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HUMALOG[®] Mix75/25[™]

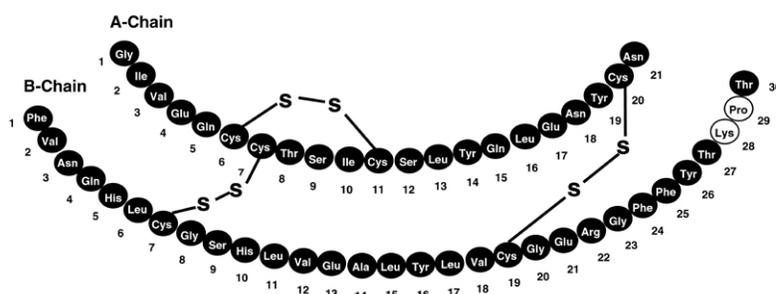
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

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DESCRIPTION

9 Humalog[®] Mix75/25[™] [75% insulin lispro protamine suspension and 25% insulin lispro
10 injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-
11 lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-
12 lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created
13 when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is
14 synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has
15 been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL
16 component) is a suspension of crystals produced from combining insulin lispro and protamine
17 sulfate under appropriate conditions for crystal formation.

18 Insulin lispro has the following primary structure:



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

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

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

28

CLINICAL PHARMACOLOGY

29

Antidiabetic Activity

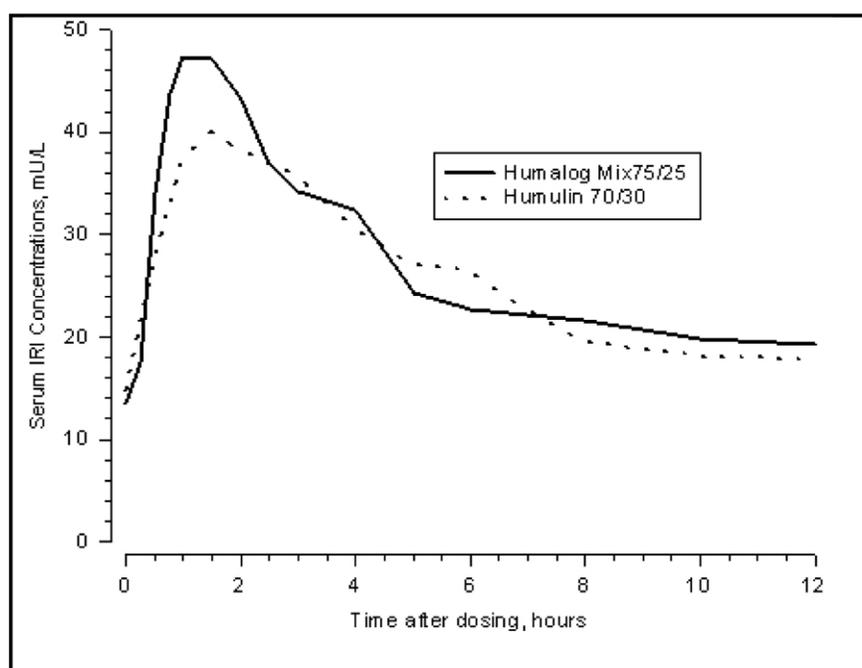
30 The primary activity of insulin, including Humalog Mix75/25, is the regulation of glucose
31 metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many
32 tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport
33 of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism.
34 In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits
35 gluconeogenesis, and promotes the conversion of excess glucose into fat.

36 Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be
37 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same

38 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 39 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared with
 40 Humulin[®] 70/30 on a unit for unit basis.

41 **Pharmacokinetics**

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



49 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
 50 **Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.**

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 healthy nondiabetic subjects given subcutaneous doses
 54 (0.3 U/kg) of Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes
 55 (median, 60 minutes) after dosing (*see* Figure 1). Identical results were found in patients with
 56 type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with Humalog
 57 Mix75/25 (*see* Figure 1).

58 Figure 1 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 to 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.

