

HUMALOG[®] Mix75/25[™]
75% INSULIN LISPRO PROTAMINE SUSPENSION AND
25% INSULIN LISPRO INJECTION
(rDNA ORIGIN)

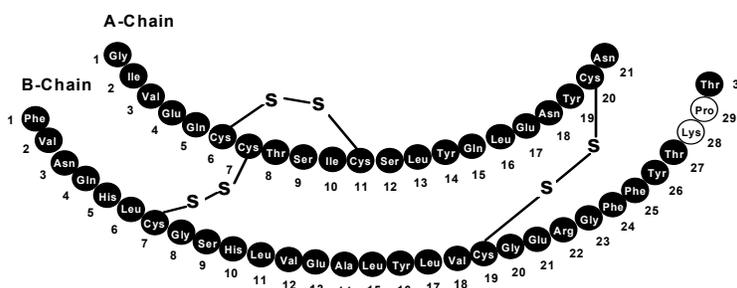
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] Mix75/25[™] [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



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.

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

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

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.

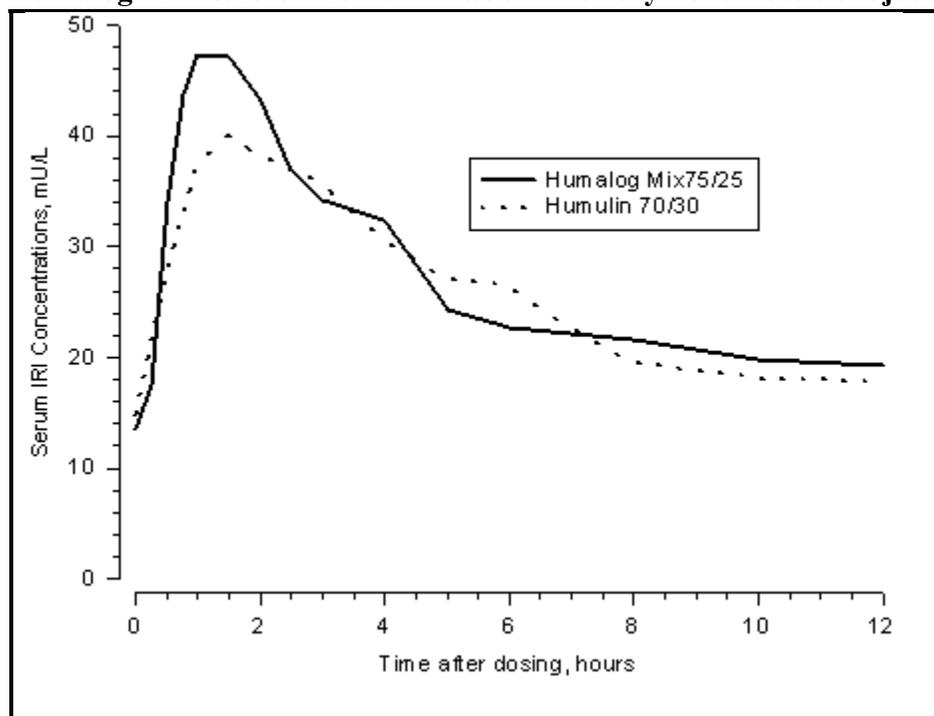
Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog[®] has the same glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared to Humulin[®] 70/30 on a unit for unit basis.

Pharmacokinetics

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

Figure 2

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



Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin lispro protamine suspension. In 30 nondiabetic subjects given subcutaneous doses (0.3 U/kg) of

56 Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes (median,
57 60 minutes) after dosing (Figure 2). Identical results were found in patients with type 1 diabetes.
58 The rapid absorption characteristics of Humalog are maintained with Humalog Mix75/25
59 (Figure 2).

