

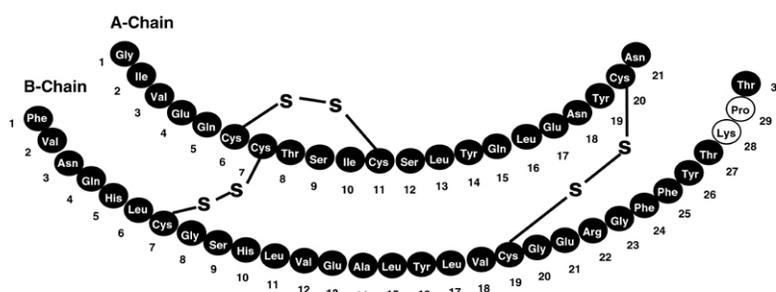
A1.0 PA 9352 FSAMP
 A1.0 NL 5741 AMP
 A1.0 NL 5751 AMP
 A1.0 NL 3693 AMP
 A1.0 NL 6832 AMP
 A1.0 PA 9164 FSAMP

HUMALOG[®]
INSULIN LISPRO INJECTION, USP
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

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

Humalog has the following primary structure:



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

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

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

CLINICAL PHARMACOLOGY

Antidiabetic Activity

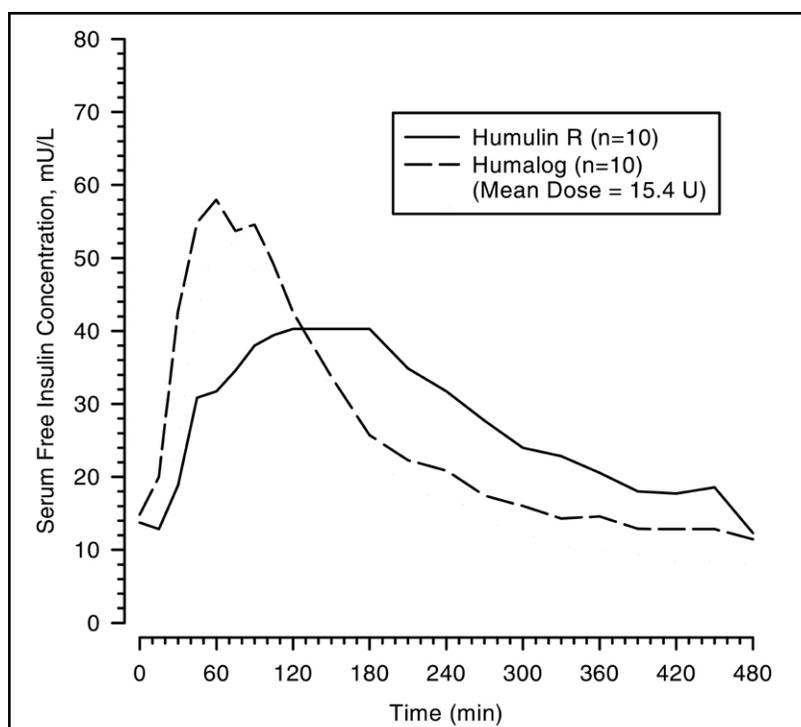
The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids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

38 Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of
39 Humalog has the same glucose-lowering effect as one unit of Regular human insulin, but its
40 effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and
41 Regular human insulin is comparable when administered to nondiabetic subjects by the
42 intravenous route.

43 **Pharmacokinetics**

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

61
62 **Figure 1: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular**
63 **Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in**
64 **10 Patients with Type 1 Diabetes. ***



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

Distribution — The volume of distribution following injection of Humalog is identical to that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

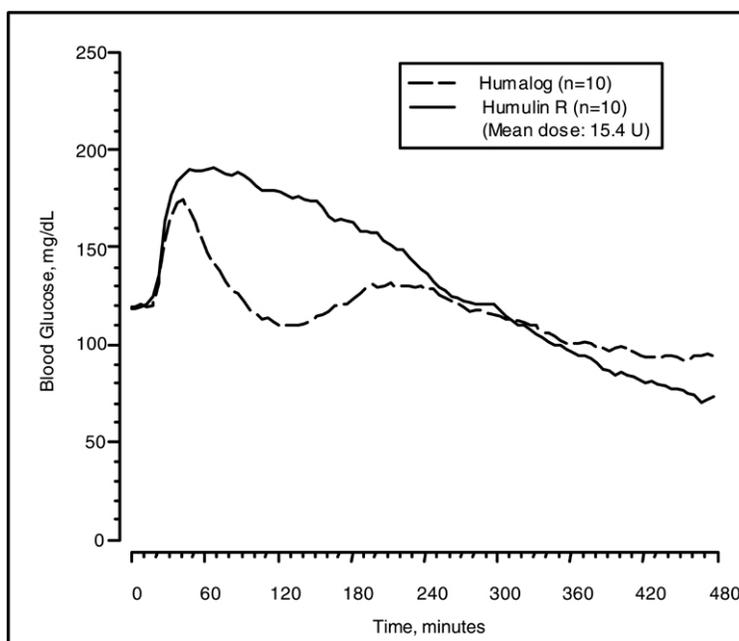
Metabolism — Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of Humalog is identical to that of Regular human insulin.