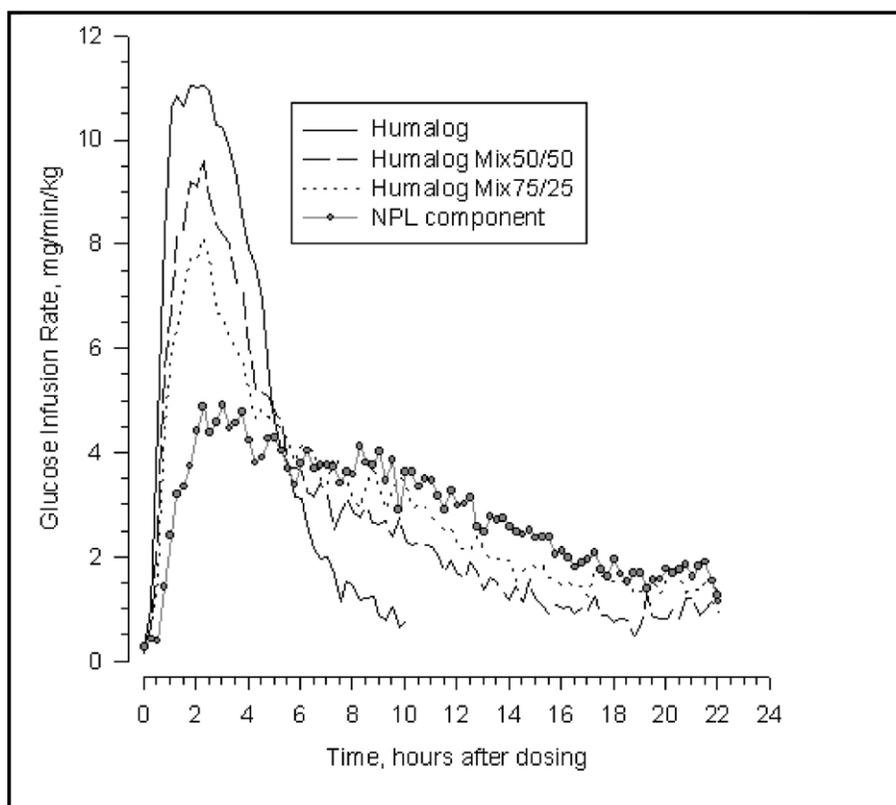
67 *Elimination* — Humalog Mix75/25 has two absorption phases, a rapid and a prolonged phase,
68 representative of the insulin lispro and insulin lispro protamine suspension components of the
69 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
70 be calculated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

72 **Pharmacodynamics**

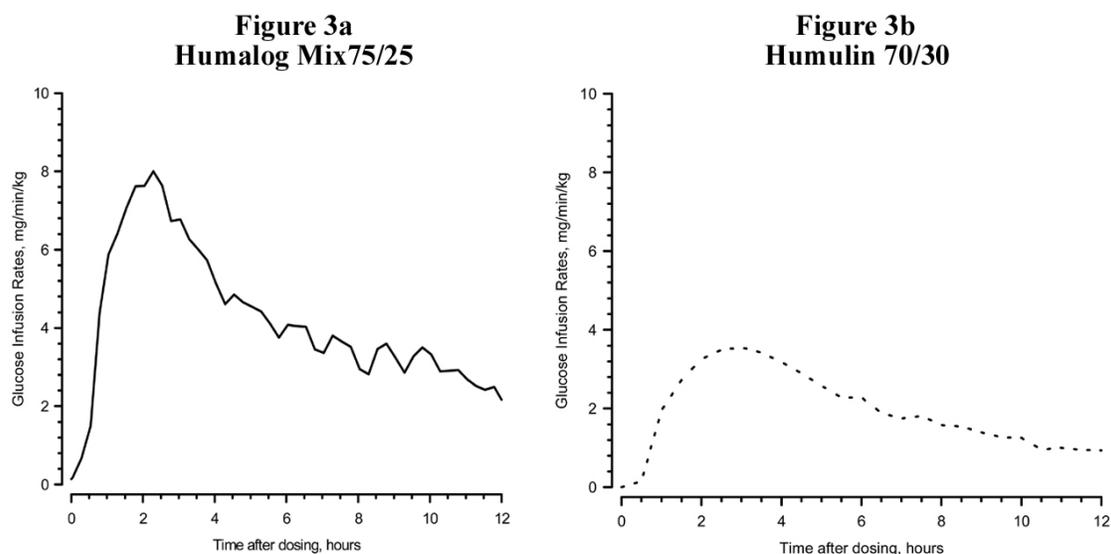
73 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
74 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
75 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
76 Humalog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

83 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-
84 lowering activity of Humalog, Humalog[®] Mix50/50[™], Humalog Mix75/25, and insulin lispro
85 protamine suspension (NPL component) were compared (*see* Figure 2). Graphs of mean glucose
86 infusion rate versus time showed a distinct insulin activity profile for each formulation. The
87 rapid onset of glucose-lowering activity characteristic of Humalog was maintained in Humalog
88 Mix75/25.