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

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

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

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

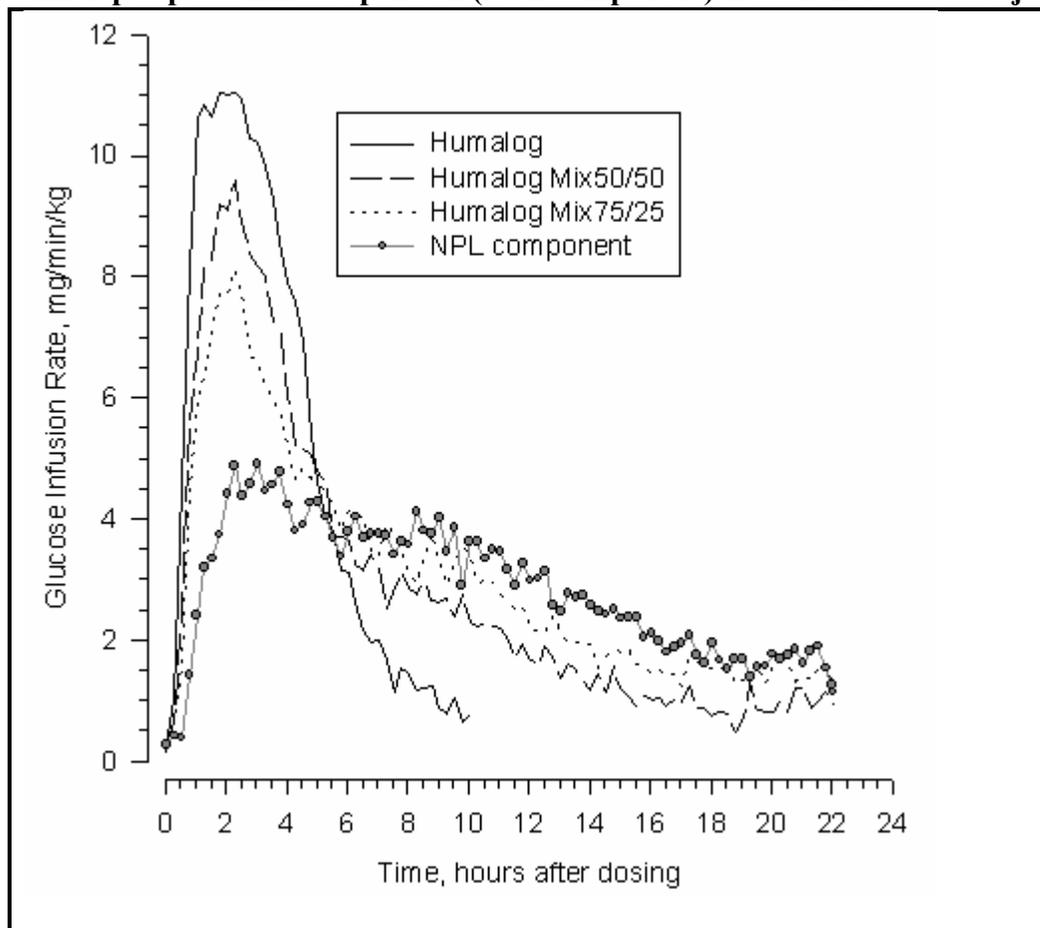
74 **Pharmacodynamics** — Studies in nondiabetic subjects and patients with diabetes
75 demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak
76 for glucose-lowering, and a shorter duration of glucose-lowering activity than regular human
77 insulin. The early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

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

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

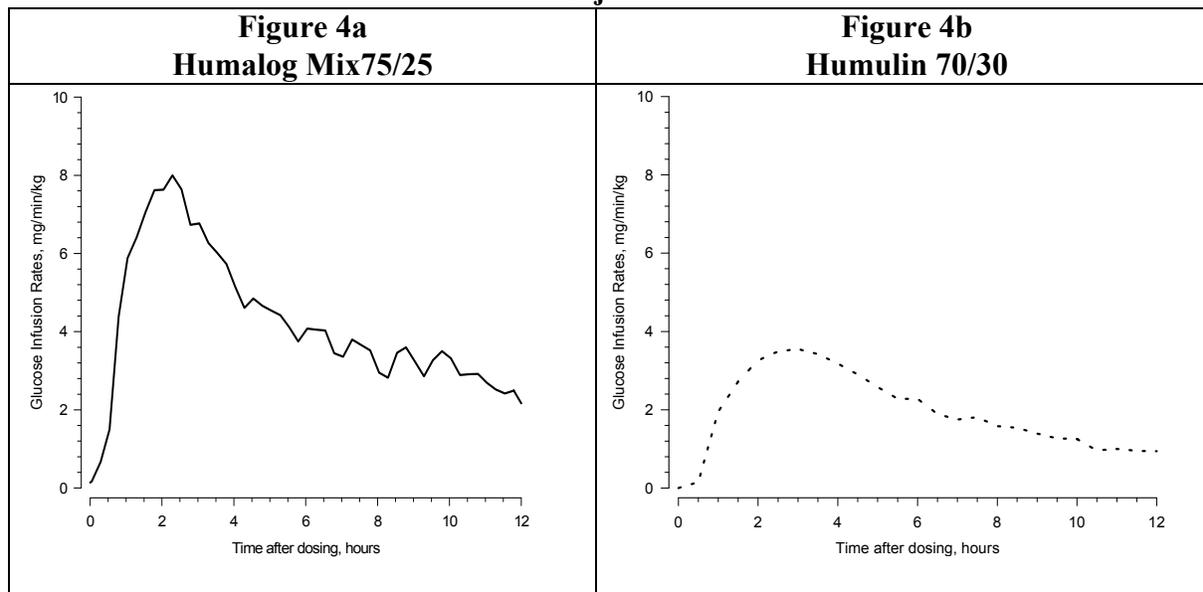
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Figure 3
Insulin activity after injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or
insulin lispro protamine suspension (NPL component) in 30 nondiabetic subjects.



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



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100 Figures 3 and 4 represent insulin activity profiles as measured by glucose clamp studies in
 101 healthy nondiabetic subjects.

102 Figure 3 shows the time activity profiles of Humalog, Humalog Mix75/25,
 103 Humalog Mix50/50, and insulin lispro protamine suspension (NPL component).

104 Figure 4 is a comparison of the time activity profiles of Humalog Mix75/25 (Figure 4a) and of
 105 Humulin 70/30 (Figure 4b) from two different studies.

106 *Special Populations*

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

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

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

117 **Obesity** — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics
 118 and glucodynamics of Humalog Mix75/25 has not been studied. In large clinical trials, which
 119 included patients with Body-Mass-Index up to and including 35 kg/m², no consistent differences
 120 were observed between Humalog and Humulin R with respect to postprandial glucose
 121 parameters.

