |
|--|-----------------------|
| 174 • sweating                                     | • drowsiness          |
| 175 • dizziness                                    | • sleep disturbances  |
| 176 • palpitation                                  | • anxiety             |
| 177 • tremor                                       | • blurred vision      |
| 178 • hunger                                       | • slurred speech      |
| 179 • restlessness                                 | • depressed mood      |
| 180 • tingling in the hands, feet, lips, or tongue | • irritability        |
| 181 • lightheadedness                              | • abnormal behavior   |
| 182 • inability to concentrate                     | • unsteady movement   |
| 183 • headache                                     | • personality changes |

184 Signs of severe hypoglycemia can include:

- |                       |            |
|-----------------------|------------|
| 185 • disorientation  | • seizures |
| 186 • unconsciousness | • death    |

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

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

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

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

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

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

### 212 **Hyperglycemia and Diabetic Ketoacidosis**

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

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

218 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in  
 219 diabetic ketoacidosis (DKA). The first symptoms of DKA usually come on gradually, over a  
 220 period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and  
 221 fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones.  
 222 Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged  
 223 hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of  
 224 consciousness, or death. Therefore, it is important that you obtain medical assistance  
 225 immediately.

### 226 **Lipodystrophy**

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

### 231 **Allergy**

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

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

### 241 **ADDITIONAL INFORMATION**

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

243 **DIABETES FORECAST** is a national magazine designed especially for patients with  
 244 diabetes and their families and is available by subscription from the American Diabetes  
 245 Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314, 1-800-

246 DIABETES (1-800-342-2383). Another publication, **DIABETES COUNTDOWN**, is available  
247 from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street, 19th Floor, New  
248 York, New York 10005-4001, 1-800-JDF-CURE (1-800-533-2873).  
249 Additional information about Humalog Mix75/25 can be obtained by calling 1-888-88-LILLY  
250 (1-888-885-4559) or consult the Eli Lilly and Company Internet Web Site at  
251 <http://www.lilly.com/diabetes>.

252 Literature issued XXX 2003

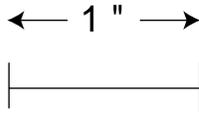
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F-67640 Fegersheim, France  
for Eli Lilly and Company  
Indianapolis, IN 46285, USA

A1.0 NL 4850 AMP

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IMPORTANT—SEE WARNINGS  
ON ACCOMPANYING INSERT

A1.0 NL 4320 AMS  
A1.0 NL 4320 AMS

Exp. Date/Control No.

**Humalog® Mix75/25™**  
75% insulin lispro protamine suspension  
25% insulin lispro injection  
(rDNA origin)

**Warning:** Any change of insulin should be made cautiously and only under medical supervision.

For subcutaneous use only. Shake carefully before using. See enclosed insert for proper technique. See accompanying insert for dosage. Each mL contains 75 units insulin lispro protamine suspension; 25 units insulin lispro; protamine sulfate, 0.28 mg; glycerin, 16 mg; dibasic sodium phosphate, 3.78 mg; m-cresol, 1.76 mg; zinc oxide content adjusted to provide 0.025 mg zinc ion; phenol, 0.715 mg; and water for injection. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH. Manufactured by Lilly France S.A.S. F-67640 Fegersheim, France for Eli Lilly and Company Indianapolis, IN 46285, USA

For information call  
1-888-885-4559

**Lilly** NDC 0002-7511-01  
10 mL VL-7511  
100 units per mL

**Rx**  
**Humalog® Mix75/25™**  
75% insulin lispro  
protamine suspension  
25% insulin lispro injection  
(rDNA origin)

Rx only  
U-100

NDC 0002-7511-01  
10 mL VL-7511  
100 units per mL

**Rx**  
**Humalog® Mix75/25™**  
75% insulin lispro protamine suspension  
25% insulin lispro injection  
(rDNA origin)

U-100

Rx only

Keep in a cold place.  
Avoid freezing.

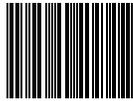


U-100

A1.0 NL 4320 AMS



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