89 In separate glucose clamp studies performed in nondiabetic subjects, pharmacodynamics of
90 Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 3. Humalog
91 Mix75/25 has a duration of activity similar to that of Humulin 70/30.



92 **Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog**
 93 **Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic**
 94 **Subjects.**
 95



96 **Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in**
 97 **Nondiabetic Subjects.**

98 Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in
 99 healthy nondiabetic subjects.

100 Figure 2 shows the time activity profiles of Humalog, Humalog Mix50/50, Humalog
 101 Mix75/25, and insulin lispro protamine suspension (NPL component).

102 Figure 3 is a comparison of the time activity profiles of Humalog Mix75/25 (*see* Figure 3a) and
 103 of Humulin 70/30 (*see* Figure 3b) from two different studies.

104 Special Populations

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

111 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
 112 Humalog Mix75/25 has not been studied.

113 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
 114 Humalog Mix75/25 has not been studied.

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

120 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
 121 pharmacodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with
 122 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
 123 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the

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

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

136 INDICATIONS AND USAGE

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

143 CONTRAINDICATIONS

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

146 WARNINGS

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

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

154 **Any change of insulin should be made cautiously and only under medical supervision.**
155 **Changes in insulin strength, manufacturer, type (e.g., Regular, NPH, analog), species, or**
156 **method of manufacture may result in the need for a change in dosage.**

157 PRECAUTIONS

158 General

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

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

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

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

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

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

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

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

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

195 **Information for Patients**

196 Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and
197 alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They
198 should also be informed about the importance of proper insulin storage, injection technique,
199 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
200 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
201 hyperglycemia, and periodic assessment for diabetes complications.

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

204 Refer patients to the Patient Information leaflet for information on normal appearance, timing
205 of dosing (within 15 minutes before a meal), storing, and common adverse effects.

206 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
207 the Patient Information leaflet that accompanies the drug product and the User Manual that
208 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
209 should be instructed on how to properly use the delivery device, prime the Pen to a stream of
210 insulin, and properly dispose of needles. Patients should be advised not to share their Pens with
211 others.

212 **Laboratory Tests**

213 As with all insulins, the therapeutic response to Humalog Mix75/25 should be monitored by
214 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
215 monitoring of long-term glycemic control.

216 **Drug Interactions**

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

220 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
 221 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
 222 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
 223 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
 224 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
 225 symptoms of hypoglycemia in some patients.

226 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

227 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
 228 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
 229 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
 230 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
 231 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

232 **Pregnancy**

233 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies with insulin lispro have
 234 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
 235 respectively, the average human dose (40 units/day) based on body surface area. The results have
 236 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
 237 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25, or
 238 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
 239 predictive of human response, this drug should be used during pregnancy only if clearly needed.

240 **Nursing Mothers**

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

245 **Pediatric Use**

246 Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not
 247 been established.

248 **Geriatric Use**

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

254 **ADVERSE REACTIONS**

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

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

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

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

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

261 **OVERDOSAGE**

262 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
 263 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
 264 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
 265 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous

266 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
267 may be necessary because hypoglycemia may recur after apparent clinical recovery.

268 **DOSAGE AND ADMINISTRATION**

269 **Table 1*: Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-
270 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%)

272 * The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the
273 total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp
274 studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.
275

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

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

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

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

HOW SUPPLIED

295
 296 Humalog Mix75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection,
 297 (rDNA origin)] is available in the following package sizes: each presentation containing 100
 298 units insulin lispro per mL (U-100).
 299

10 mL vials	NDC 0002-7511-01 (VL-7511)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8794-59 (HP-8794)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8797-59 (HP-8797)

300
 301 *Storage* — Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 302 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated [below
 303 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 304 Humalog Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used
 305 within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect from direct
 306 heat and light. See table below:
 307

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

308
 309 Literature revised Month dd, yyyy

310 **KwikPens manufactured by**
 311 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
 312 **Pens manufactured by**
 313 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 314 **Lilly France, F-67640 Fegersheim, France**
 315 **Vials manufactured by**
 316 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 317 **Lilly France, F-67640 Fegersheim, France**
 318
 319 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
 320

321 **www.humalog.com**

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 323
 324

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Patient Information

Humalog[®] (HU-ma-log) Mix75/25[™] 75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. Your insulin dose and the time you take your dose can change with different types of insulin.