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

Pharmacodynamics

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

Figure 2: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes.*



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

Special Populations

Age and Gender — Information on the effect of age and gender on the pharmacokinetics of Humalog is unavailable. However, in large clinical trials, sub-group analysis based on age and gender did not indicate any difference in postprandial glucose parameters between Humalog and Regular human insulin.

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

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

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

Renal Impairment — Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and Regular human insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose reductions of insulin, including Humalog, may be necessary in patients with renal dysfunction.

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

CLINICAL STUDIES

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

Table 1: Comparison of Means of Glycemic Parameters at the End of Combined Treatment Periods. All Randomized Patients in Cross-Over Studies (3 Months for Each Treatment)

Type 1, N=1008		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^{a*}
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA _{1c} (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^a
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA _{1c} (%)	8.2 ± 1.3	8.2 ± 1.4

^a Mean ± Standard Deviation.

* REGULAR insulin human injection, USP (rDNA origin).

In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA_{1c} did not differ between patients treated with Regular human insulin and those treated with Humalog.

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

Humalog in Combination with Sulfonylurea Agents — In a two-month study in patients with fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were randomized to one of three treatment regimens; Humulin[®] NPH at bedtime plus SU, Humalog three times a day before meals plus SU, or Humalog three times a day before meals and Humulin NPH at bedtime. The combination of Humalog and SU resulted in an improvement in HbA_{1c} accompanied by a weight gain (*see* Table 2).

Table 2: Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone

	Humulin N h.s. + SU ^a	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA _{1c} (%) at baseline	9.9	10.0	10.0
HbA _{1c} (%) at 2-months	8.7	8.4	8.5

HbA _{1c} (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia* (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

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

* blood glucose ≤36 mg/dL or needing assistance from third party.

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

190 **External Insulin Pumps: When used in an external insulin pump, Humalog should not be**
191 **diluted or mixed with any other insulin. Patients should carefully read and follow the**
192 **external insulin pump manufacturer’s instructions and the “INFORMATION FOR THE**
193 **PATIENT” insert before using Humalog.**

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

200 PRECAUTIONS

201 General

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

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

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

215 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
216 with the administration of Humalog. Rapid changes in serum glucose concentrations may induce
217 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early
218 warning symptoms of hypoglycemia may be different or less pronounced under certain
219 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
220 beta-blockers, or intensified diabetes control.

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

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

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

230 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
231 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
232 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized

233 allergy, including anaphylactic reaction, may be life threatening. In controlled clinical trials,
 234 pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and
 235 30 patients receiving Humalog (N=2944) (p=0.053). Localized reactions and generalized
 236 myalgias have been reported with the use of cresol as an injectable excipient.

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

241 **Usage in External Insulin Pumps** — **The infusion set (reservoir syringe, tubing, and**
 242 **catheter), Disetronic® D-TRON®^{2,3} or D-TRON®^{2,3}plus cartridge adapter, and Humalog**
 243 **in the external insulin pump reservoir should be replaced and a new infusion site selected**
 244 **every 48 hours or less. Humalog in the external insulin pump should not be exposed to**
 245 **temperatures above 37°C (98.6°F).**

246 In the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump, Humalog 3 mL cartridges may be used for up
 247 to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and
 248 a new infusion site should be selected every 48 hours or less.

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

253 **Information for Patients**

254 Patients should be informed of the potential risks and advantages of Humalog and alternative
 255 therapies. Patients should also be informed about the importance of proper insulin storage,
 256 injection technique, timing of dosage, adherence to meal planning, regular physical activity,
 257 regular blood glucose monitoring, periodic hemoglobin A_{1c} testing, recognition and management
 258 of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

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

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

264 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
 265 the “INFORMATION FOR THE PATIENT” insert that accompanies the drug product and the
 266 User Manual that accompanies the delivery device and re-read them each time the prescription is
 267 renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen,
 268 and properly dispose of needles. Patients should be advised not to share their Pens with others.