122 **Renal Impairment** — The effect of renal impairment on the pharmacokinetics and
 123 glucodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with type 2
 124 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog
 125 and human regular insulin were generally maintained. However, the sensitivity of the patients to
 126 insulin did change, with an increased response to insulin as the renal function declined. Careful

127 glucose monitoring and dose reductions of insulin, including Humalog Mix75/25, may be
128 necessary in patients with renal dysfunction.

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

138 **INDICATIONS AND USAGE**

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

145 **CONTRAINDICATIONS**

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

148 **WARNINGS**

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

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

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

160 **PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

232 *Pregnancy — Teratogenic Effects — Pregnancy Category B* — Reproduction studies with
 233 insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and
 234 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The
 235 results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro.
 236 There are, however, no adequate and well-controlled studies with Humalog or
 237 Humalog Mix75/25 in pregnant women. Because animal reproduction studies are not always
 238 predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

251 **ADVERSE REACTIONS**

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

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

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

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

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

258 **OVERDOSAGE**

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

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%) |

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

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

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 30-60 minutes before a meal.

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

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

HOW SUPPLIED

291
 292 Humalog Mix75/25 vials are available in the following package size:
 293 100 units per mL (U-100)
 294 10 mL vials

295 NDC 0002-7511-01 (VL-7511)

296 Humalog Mix75/25 Pen, a disposable insulin delivery device, is available in the following
 297 package size:

298 5 x 3 mL disposable insulin delivery devices NDC 0002-8794-59 (HP-8794)

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 300 *Storage* — Humalog Mix75/25 should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but
 301 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated (below
 302 86°F [30°C]) vials must be used within 28 days or be discarded, even if they still contain
 303 Humalog Mix75/25. Unrefrigerated (below 86°F [30°C]) Pens must be used within 10 days or be
 304 discarded, even if they still contain Humalog Mix75/25. Protect from direct heat and light. See
 305 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. |
| 3 mL Pen | 10 days | Until expiration date | 10 days. Do not refrigerate. |

306 Literature issued XXX 2003

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

308 A3.0 NL 3710 AMP

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**INFORMATION FOR THE PATIENT
3 ML DISPOSABLE INSULIN DELIVERY DEVICE**

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**HUMALOG[®] Mix75/25[™] Pen
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[®] Mix75/25[™] (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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TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE “DISPOSABLE INSULIN DELIVERY DEVICE USER MANUAL” AND THIS “INFORMATION FOR THE PATIENT” INSERT BEFORE USING THIS PRODUCT. BEFORE EACH INJECTION, YOU SHOULD PRIME THE PEN, A NECESSARY STEP TO MAKE SURE THE PEN IS READY TO DOSE. PRIMING THE PEN IS IMPORTANT TO CONFIRM THAT INSULIN COMES OUT WHEN YOU PUSH THE INJECTION BUTTON AND TO REMOVE AIR THAT MAY COLLECT IN THE INSULIN CARTRIDGE DURING NORMAL USE. IF YOU DO NOT PRIME, YOU MAY RECEIVE A WRONG DOSE (*see also INSTRUCTIONS FOR PEN USE section*).

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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 premeal glucose levels are consistently above 130 mg/dL, bedtime glucose levels are consistently above 160 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show

48 below-targeted glucose levels, you should also let your doctor know. Proper control of your
49 diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead
50 an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin
51 injections as prescribed.

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

55 HUMALOG Mix75/25

56 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 Mix75/25 is a mixture of 75% insulin lispro protamine
60 suspension and 25% insulin lispro, (rDNA origin). It is a longer-acting insulin combined with the
61 more rapid onset of action of Humalog. The duration of activity is similar to that of
62 Humulin[®] 70/30 and may last up to 24 hours following injection. The time course of
63 Humalog Mix75/25 action, like that of other insulins, may vary in different individuals or at
64 different times in the same individual, based on dose, site of injection, blood supply,
65 temperature, and physical activity. Humalog Mix75/25 is a sterile suspension and is for
66 subcutaneous injection. It should not be used intravenously. The concentration of
67 Humalog Mix75/25 is 100 units/mL (U-100).

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

71 Identification

72 Insulin lispro injection (rDNA origin), manufactured by Eli Lilly and Company, has the
73 trademark Humalog. Humalog products are available in two formulations — Humalog and
74 Humalog Mix75/25. Your doctor has prescribed the type of insulin that he/she believes is best
75 for you.

76 **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND**
77 **DIRECTION. YOU SHOULD NOT MIX HUMALOG Mix75/25 WITH ANOTHER**
78 **INSULIN.**

79 The Humalog Mix75/25 Pen is available in boxes of 5 disposable insulin delivery devices
80 ("insulin Pens"). The Humalog Mix75/25 Pen is not designed to allow any other insulin to be
81 mixed in its cartridge of Humalog Mix75/25, or for the cartridge to be removed.