Make sure you have the right type and strength of insulin prescribed for you.

Read the Patient Information that comes with Humalog Mix75/25 before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have questions about managing your diabetes.

What is Humalog Mix75/25?

Humalog Mix75/25 is a mixture of fast-acting and longer-acting man-made insulins. Humalog Mix75/25 is used to control high blood sugar (glucose) in people with diabetes.

Humalog Mix75/25 comes in:

- 10 mL vials (bottles) for use with a syringe
- Prefilled pens

Who should not take Humalog Mix75/25?

Do not take Humalog Mix75/25 if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog Mix75/25.
- you are allergic to anything in Humalog Mix75/25. See the end of this leaflet for a complete list of ingredients in Humalog Mix75/25.

Tell your healthcare provider:

- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog Mix75/25.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog Mix75/25 has not been studied in pregnant or nursing women.
- **about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.** Many medicines can affect your blood

35 sugar levels and insulin needs. Your Humalog Mix75/25 dose may need to change if you
36 take other medicines.

37 Know the medicines you take. Keep a list of your medicines with you to show to all of your
38 healthcare providers.

39

40 **How should I use Humalog Mix75/25?**

41 Talk to your healthcare provider if you have any questions. Your healthcare provider will tell
42 you the right syringes to use with Humalog Mix75/25 vials. Your healthcare provider should
43 show you how to inject Humalog Mix75/25 before you start using it. **Read the User Manual**
44 **that comes with your Humalog Mix75/25 prefilled pen.**

- 45 • **Use Humalog Mix75/25 exactly as prescribed by your healthcare provider.**
- 46 • **Humalog Mix75/25 starts working faster than other insulins that contain regular**
47 **human insulin.** Inject Humalog Mix75/25 fifteen minutes or less before a meal. If you do
48 not plan to eat within 15 minutes, delay the injection until the correct time (15 minutes
49 before eating).
- 50 • **Check your blood sugar levels as told by your healthcare provider.**
- 51 • **Mix Humalog Mix75/25 well before each use.** For Humalog Mix75/25 in a vial, carefully
52 shake or rotate the vial until completely mixed. For prefilled pens, carefully follow the
53 User Manual for instructions on mixing the pen. Humalog Mix75/25 should be cloudy or
54 milky after mixing well.
- 55 • Look at your Humalog Mix75/25 before each injection. If it is not evenly mixed or has
56 solid particles or clumps in it, do not use. Return it to your pharmacy for new Humalog
57 Mix75/25.
- 58 • **Inject your dose of Humalog Mix75/25 under the skin of your stomach area, upper**
59 **arm, upper leg, or buttocks. Never inject Humalog Mix75/25 into a muscle or vein.**
- 60 • **Change (rotate) your injection site with each dose.**
- 61 • **Your insulin needs may change because of:**
 - 62 • illness
 - 63 • stress
 - 64 • other medicines you take
 - 65 • changes in eating
 - 66 • physical activity changes
- 67 Follow your healthcare provider's instructions to make changes in your insulin dose.
- 68 • **Never mix Humalog Mix75/25 in the same syringe with other insulin products.**
- 69 • **Never use Humalog Mix75/25 in an insulin pump.**
- 70 • **Always carry a quick source of sugar to treat low blood sugar, such as glucose tablets,**
71 **hard candy, or juice.**

72 **What are the possible side effects of Humalog Mix75/25?**

73 **Low Blood Sugar (Hypoglycemia).** Symptoms of low blood sugar include:

- 74 • hunger
- 75 • dizziness
- 76 • feeling shaky or shakiness
- 77 • lightheadedness
- 78 • sweating
- 79 • irritability
- 80 • headache
- 81 • fast heartbeat
- 82 • confusion

83 Low blood sugar symptoms can happen suddenly. Symptoms of low blood sugar may be
84 different for each person and may change from time to time. Severe low blood sugar can cause
85 seizures and death. Low blood sugar may affect your ability to drive a car or use mechanical
86 equipment, risking injury to yourself or others. Know your symptoms of low blood sugar. Low
87 blood sugar can be treated by drinking juice or regular soda or eating glucose tablets, sugar, or
88 hard candy. Follow your healthcare provider's instructions for treating low blood sugar. Talk to
89 your healthcare provider if low blood sugar is a problem for you.