269 *For Patients Using External Insulin Pumps:* Patients using an external infusion pump should
 270 be trained in intensive insulin therapy and in the function of their external insulin pump and
 271 pump accessories. Humalog may be used with the MiniMed®¹ Models 506, 507, and 508
 272 insulin pumps using MiniMed®¹ Polyfin®¹ infusion sets. Humalog may also be used in
 273 Disetronic®² H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and
 274 the Disetronic D-TRON®^{2,3} and D-TRON®^{2,3}plus insulin pumps (with Humalog 3 mL
 275 cartridges) using Disetronic Rapid®² infusion sets.

276 **The infusion set (reservoir syringe, tubing, catheter), D-TRON®^{2,3} or D-TRON®^{2,3}plus**
 277 **cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced,**
 278 **and a new infusion site selected every 48 hours or less. Humalog in the external pump**

279 **should not be exposed to temperatures above 37°C (98.6°F).** A Humalog 3 mL cartridge used
280 in the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump should be discarded after 7 days, even if it still
281 contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported
282 to medical personnel, and a new site selected.

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

285 **Laboratory Tests**

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

289 **Drug Interactions**

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

294 Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity,
295 such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine
296 oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking
297 agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.
298 Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

299 **Mixing of Insulins** — Care should be taken when mixing all insulins as a change in peak
300 action may occur. The American Diabetes Association warns in its Position Statement on Insulin
301 Administration, “On mixing, physiochemical changes in the mixture may occur (either
302 immediately or over time). As a result, the physiological response to the insulin mixture may
303 differ from that of the injection of the insulins separately.” Mixing Humalog with Humulin N or
304 Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given
305 alone or mixed with Humulin N, Humalog results in a more rapid absorption and
306 glucose-lowering effect compared with Regular human insulin.

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

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

313 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
314 cartridge, for the Humalog in the cartridge to be diluted or for the cartridge to be refilled with
315 insulin. Humalog should not be diluted or mixed with any other insulin when used in an external
316 insulin pump.

317 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

323 **Pregnancy**

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

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

339 **Nursing Mothers**

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

344 **Pediatric Use**

345 In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years,
346 comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group:
347 Regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%,
348 and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of adolescents
349 (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA_{1c} was achieved
350 regardless of treatment group: Regular human insulin 30 to 45 minutes before meals 8.7% and
351 Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all
352 three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in
353 dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the
354 Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND ADMINISTRATION).

355 **Geriatric Use**

356 Of the total number of subjects (n=2834) in eight clinical studies of Humalog, twelve percent
357 (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes.
358 HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic
359 studies to assess the effect of age on the onset of Humalog action have not been performed.

360 **ADVERSE REACTIONS**

361 Clinical studies comparing Humalog with Regular human insulin did not demonstrate a
362 difference in frequency of adverse events between the two treatments.

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

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

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

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

OVERDOSAGE

367
368 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
369 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
370 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
371 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
372 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
373 may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

374
375 Humalog is intended for subcutaneous administration, including use in select external
376 insulin pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage
377 regimens of Humalog will vary among patients and should be determined by the Health Care
378 Professional familiar with the patient's metabolic needs, eating habits, and other lifestyle
379 variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to
380 Regular human insulin (i.e., one unit of Humalog has the same glucose-lowering effect as one
381 unit of Regular human insulin), but with more rapid activity. The quicker glucose-lowering
382 effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An
383 adjustment of dose or schedule of basal insulin may be needed when a patient changes from
384 other insulins to Humalog, particularly to prevent pre-meal hyperglycemia.

385 When used as a meal-time insulin, Humalog should be given within 15 minutes before or
386 immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal.
387 To achieve optimal glucose control, the amount of longer-acting insulin being given may need to
388 be adjusted when using Humalog.

389 The rate of insulin absorption and consequently the onset of activity are known to be affected
390 by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently
391 faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human
392 insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients
393 with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its
394 rapid onset of action and has less variability in its onset of action among injection sites compared
395 with Regular human insulin (*see* PRECAUTIONS). After abdominal administration, Humalog
396 concentrations are higher than those following deltoid or thigh injections. Also, the duration of
397 action of Humalog is slightly shorter following abdominal injection, compared with deltoid and
398 femoral injections. As with all insulin preparations, the time course of action of Humalog may
399 vary considerably in different individuals or within the same individual. Patients must be
400 educated to use proper injection techniques.