82 Always examine the appearance of Humalog Mix75/25 suspension in the insulin Pen before
83 administering a dose. Roll the Pen between the palms 10 times. Holding the Pen by one end,
84 invert it 180° slowly 10 times to allow the glass bead to travel the full length of the cartridge
85 with each inversion. Humalog Mix75/25 should look uniformly cloudy or milky after mixing. If
86 not, repeat the above steps until the contents are mixed. Pens containing Humalog Mix75/25
87 suspension should be examined frequently. Do not use if the insulin substance (the white
88 material) remains visibly separated from the liquid after mixing. Do not use a
89 Humalog Mix75/25 Pen if there are clumps in the insulin after mixing. Do not use a
90 Humalog Mix75/25 Pen if solid white particles stick to the bottom or wall of the cartridge,
91 giving a frosted appearance. Always check the appearance of the Humalog Mix75/25 suspension
92 before using. If you note anything unusual in its appearance or notice your insulin requirements
93 changing markedly, consult your doctor.

94 Storage

95 **Not in-use (unopened):** Humalog Mix75/25 Pens not in-use should be stored in a refrigerator
96 but not in the freezer. Do not use Humalog Mix75/25 Pen if it has been frozen.

97 **In-use:** Humalog Mix75/25 Pens in-use should **NOT** be refrigerated but should be kept at
98 room temperature (below 86°F [30°C]) away from direct heat and light. Humalog Mix75/25
99 Pens in-use must be discarded **after 10 days**, even if they still contain Humalog Mix75/25.

100 Do not use Humalog Mix75/25 Pens after the expiration date stamped on the label.

101 **INSTRUCTIONS FOR PEN USE**

102 **It is important to read, understand, and follow the instructions in the “Disposable Insulin**
 103 **Delivery Device User Manual” before using. Failure to follow instructions may result in a**
 104 **wrong insulin dose. The Pen must be primed before each injection to make sure the Pen is**
 105 **ready to dose. Performing the priming step is important to confirm that insulin comes out**
 106 **when you push the injection button, and to remove air that may collect in the insulin**
 107 **cartridge during normal use.**

108 **NEVER SHARE INSULIN PENS OR NEEDLES.**

109 **PREPARING THE **INSULIN** PEN FOR INJECTION**

- 110 1. Inspect the appearance of Humalog Mix75/25 suspension in the Humalog Mix75/25 Pen.
 111 It should look uniformly cloudy or milky after mixing. Once the Humalog Mix75/25 Pen
 112 is in use, inspect the insulin in the Humalog Mix75/25 Pen before each injection.
- 113 2. Follow the instructions in the “Disposable Insulin Delivery Device User Manual” for
 114 these steps:
 - 115 • Preparing the Pen
 - 116 • Attaching the Needle
 - 117 • Priming the Pen. **The Pen must be primed before each injection to make sure the**
 118 **Pen is ready to dose.** Performing the priming step is important to confirm that insulin
 119 comes out when you push the injection button, and to remove air that may collect in the
 120 insulin cartridge during normal use.
 - 121 • Setting a Dose
 - 122 • Injecting a Dose
 - 123 • Following an Injection

124 **PREPARING FOR INJECTION**

- 125 1. Wash your hands.
- 126 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
 127 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 128 3. Cleanse the skin with alcohol where the injection is to be made.
- 129 4. With one hand, stabilize the skin by spreading it or pinching up a large area.
- 130 5. Inject the dose as instructed by your doctor. Hold the needle under the skin for at least
 131 5 seconds.
- 132 6. After dispensing a dose, pull the needle out and apply gentle pressure over the injection
 133 site for several seconds. **Do not rub the area.**
- 134 7. Immediately after an injection, remove the needle from the Humalog Mix75/25 Pen.
 135 Doing so will guard against contamination, and prevent leakage of Humalog Mix75/25,
 136 reentry of air, and needle clogs. **Do not reuse needles.** Place the used needle in a
 137 puncture-resistant disposable container and properly dispose of it as directed by your
 138 Health Care Professional.

139 **DOSAGE**

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

145 **Illness**

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

150 **Pregnancy**

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

155 **Medication**

156 Insulin requirements may be increased if you are taking other drugs with hyperglycemic
 157 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 158 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 159 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and
 160 certain antidepressants. Your health care professional is aware of these and other medications
 161 that may affect your diabetes control. Therefore, always discuss any medications you are taking
 162 with your doctor.

163 **Exercise**

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

168 **Travel**

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

171 **COMMON PROBLEMS OF DIABETES**

172 **Hypoglycemia (Insulin Reaction)**

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

- 175 1. **Missing or delaying meals**
- 176 2. Taking too much insulin
- 177 3. Exercising or working more than usual
- 178 4. An infection or illness (especially with diarrhea or vomiting)
- 179 5. A change in the body's need for insulin
- 180 6. Diseases of the adrenal, pituitary or thyroid gland, or progression of kidney or liver
 181 disease
- 182 7. Interactions with other drugs that lower blood glucose, such as oral antidiabetic agents,
 183 salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants
- 184 8. Consumption of alcoholic beverages

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

- | | |
|--|-----------------------|
| 186 • sweating | • drowsiness |
| 187 • dizziness | • sleep disturbances |
| 188 • palpitation | • anxiety |
| 189 • tremor | • blurred vision |
| 190 • hunger | • slurred speech |
| 191 • restlessness | • depressed mood |
| 192 • tingling in the hands, feet, lips, or tongue | • irritability |
| 193 • lightheadedness | • abnormal behavior |
| 194 • inability to concentrate | • unsteady movement |
| 195 • headache | • personality changes |

196 Signs of severe hypoglycemia can include:

- | | |
|-----------------------|------------|
| 197 • disorientation | • seizures |
| 198 • unconsciousness | • death |

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

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

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

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

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

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

224 **Hyperglycemia and Diabetic Ketoacidosis**

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

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

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

238 **Lipodystrophy**

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

243 **Allergy**

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

248 *Systemic Allergy* — Less common, but potentially more serious, is generalized allergy to
249 insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in
250 blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life

251 threatening. If you think you are having a generalized allergic reaction, notify a doctor
252 immediately.