- 91 • **Serious allergic reactions** (whole body allergic reaction). Severe, life-threatening allergic
92 reactions can happen with insulin. Get medical help right away if you develop a rash over
93 your whole body, have trouble breathing, wheezing, a fast heartbeat, or sweating.
- 94 • **Reactions at the injection site** (local allergic reaction). You may get redness, swelling,
95 and itching at the injection site. If you keep having injection site reactions or they are
96 serious, you need to call your healthcare provider. Do not inject insulin into a skin area that
97 is red, swollen, or itchy.
- 98 • **Skin thickens or pits at the injection site (lipodystrophy).** This can happen if you don't
99 change (rotate) your injection sites enough.

100 These are not all the side effects from Humalog Mix75/25. Ask your healthcare provider or
101 pharmacist for more information.

102

103 **How should I store Humalog Mix75/25?**

- 104 • **Store all unopened (unused) Humalog Mix75/25 in the original carton in a**
105 **refrigerator at 36°F to 46°F (2°C to 8°C).** Do not freeze.
- 106 • Do not use Humalog Mix75/25 that has been frozen.
- 107 • Do not use after the expiration date printed on the carton and label.
- 108 • Protect Humalog Mix75/25 from extreme heat, cold or light.

109 **After starting use (open):**

- 110 • **Vials:** Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28
- 111 days. Keep open vials away from direct heat or light. Throw away an opened vial 28 days
- 112 after first use, even if there is insulin left in the vial.
- 113 • **Prefilled Pens:** Do not store a prefilled pen that you are using in the refrigerator. Keep at
- 114 room temperature below 86°F (30°C) for up to 10 days. Throw away a prefilled pen 10
- 115 days after first use, even if there is insulin left in the pen.

116 **General information about Humalog Mix75/25**

117 Use Humalog Mix75/25 only to treat your diabetes. Do not share it with anyone else, even if

118 they also have diabetes. It may harm them.

119

120 This leaflet summarized the most important information about Humalog Mix75/25. If you would

121 like more information about Humalog Mix75/25 or diabetes, talk with your healthcare provider.

122 You can ask your healthcare provider or pharmacist for information about Humalog Mix75/25

123 that is written for health professionals.

124

125 For questions you may call 1-800-LillyRx (1-800-545-5979) or visit www.humalog.com.

126

127 **What are the ingredients in Humalog Mix75/25?**

128 **Active ingredients:** insulin lispro protamine suspension and insulin lispro.

129

130 **Inactive ingredients:** protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, zinc

131 oxide (zinc ion), phenol and water for injection.

132 Patient Information issued/revised Month DD, YYYY

133 **KwikPens manufactured by**

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

135 **Pens manufactured by**

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

137 **Lilly France, F-67640 Fegersheim, France**

138 **Vials manufactured by**

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

140 **Lilly France, F-67640 Fegersheim, France**

141

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

143 **www.humalog.com**

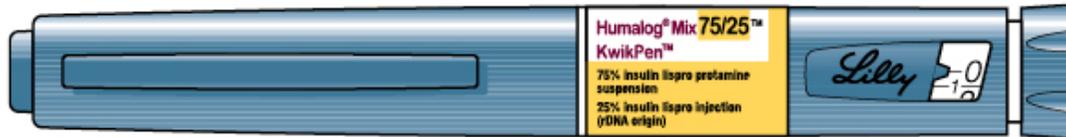
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Instructions for Use
HUMALOG® Mix75/25™ KwikPen™
75% insulin lispro protamine suspension and
25% insulin lispro injection (rDNA origin)