401 Humalog in a vial may be diluted with STERILE DILUENT for Humalog[®], Humulin[®] N,
402 Humulin[®] R, , Humulin[®] 70/30, and Humulin[®] R U-500 to a concentration of 1:10 (equivalent to
403 U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when
404 stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog
405 contained in a cartridge or Humalog used in an external insulin pump.

406 Parenteral drug products should be inspected visually before use whenever the solution and the
407 container permit. If the solution is cloudy, contains particulate matter, is thickened, or is
408 discolored, the contents must not be injected. Humalog should not be used after its expiration
409 date.

410 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
411 cartridge or for the cartridge to be refilled with insulin.

412 *External Insulin Pumps* — Humalog may be used with MiniMed®¹ Models 506, 507, and 508
 413 insulin pumps using MiniMed®¹ Polyfin®¹ infusion sets. Humalog may also be used in the
 414 Disetronic®² H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the
 415 Disetronic D-TRON®^{2,3} and D-TRON®^{2,3}plus pumps (with Humalog 3 mL cartridges) using
 416 Disetronic Rapid®² infusion sets.

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

419 HOW SUPPLIED

420 Humalog [insulin lispro injection, USP (rDNA origin)] vials are available in the following
 421 package size:

422 100 units per mL (U-100)

423 10 mL vials

NDC 0002-7510-01 (VL-7510)

424 Humalog [insulin lispro injection, USP (rDNA origin)] cartridges are available in the following
 425 package size:

426 5 x 3 mL cartridges³

NDC 0002-7516-59 (VL-7516)

427 Humalog [insulin lispro injection, USP (rDNA origin)] Pen, a disposable insulin delivery
 428 device, is available in the following package size:

429 5 x 3 mL disposable insulin delivery devices

NDC 0002-8725-59 (HP-8725)

430

431

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

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

³ 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device and Disetronic D-TRON® and D-TRON®plus pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®, HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

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

432

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

437

	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 Cartridge	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL Pen	28 days	Until expiration date	28 days, Do not refrigerate.

438
439 *Use in an External Insulin Pump* — A Humalog 3 mL cartridge used in the D-TRON^{®2,3} or
440 D-TRON^{®2,3}plus should be discarded after 7 days, even if it still contains Humalog. Infusion
441 sets, D-TRON^{®2,3} and D-TRON^{®2,3}plus cartridge adapters, and Humalog in the external
442 insulin pump reservoir should be discarded every 48 hours or less.

443 Literature issued/revised Month dd, yyyy

444 **Pens manufactured by**

445 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
446 **Lilly France, F-67640 Fegersheim, France**

447 **Vials manufactured by**

448 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
449 **Hospira, Inc., Lake Forest, IL 60045, USA or**

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

451 **Cartridges manufactured by**

452 **Lilly France, S.A.S. F-67640 Fegersheim, France**

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

455

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

A1.0 PA 9352 FSAMP
A1.0 NL 5741 AMP
A1.0 NL 5751 AMP
A1.0 NL 3693 AMP
A1.0 NL 6832 AMP
A1.0 PA 9164 FSAMP

456

A1.0 NL 5731 AMP
A1.0 NL 6822 AMP
A1.0 NL 5761 AMP

INFORMATION FOR THE PATIENT
10 mL Vial (1000 Units per vial)

HUMALOG[®]
INSULIN LISPRO INJECTION, USP
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

WARNINGS

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

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG OR THE LONGER-ACTING INSULIN, OR BOTH.

PATIENTS TAKING HUMALOG 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.

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

DIABETES

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.

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 your 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

44 is maintained as close to normal as possible. The American Diabetes Association recommends
45 that if your pre-meal glucose levels are consistently above 130 mg/dL or your hemoglobin A_{1c}
46 (HbA_{1c}) is more than 7%, you should talk to your doctor. A change in your diabetes therapy may
47 be needed. If your blood tests consistently show below-normal glucose levels, you should also let
48 your doctor know. Proper control of your diabetes requires close and constant cooperation with
49 your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet,
50 exercise regularly, and take your insulin injections as prescribed by your doctor.

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

54

HUMALOG

Description

56 Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special
57 non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically
58 altered to produce this human insulin analog. Humalog consists of zinc-insulin lispro crystals
59 dissolved in a clear fluid. The time course of Humalog action, like that of other insulins, may
60 vary in different individuals or at different times in the same individual, based on dose, site of
61 injection, blood supply, temperature, and physical activity. Humalog is a sterile solution and is
62 for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog
63 is 100 units/mL (U-100).