253 **ADDITIONAL INFORMATION**

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

255 **DIABETES FORECAST** is a national magazine designed especially for patients with
256 diabetes and their families and is available by subscription from the American Diabetes
257 Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314,
258 1-800-DIABETES (1-800-342-2383). Another publication, **DIABETES COUNTDOWN**, is
259 available from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street,
260 19th Floor, New York, New York 10005-4001, 1-800-JDF-CURE (1-800-533-2873).

261 Additional information about Humalog Mix75/25 and Humalog Mix75/25 Pen can be obtained
262 by calling 1-888-88-LILLY (1-888-885-4559) or consult the Eli Lilly and Company Internet
263 Web Site at <http://www.lilly.com/diabetes>.

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A3.0 NL 3730 AMP

Lilly

Disposable Insulin Delivery Device
User Manual

Instructions for Use

Read and follow these step by step instructions carefully. Failure to follow these instructions completely, including the priming step, may result in a wrong insulin dose. Also, read the *Information for the Patient* insert enclosed in your Pen box.

Pen Features

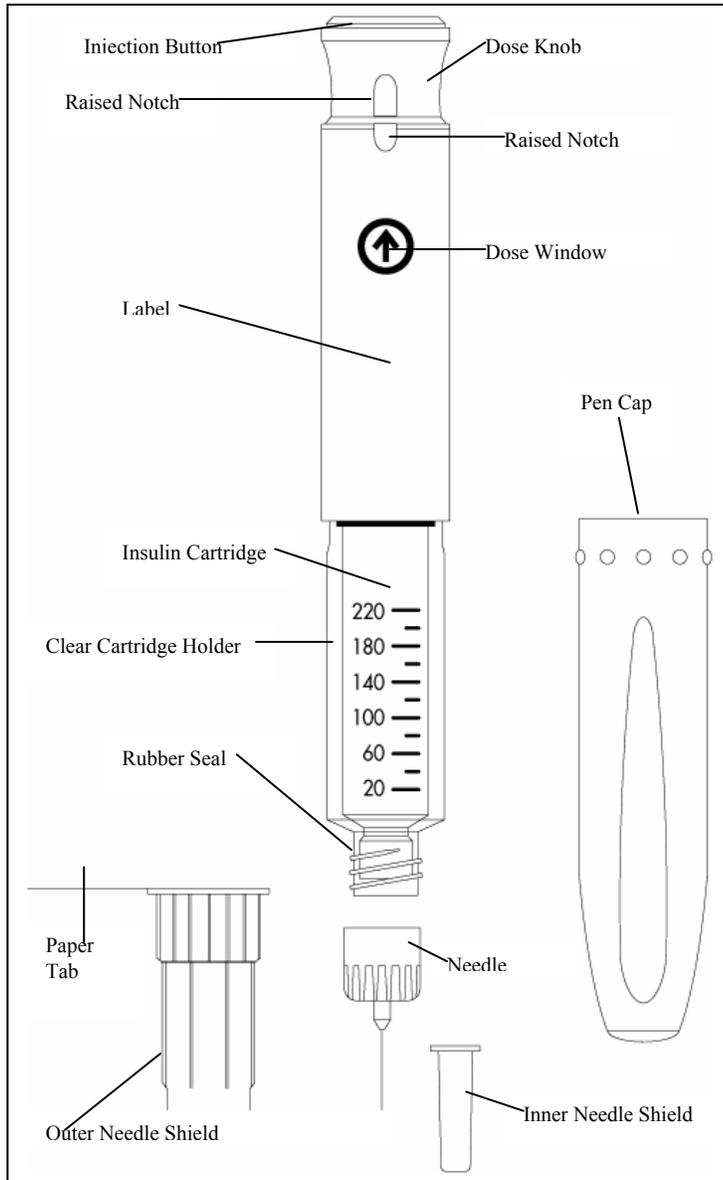
- A multiple dose, disposable insulin delivery device (“insulin Pen”) containing 3 mL (300 units) of U-100 insulin
- Delivers up to 60 units per dose
- Doses can be dialed by single units



Table of Contents

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Pen Parts



Important Notes

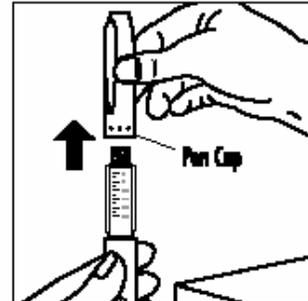
- **Please read these instructions carefully before using your Pen. Failure to follow these instructions completely, including the priming step, may result in a wrong dose.**
- Use a new needle for each injection.
- Be sure a needle is attached to the Pen before priming, setting (dialing) the dose and injecting your insulin.
- **The Pen must be primed before each injection to make sure the Pen is ready to dose.** Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use. **See Section III. *Priming the Pen*, pages 10-13.**
- **If you do not prime, you may receive a wrong dose.**
- The numbers on the clear cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your Pen.