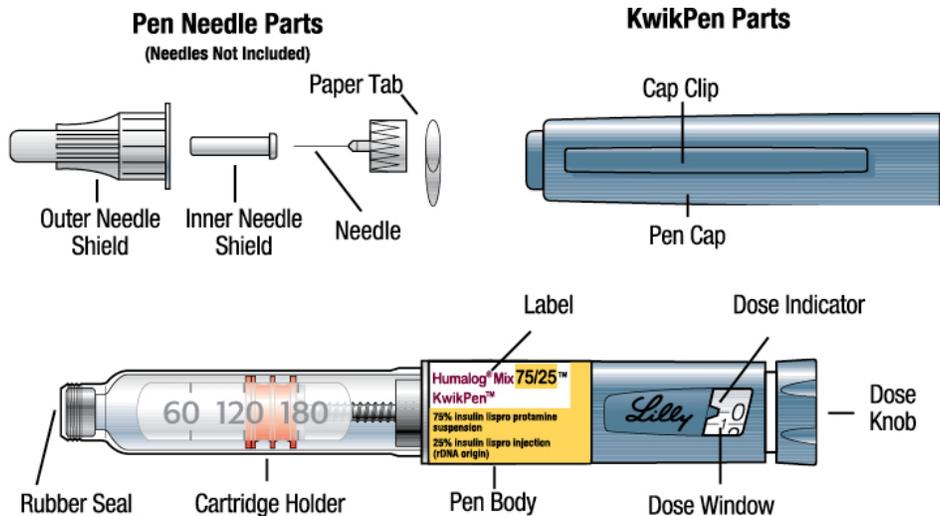


Read the Instructions for Use before you start taking HUMALOG Mix75/25 and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

HUMALOG® Mix75/25™ KwikPen™ (“Pen”) is a disposable pen containing 3 mL (300 units) of U-100 HUMALOG® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)] insulin. You can inject from 1 to 60 units in a single injection.

Do not share your HUMALOG Mix75/25 KwikPen or needles with anyone else. You may give an infection to them or get an infection from them.

This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

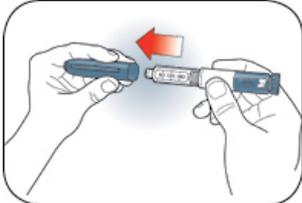
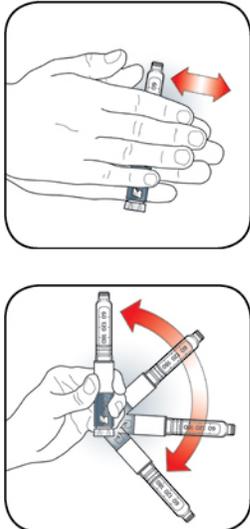


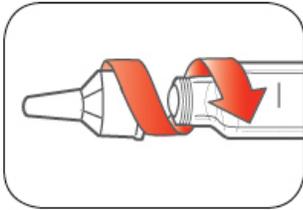
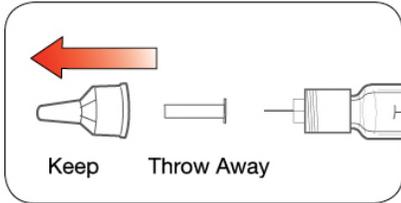
Supplies you will need to give your HUMALOG Mix75/25 injection:

- HUMALOG Mix75/25 KwikPen
- HUMALOG Mix75/25 KwikPen compatible needle (Becton, Dickinson and Company Pen Needles recommended)
- Alcohol swab

Preparing HUMALOG Mix75/25 KwikPen:

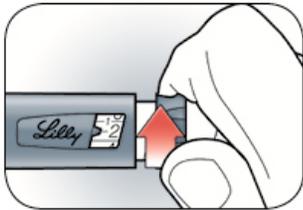
- Wash your hands with soap and water.
- Check the HUMALOG Mix75/25 KwikPen Label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use HUMALOG Mix75/25 past the expiration date printed on the Label.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles.