64 Humalog starts lowering blood glucose more quickly and has a shorter duration of action
65 compared with Regular human insulin. This means that your dose of Humalog should be given
66 within 15 minutes before or immediately after a meal (Regular human insulin works best when
67 given 30 to 60 minutes before a meal). The short duration of action of Humalog means that if
68 you have type 1 diabetes, you also need to use a longer-acting insulin to give the best glucose
69 control (except when using an external insulin pump). If you have type 2 diabetes, Humalog may
70 be used without a longer-acting insulin when used in combination therapy with sulfonylurea
71 agents.

Identification

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

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

77 Always check the carton and bottle label of the Humalog you receive from your pharmacy to
78 make sure it is the same as prescribed by your doctor.

79 Always check the appearance of your bottle of Humalog before withdrawing each dose.
80 Humalog is a clear and colorless liquid with a water-like appearance and consistency.

81 Do not use Humalog:

- 82 • if it appears cloudy, thickened, or slightly colored, or
- 83 • if solid particles are visible.

84 If you see anything unusual in the appearance of Humalog solution in your bottle or notice
85 your insulin requirements changing, talk to your doctor.

Storage

87 Humalog may be diluted with the appropriate sterile diluent only under the direction of your
88 doctor. **However, do not dilute Humalog when used in an external insulin pump.**

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

91 **Not in-use (unopened):** Humalog bottles not in-use should be stored in a refrigerator, but not
 92 in the freezer.

93 **In-use (opened):** The Humalog bottle you are currently using can be kept unrefrigerated, for
 94 **up to 28 days**, as long as it is kept at room temperature [below 86°F (30°C)] away from direct
 95 heat and light. The Humalog bottle you are currently using must be discarded **28 days** after the
 96 first use, even if it still contains Humalog.

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

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

103 INSTRUCTIONS FOR INSULIN VIAL USE

104 *Use with Syringes*

105 **NEVER SHARE NEEDLES AND SYRINGES.**

106 **Correct Syringe Type**

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

111 **Syringe Use**

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

113 Disposable syringes and needles should be used only once and then discarded by placing the
 114 used needle in a puncture-resistant disposable container. Properly dispose of the puncture-
 115 resistant container as directed by your Health Care Professional.

116 **Preparing the Dose**

- 117 1. Wash your hands.
- 118 2. Inspect the insulin. Humalog solution should look clear and colorless. Do not use
 119 Humalog if it appears cloudy, thickened, or slightly colored, or if you see particles in the
 120 solution. Do not use Humalog if you notice anything unusual in its appearance.
- 121 3. If using a new Humalog bottle, flip off the plastic protective cap, but **do not** remove the
 122 stopper. Wipe the top of the bottle with an alcohol swab.
- 123 4. If you are mixing insulins, refer to the “Mixing Humalog with Longer-Acting Human
 124 Insulins” section below.
- 125 5. Draw an amount of air into the syringe that is equal to the Humalog dose. Put the needle
 126 through rubber top of the Humalog bottle and inject the air into the bottle.
- 127 6. Turn the Humalog bottle and syringe upside down. Hold the bottle and syringe firmly in
 128 one hand.
- 129 7. Making sure the tip of the needle is in the Humalog solution, withdraw the correct dose of
 130 Humalog into the syringe.
- 131 8. Before removing the needle from the Humalog bottle, check the syringe for air bubbles. If
 132 bubbles are present, hold the syringe straight up and tap its side until the bubbles float to
 133 the top. Push the bubbles out with the plunger and then withdraw the correct dose.
- 134 9. Remove the needle from the bottle and lay the syringe down so that the needle does not
 135 touch anything.

- 136 10. If you do not need to mix your Humalog with a longer-acting insulin, go to the “Injection
137 Instructions” section below and follow the directions.