Important Notes (Continued)

- Keep your Pen out of the reach of children.
- Pens that have not been used should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen. Refer to the *Information for the Patient* insert for complete storage instructions.
- After a Pen is used for the first time, it should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] and away from direct heat and light.
- An unrefrigerated Pen should be discarded according to the time specified in the *Information for the Patient* insert, even if it still contains insulin.
- Never use a Pen after the expiration date stamped on the label.
- Do not store your Pen with the needle attached. Doing so may allow insulin to leak from the Pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra Pen in case yours is lost or damaged.
- Dispose of empty Pens as instructed by your Health Care Professional and without the needle attached.
- This Pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- **Any changes in insulin should be made cautiously and only under medical supervision.**

I. Preparing the Pen

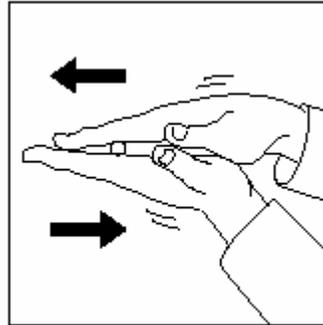
1. Before proceeding, refer to the *Information for the Patient* insert for instructions on checking the appearance of your insulin.
2. Check the label on the Pen to be sure the Pen contains the type of insulin that has been prescribed for you.
3. Always wash your hands before preparing your Pen for use.
4. Pull the Pen cap to remove.



I. Preparing the Pen (Continued)

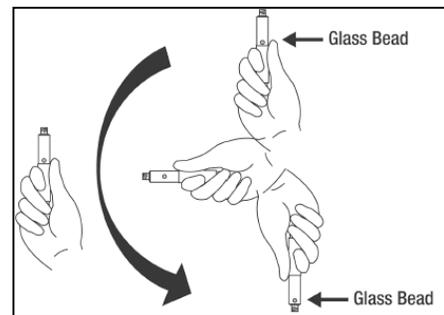
5. If your insulin is a suspension (cloudy):

- a. Roll the Pen back and forth 10 times then perform step b.

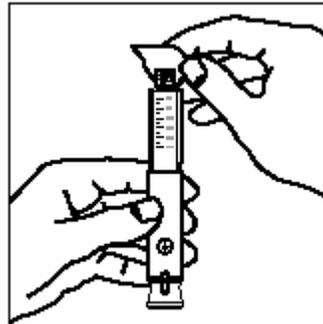


- b. Gently turn the Pen up and down 10 times until the insulin is evenly mixed.

Note: Suspension (cloudy) insulin cartridges contain a small glass bead to assist in mixing.



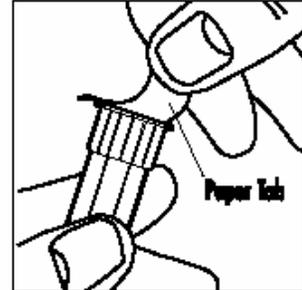
6. Use an alcohol swab to wipe the rubber seal on the end of the Pen.



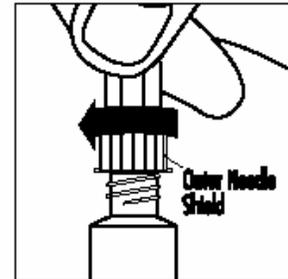
II. Attaching the Needle

This device is suitable for use with Becton Dickinson and Company's insulin pen needles.

1. Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.
2. Remove the paper tab from the outer needle shield.

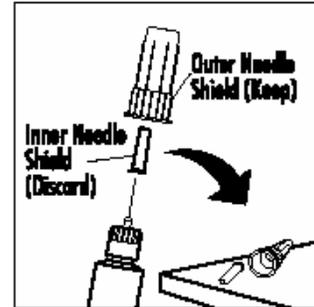


3. Attach the capped needle onto the end of the Pen by turning it clockwise until tight.



II. Attaching the Needle (Continued)

4. Hold the Pen with the needle pointing up and remove the **outer needle shield**. **Keep it to use during needle removal.**

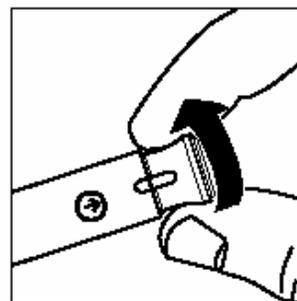


5. **Remove the inner needle shield and discard.**

III. Priming the Pen

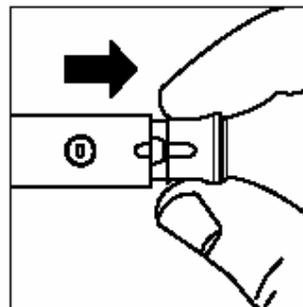
- **Always use a new needle for each injection.**
- **The Pen must be primed before each injection to make sure the Pen is ready to dose.**
Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.
- **If you do not prime, you may receive a wrong dose.**

1. You cannot prime your Pen until you can see the arrow (→) in the dose window. If a number or a blank space is in the dose window, push in the injection button completely until a diamond (◆) or arrow (→) is seen. When diamonds (◆) can be seen in the dose window, turn the dose knob clockwise until the arrow (→) is seen and the notches on the Pen and dose knob are in line.