<p>Step 1:</p> <p>Pull the Pen Cap straight off.</p> <p>Wipe the Rubber Seal with an alcohol swab.</p> <ul style="list-style-type: none">• Do not twist the cap.• Do not remove the KwikPen Label.	
<p>Step 2:</p> <p>Gently roll the Pen ten times.</p> <p>Invert the Pen ten times.</p> <p>HUMALOG Mix75/25 should look white and cloudy after mixing. Do not use if it looks clear or contains any lumps or particles.</p>	

<p>Step 3: Pull off the Paper Tab from Outer Needle Shield.</p>	
<p>Step 4: Push the capped Needle straight onto the Pen and turn the Needle forward until it is tight.</p>	
<p>Step 5: Pull off the Outer Needle Shield. Do not throw it away. Pull off the Inner Needle Shield and throw it away.</p>	

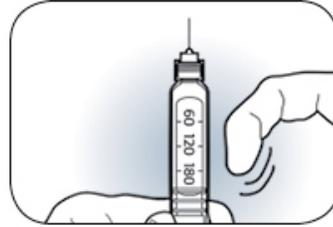
Priming your HUMALOG Mix75/25 KwikPen:

Prime before each injection. Priming ensures the Pen is ready to dose and removes air that may collect in the cartridge during normal use. If you **do not** prime before each injection, you may get too much or too little insulin.

<p>Step 6: Turn the Dose Knob to select 2 units.</p>	
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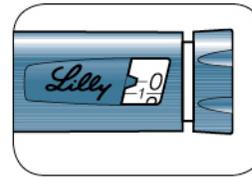
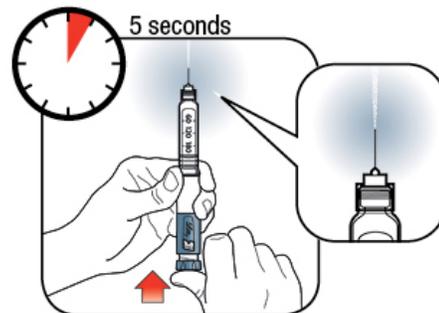
Step 7:

Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.

**Step 8:**

Hold your Pen with Needle pointing up. Push the Dose Knob in until it stops, and "0" is seen in the Dose Window. Hold the Dose Knob in and **count to 5 slowly**.

- A stream of insulin should be seen from the needle.
 - If you **do not** see a stream of insulin, repeat steps 6 to 8, no more than 4 times.
 - If you **still do not** see a stream of insulin, change the needle and repeat steps 6 to 8.

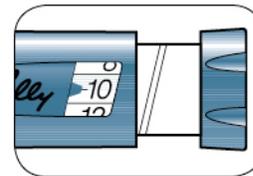
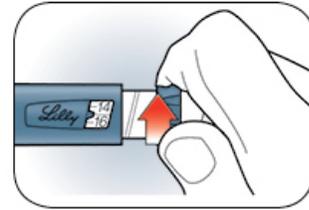


Selecting your dose:

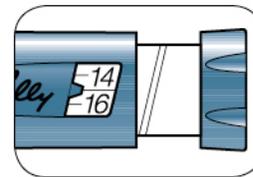
Step 9:

Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.

- The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator.
- The **even** numbers are printed on the dial. The **odd** numbers, after the number 1, are shown as full lines.



(10 units shown)

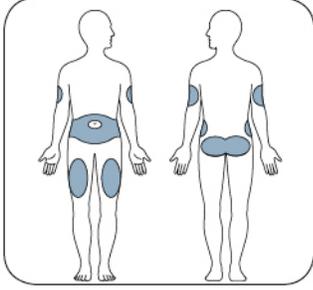
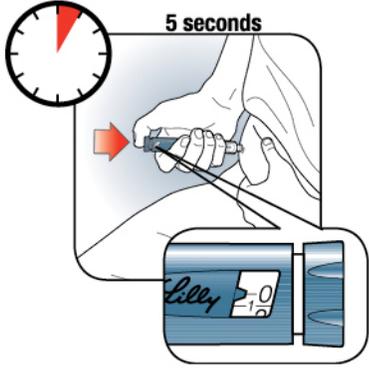


(15 units shown)

- The HUMALOG Mix75/25 KwikPen will not let you dial more than the number of units left in the Pen.
- If your dose is more than the number of units left in the Pen, you may either:
 - inject the amount left in your Pen and then use a new Pen to give the rest of your dose, **or**
 - get a new Pen and inject the full dose.
- The Pen is designed to deliver a total of 300 units of insulin. The cartridge contains an additional small amount of insulin that can't be delivered.

Giving your HUMALOG Mix75/25 injection:

- Inject your HUMALOG Mix75/25 as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting HUMALOG Mix75/25.