138 **Mixing Humalog with Longer-Acting Human Insulins**

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

- 141 1. Humalog should be mixed with longer-acting human insulins only on the advice of your
142 doctor.
- 143 2. Draw an amount of air into the syringe that is equal to the amount of longer-acting insulin
144 you are taking. Insert the needle into the longer-acting insulin bottle and inject the air.
145 Withdraw the needle.
- 146 3. Draw an amount of air into the syringe that is equal to the amount of Humalog you are
147 taking. Insert the needle into the Humalog bottle and inject the air, but **do not** withdraw
148 the needle.
- 149 4. Turn the Humalog bottle and syringe upside down.
- 150 5. Making sure the tip of the needle is in the Humalog solution, withdraw the correct dose of
151 Humalog into the syringe.
- 152 6. Before removing the needle from the Humalog bottle, check the syringe for air bubbles. If
153 bubbles are present, hold the syringe straight up and tap its side until the bubbles float to
154 the top. Push the bubbles out with the plunger and then withdraw the correct dose.
- 155 7. Remove the syringe with the needle from the Humalog bottle and insert it into the
156 longer-acting insulin bottle. Turn the longer-acting insulin bottle and syringe upside
157 down. Hold the bottle and syringe firmly in one hand and shake gently. Making sure the
158 tip of the needle is in the longer-acting insulin, withdraw the correct dose of longer-acting
159 insulin.
- 160 8. Remove the needle from the bottle and lay the syringe down so that the needle does not
161 touch anything.
- 162 9. Follow the directions under “Injection Instructions” section below.

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

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

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

- 168 • the sequence of mixing, or
- 169 • the model and brand of syringe or needle that your doctor has prescribed.

170 **Injection Instructions**

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

181 Use in an External Insulin Pump

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

184 Humalog may be used with the MiniMed®¹ Models 506, 507, and 508 insulin pumps using
185 MiniMed®¹ Polyfin®¹ infusion sets. Humalog may also be used in the Disetronic®²

186 H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), using the
187 Disetronic®² Rapid®² infusion set.

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

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

195 **DOSAGE**

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

201 **Illness**

202 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
203 Even if you are not eating, you will still require insulin. You and your doctor should establish a
204 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
205 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

206 **Pregnancy**

207 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
208 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
209 are nursing a baby, talk to your doctor. Humalog has not been tested in pregnant or nursing
210 women.

211 **Geriatric Use**

212 Elderly patients using Humalog had HbA_{1c} values and hypoglycemia rates similar to those
213 observed in younger patients. The onset of action of Humalog may be different in elderly
214 patients.

215 **Medication**

216 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
217 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
218 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
219 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
220 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
221 Professional may be aware of other medications that may affect your diabetes control. Therefore,
222 always discuss any medications you are taking with your doctor.

223 **Exercise**

224 Exercise may lower your body's need for insulin during and for some time after the physical
225 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
226 involves the area of injection site (for example, the leg should not be used for injection just prior
227 to running). Discuss with your doctor how you should adjust your insulin regimen to
228 accommodate exercise.

229 **Travel**

230 When traveling across more than 2 time zones, you should talk to your doctor concerning
231 adjustments in your insulin schedule.

COMMON PROBLEMS OF DIABETES

232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247

Hypoglycemia (Low Blood Sugar)

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

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

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

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

Signs of severe hypoglycemia can include:

- | | |
|-------------------|------------|
| • disorientation | • seizures |
| • unconsciousness | • death |

248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266

Therefore, it is important that assistance be obtained immediately.

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

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

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

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

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

273 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

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

287 **Lipodystrophy**

288 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
 289 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
 290 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
 291 the problem.

292 **Allergy**

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

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

302 **ADDITIONAL INFORMATION**

303 Information about diabetes may be obtained from your diabetes educator.

304 Additional information about diabetes and Humalog can be obtained by calling The Lilly
 305 Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

306
 307 ¹ MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

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

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

311 **Vials manufactured by**
312 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
313 **Hospira, Inc., Lake Forest, IL 60045, USA or**
314 **Lilly France, F-67640 Fegersheim, France**
315
316 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
317

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

318 A1.0 NL 5731 AMP
319 A1.0 NL 6822 AMP
A1.0 NL 5761 AMP

PRINTED IN USA

1
2
3
4

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

5
6
7

**HUMALOG[®] Pen
INSULIN LISPRO INJECTION, USP
(rDNA ORIGIN)**

8

100 UNITS PER ML (U-100)

9

WARNINGS

10
11
12
13
14
15
16
17
18
19

THIS LILLY HUMAN INSULIN ANALOG IS DIFFERENT FROM OTHER INSULINS BECAUSE IT HAS A RAPID ONSET AND SHORTER DURATION OF ACTION. THE RAPID ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF HUMALOG[®] [INSULIN LISPRO INJECTION, USP (rDNA ORIGIN)] WITHIN 15 MINUTES BEFORE OR IMMEDIATELY AFTER EATING A MEAL. THE SHORT DURATION OF ACTION OF HUMALOG MEANS THAT IF YOU HAVE TYPE 1 DIABETES, YOU ALSO NEED TO USE A LONGER-ACTING INSULIN TO GIVE THE BEST GLUCOSE CONTROL. IF YOU HAVE TYPE 2 DIABETES, HUMALOG MAY BE USED WITHOUT A LONGER-ACTING INSULIN WHEN USED IN COMBINATION THERAPY WITH SULFONYLUREA AGENTS.