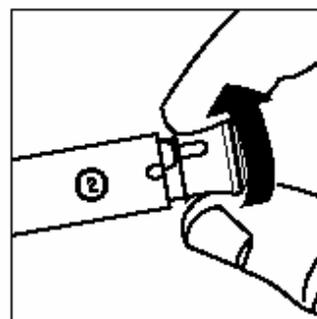


III. Priming the Pen (Continued)

2. With the arrow in the dose window, pull the dose knob out in the direction of the arrow until a “0” is seen in the dose window.

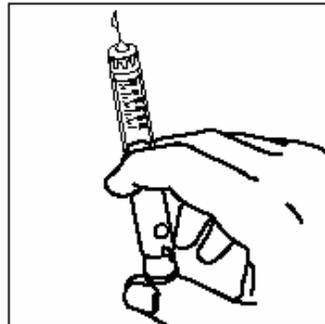


3. Turn the dose knob clockwise until the number “2” is seen in the dose window. If the number you have dialed is too high, simply turn the dose knob backward until the number 2 is seen in the dose window.



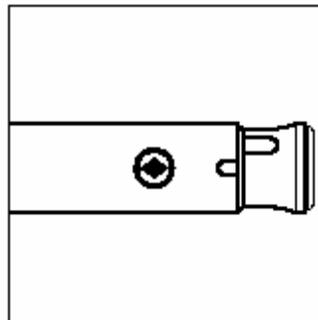
III. Priming the Pen (Continued)

4. Hold your Pen with the needle pointing up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top. Using your thumb, if possible, push in the injection button completely and maintain pressure until the insulin flow stops. You should see either a drop or a stream of insulin come out of the tip of the needle. If insulin does not come out of the tip of the needle, repeat steps 1 through 4. If after several attempts insulin does not come out of the tip of the needle, refer to the “Questions and Answers” section at the end of this manual.



III. Priming the Pen (Continued)

5. At the completion of the priming step, a diamond (◆) must be seen in the dose window.



Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the Pen, this small air bubble will not affect your insulin dose.

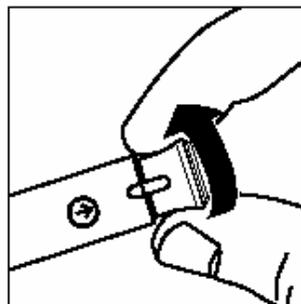
6. Now you are ready to set your dose. See next page.

IV. Setting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
- **Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in an inaccurate insulin dose.***

1. Pen has been primed and a diamond (◆) can be seen in the dose window.

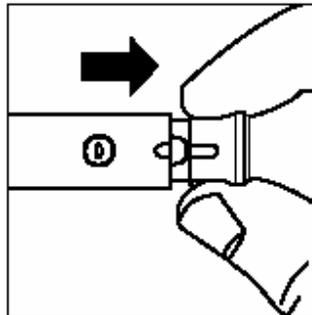
2. Turn the dose knob clockwise until the arrow (→) is seen in the dose window and the notches on the Pen and dose knob are in line.



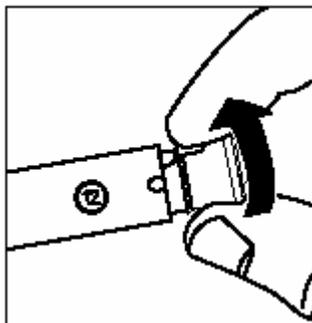
* See Page 16.

IV. Setting a Dose (Continued)

3. With the arrow (→) in the dose window, pull the dose knob out in the direction of the arrow until a “0” is seen in the dose window. A dose cannot be dialed until the dose knob is pulled out.



4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialed is too high, simply turn the dose knob backward until the correct dose is seen in the dose window.



5. If you cannot dial a full dose, see the “Questions and Answers” section at the end of this manual.

V. Injecting a Dose

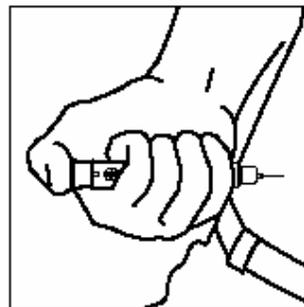
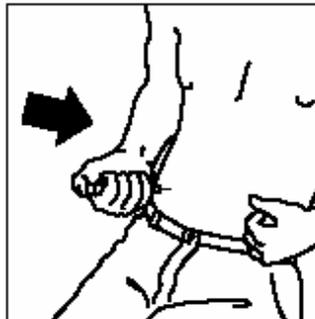
- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
- **Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in an inaccurate insulin dose.***
- **The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the “Questions and Answers” section at the end of this manual.**

* If you have set (dialed) a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the “Questions and Answers” section.

V. Injecting a Dose (Continued)

1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.

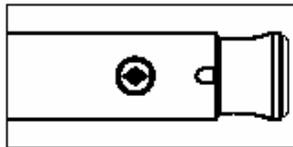
Inject the insulin by using your thumb, if possible, to completely push in the injection button. When the injection button has been completely pushed in (**a diamond (♦) or arrow (→) must be seen in the dose window to indicate that the injection button has been completely pushed in**), continue to hold it down and count **slowly** to 5. After dispensing a dose, pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.