<p>Step 10:</p> <p>Choose your injection site.</p> <p>HUMALOG Mix75/25 is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.</p> <p>Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.</p>	
<p>Step 11:</p> <p>Insert the Needle into your skin.</p>	
<p>Step 12:</p> <p>Put your thumb on the Dose Knob and push the Dose Knob in until it stops. Hold the Dose Knob in and slowly count to 5.</p>	

Step 13:

Pull the Needle out of your skin.

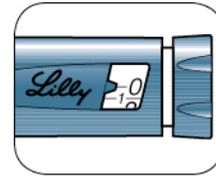
You should see "0" in the Dose Window.
If you do not see "0" in the Dose Window,
you did not receive your full dose.

If you see blood after you take the
Needle out of your skin, press the
injection site lightly with a piece of gauze
or an alcohol swab. **Do not** rub the area.

A drop of insulin at the needle tip is
normal. It will not affect your dose.

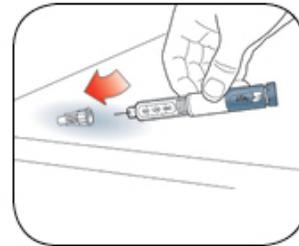
**If you do not think you received your
full dose, do not take another dose.**

Call Lilly or your healthcare provider for
assistance.



Step 14:

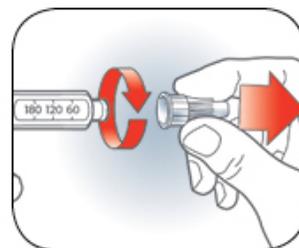
Carefully replace the Outer Needle Shield.



Step 15:

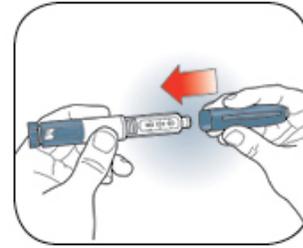
Unscrew the capped Needle and throw it
away.

Do not store the Pen with the Needle
attached to prevent leaking, blocking of
the Needle, and air from entering the
Pen.



Step 16:

Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.

**After your injection:**

- Put your used needles and pens in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>

How should I store my HUMALOG Mix75/25 KwikPen?

- Store unused HUMALOG Mix75/25 Pens in the refrigerator at 36°F to 46°F (2°C to 8°C). The Pen you are currently using can be stored out of the refrigerator below 86°F (30°C).
- **Do not** freeze HUMALOG Mix75/25. **Do not** use HUMALOG Mix75/25 if it has been frozen.
- Unused HUMALOG Mix75/25 Pens may be used until the expiration date printed on the Label, if kept in the refrigerator.
- The HUMALOG Mix75/25 Pen you are using should be thrown away after 10 days, even if it still has insulin left in it.
- Keep HUMALOG Mix75/25 away from heat and out of the light.

General information about the safe and effective use of HUMALOG Mix75/25 KwikPen

- **Keep HUMALOG Mix75/25 KwikPen and needles out of the reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.
- If you can not remove the Pen Cap, gently twist the Pen Cap back and forth, and then pull the Pen Cap straight off.
- If it is hard to push the Dose Knob or the Pen is not working the right way:
 - Your Needle may be blocked. Put on a new Needle and prime the Pen.
 - You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new one.
 - It may help to push the Dose Knob more slowly during your injection.
- Use the space below to keep track of how long you should use each HUMALOG Mix75/25 KwikPen.
 - Write down the date you start using your HUMALOG Mix75/25 KwikPen. Count forward 10 days.
 - Write down the date you should throw it away.

Example:

Pen 1 - First used on _____ + 10 days = Throw out on _____
Date Date

Pen 1 - First used on _____ Throw out on _____
Date Date

Pen 2 - First used on _____ Throw out on _____
Date Date

Pen 3 - First used on _____ Throw out on _____
Date Date

Pen 4 - First used on _____ Throw out on _____
Date Date

Pen 5 - First used on _____ Throw out on _____
Date Date

If you have any questions or problems with your HUMALOG Mix75/25 KwikPen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMALOG Mix75/25 KwikPen and insulin, go to www.humalog.com.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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Marketed by: Lilly USA, LLC

Indianapolis, IN 46285, USA

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Humalog Mix75/25 KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2000.

Revised: Month Day, Year