20
21
22
23
24

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG OR THE LONGER-ACTING INSULIN, OR BOTH.

25
26
27
28

PATIENTS TAKING HUMALOG 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.

29
30
31

TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE USER MANUAL AND THIS “INFORMATION FOR THE PATIENT” INSERT BEFORE USING THIS PRODUCT.

32
33
34
35
36
37
38

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 TOO MUCH OR TOO LITTLE INSULIN (*see also* INSTRUCTIONS FOR INSULIN PEN USE section).

39

DIABETES

40
41
42

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.

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

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

57 HUMALOG

58 Description

59 Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special
60 non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically
61 altered to produce this human insulin analog. Humalog consists of zinc-insulin lispro crystals
62 dissolved in a clear fluid. The time course of Humalog action, like that of other insulins, may
63 vary in different individuals or at different times in the same individual, based on dose, site of
64 injection, blood supply, temperature, and physical activity. Humalog is a sterile solution and is
65 for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog
66 is 100 units/mL (U-100).

67 Humalog starts lowering blood glucose more quickly and has a shorter duration of action
68 compared with Regular human insulin. This means that your dose of Humalog should be given
69 within 15 minutes before or immediately after a meal (Regular insulin works best when given 30
70 to 60 minutes before a meal). The short duration of action of Humalog means that if you have
71 type 1 diabetes, you also need to use a longer-acting insulin to give the best glucose control. If
72 you have type 2 diabetes, Humalog may be used without a longer-acting insulin when used in
73 combination therapy with sulfonylurea agents.

74 Identification

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

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

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

82 Always check the carton and Pen label of the Humalog you receive from your pharmacy to
83 make sure it is the same as prescribed by your doctor.

84 Always check the appearance of Humalog solution in your insulin Pen before using. Humalog
85 is a clear and colorless liquid with a water-like appearance and consistency.

86 Do not use Humalog:

- 87 • if it appears cloudy, thickened, or slightly colored, or
- 88 • if solid particles are visible.

89 If you see anything unusual in the appearance of the Humalog in your Pen or notice your
90 insulin requirements changing, talk to your doctor.

91 Never attempt to remove the cartridge from the Humalog Pen. Inspect the cartridge through the
92 clear cartridge holder.

93 **Storage**

94 **Not in-use (unopened):** Humalog Pens not in-use should be stored in a refrigerator, but not in
95 the freezer.

96 **In-use (opened):** Humalog Pens in-use should **NOT** be refrigerated but should be kept at room
97 temperature [below 86°F (30°C)] away from direct heat and light. The Humalog Pen you are
98 currently using must be discarded **28 days** after the first use, even if it still contains Humalog.

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

101 **INSTRUCTIONS FOR INSULIN PEN USE**

102 **It is important to read, understand, and follow the instructions in the Insulin Delivery**
103 **Device User Manual before using. Failure to follow instructions may result in getting too**
104 **much or too little insulin. The needle must be changed and the Pen must be primed before**
105 **each injection to make sure the Pen is ready to dose. Performing these steps before each**
106 **injection is important to confirm that insulin comes out when you push the injection**
107 **button, and to remove air that may collect in the insulin cartridge during normal use.**

108 **Every time you inject:**

- 109 • Use a new needle.
- 110 • Prime to make sure the Pen is ready to dose.
- 111 • Make sure you got your full dose.

112 **NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.**

113 **PREPARING FOR INJECTION**

- 114 1. Wash your hands.
- 115 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
116 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 117 3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
118 injection.
- 119 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
120 site for several seconds. **Do not rub the area.**
- 121 5. After the injection, remove the needle from the Humalog Pen. **Do not reuse needles.**
- 122 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
123 the puncture-resistant container as directed by your Health Care Professional.

124 **DOSAGE**

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

130 **Illness**

131 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
132 Even if you are not eating, you will still require insulin. You and your doctor should establish a
133 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
134 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

135 **Pregnancy**

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

140 **Geriatric Use**

141 Elderly patients using Humalog had HbA_{1c} values and hypoglycemia rates similar to those
142 observed in younger patients. The onset of action of Humalog may be different in elderly
143 patients.