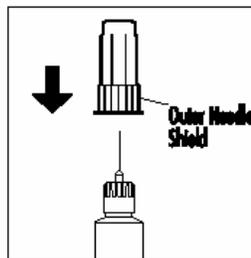
VI. Following an Injection

Do not store or dispose of the Pen with a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.

1. Check that the injection button has been completely pushed in and you can see a diamond (◆) or arrow (→) in the dose window. If a diamond (◆) or arrow (→) cannot be seen in the dose window, your full dose has not been delivered. Contact your Health Care Professional immediately for additional instructions.

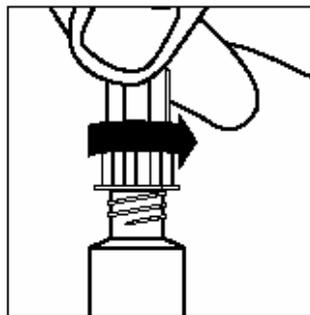


2. Carefully replace the **outer needle shield**.

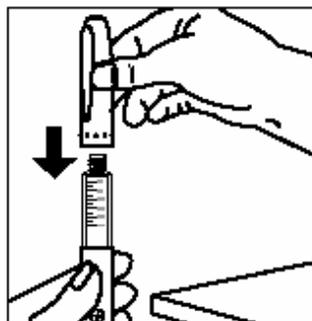


VI. Following an Injection (Continued)

3. Remove the capped needle by turning it counterclockwise and dispose of it as directed by your Health Care Professional. Place the used needle in a puncture-resistant disposable container and properly dispose of it as directed by your Health Care Professional.



4. Replace the cap on the Pen.



5. The Pen that you are using should **NOT** be refrigerated but kept at room temperature [below 86°F (30°C)] and away from direct heat and light. It should be discarded according to the time specified in the *Information for the Patient* insert, even if it still contains insulin.

Questions and Answers

| Problem | Action |
|---|---|
| Dose dialed and injection button pushed in without a needle attached. | To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window. 3) Prime the Pen. |
| Insulin does not come out of the needle. | To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window. 3) Prime the Pen. |

Questions and Answers (Continued)

| Problem | Action |
|---|---|
| Wrong dose (too high or too low) dialed. | If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose. |
| Not sure how much insulin remains in the cartridge. | Hold the Pen with the needle end pointing down. The scale (20 units between marks) on the clear cartridge holder shows an estimate of the number of units remaining. These numbers should not be used for measuring an insulin dose. |

Questions and Answers (Continued)

| Problem | Action |
|---|--|
| Full dose cannot be dialed. | <p>The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the Pen, you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the Pen you may either:</p> <ol style="list-style-type: none"> 1) Give the partial dose and then give the remaining dose using a new Pen, or 2) Give the full dose with a new Pen. |
| A small amount of insulin remains in the cartridge but a dose cannot be dialed. | The Pen design prevents the cartridge from being completely emptied. The Pen has delivered 300 units of usable insulin. |

Questions and Answers (Continued)

| Problem | Action |
|--|---|
| Cannot completely push in the injection button when priming the Pen or injecting a dose. | <ol style="list-style-type: none">1) Needle is not attached or is clogged.<ol style="list-style-type: none">a. Attach a new needle.b. Push in the injection button completely (even if a “0” is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window.c. Prime the Pen.2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in. |

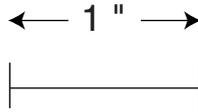
**For additional information call,
1-888-88-LILLY**

Literature issued XXX 2003

Eli Lilly and Company, Indianapolis, IN 46285, USA

A3.0 NL 3730 AMP

PRINTED IN USA



Control No.:

Exp Date:

Lilly NDC 0002-8794-01
3 mL HP-8794

Humalog® Mix75/25™ Pen

75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)

100 units per mL
disposable insulin delivery device

Rx only **U-100**

Eli Lilly and Company, Indianapolis, IN 46285, USA

NL 9230AMX



5 x 3 mL
HP8794
100 units per mL

Lilly

Humalog[®] Mix75/25[™] Pen

75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)
disposable insulin delivery device

Rx only



Exp. Date / Control No.

This device is suitable for use with Becton Dickinson and Company's insulin pen needles or their equivalent.
(needle not included)

Eli Lilly and Company
Indianapolis, IN 46285, USA
For information call 1-888-885-4559

Lilly

NL 2530 AMS

If the seal is broken before first use, contact pharmacist

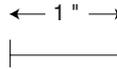
Keep in a cold place. Avoid freezing.
Shake carefully before using. See enclosed insert for proper technique.
Warning: Any change of insulin should be made cautiously and only under medical supervision.
For subcutaneous use only.
See accompanying insert for dosage.

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.

**IMPORTANT - SEE WARNINGS
ON ACCOMPANYING INSERT**



3 0002-8794-59 3



Lilly
**Humalog[®] Mix75/25[™]
Pen** 75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)
disposable insulin delivery device
U-100
5 x 3 mL
100 units per mL
HP8794

C-1004

**Humalog[®] Mix75/25[™] U-100
Pen** 5 x 3 mL 100 units per mL HP8794
75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)
disposable insulin delivery device

NL 2530 AMS
NL 2530 AMS