144 **Medication**

145 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
146 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
147 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
148 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
149 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
150 Professional may be aware of other medications that may affect your diabetes control. Therefore,
151 always discuss any medications you are taking with your doctor.

152 **Exercise**

153 Exercise may lower your body's need for insulin during and for some time after the physical
154 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
155 involves the area of injection site (for example, the leg should not be used for injection just prior
156 to running). Discuss with your doctor how you should adjust your insulin regimen to
157 accommodate exercise.

158 **Travel**

159 When traveling across more than 2 time zones, you should talk to your doctor concerning
160 adjustments in your insulin schedule.

161 **COMMON PROBLEMS OF DIABETES**

162 **Hypoglycemia (Low Blood Sugar)**

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

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

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

202 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

208 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
209 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
210 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,

211 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose
 212 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
 213 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
 214 of consciousness, or death. Therefore, it is important that you obtain medical assistance
 215 immediately.

216 **Lipodystrophy**

217 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
 218 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
 219 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
 220 the problem.

221 **Allergy**

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

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

231 **ADDITIONAL INFORMATION**

232 Information about diabetes may be obtained from your diabetes educator.

233 Additional information about diabetes and Humalog can be obtained by calling The Lilly
 234 Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

235 Patient Information issued/revised Month dd, yyyy

236 **Pens manufactured by**

237 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 238 **Lilly France, F-67640 Fegersheim, France**

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

241

Copyright © 1998, yyyy, Eli Lilly and Company. All rights reserved.

242 A1.0 NL 3701 AMP
 243 A1.0 PA 9154 FSAMP

PRINTED IN USA

1
2
3

**INFORMATION FOR THE PATIENT
CARTRIDGE**

4
5
6
7

**HUMALOG[®]
INSULIN LISPRO INJECTION, USP
(rDNA ORIGIN)
100 UNITS PER ML (U-100)**

8

3 ML CARTRIDGE

9 For use in Eli Lilly and Company's HumaPen[®] MEMOIR^{™1} and HumaPen[®] LUXURA[™]
10 HD¹ insulin delivery devices, Owen Mumford, Ltd.'s Autopen^{®2} 3 mL insulin delivery
11 device (reusable insulin Pen), Disetronic^{®3} D-TRON^{®3} or D-TRON^{®3}plus insulin pumps.

12

WARNINGS

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

24 **ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY**
25 **UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER,**
26 **TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF**
27 **MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING**
28 **OR DOSAGE OF HUMALOG OR THE LONGER-ACTING INSULIN, OR BOTH.**

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

33 **USE IN REUSABLE INSULIN PEN: TO OBTAIN AN ACCURATE DOSE,**
34 **CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE**
35 **MANUFACTURER'S INSTRUCTIONS AND THIS "INFORMATION FOR THE**
36 **PATIENT" INSERT BEFORE USING THIS PRODUCT IN AN INSULIN PEN (*see***
37 **INSTRUCTIONS FOR USE section).**

38 **USE IN AN EXTERNAL INSULIN PUMP: CAREFULLY READ AND FOLLOW THE**
39 **EXTERNAL INSULIN PUMP MANUFACTURER'S INSTRUCTIONS AND THIS**
40 **"INFORMATION FOR THE PATIENT" INSERT BEFORE USING THIS PRODUCT IN**
41 **AN EXTERNAL INSULIN PUMP (*see* INSTRUCTIONS FOR USE section).**

DIABETES

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.

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

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

HUMALOG

Description

Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce this human insulin analog. Humalog consists of zinc-insulin lispro crystals dissolved in a clear fluid. The time course of Humalog action, like that of other insulins, may vary in different individuals or at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity. Humalog is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog is 100 units/mL (U-100).

Humalog starts lowering blood glucose more quickly and has a shorter duration of action compared with Regular human insulin. This means that your dose of Humalog should be given within 15 minutes before or immediately after eating a meal (Regular human insulin works best when given 30 to 60 minutes before eating a meal). The short duration of action of Humalog means that if you have type 1 diabetes, you also need to use a longer-acting insulin to give the best glucose control (except when using an external insulin pump). If you have type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Identification

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

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

3 mL Cartridge

Humalog[®] 3 mL cartridges are for use in Eli Lilly and Company's HumaPen[®] MEMOIR^{™1} and HumaPen[®] LUXURA[™] HD¹ insulin delivery devices, Owen Mumford, Ltd.'s Autopen^{®2} 3 mL insulin delivery device (reusable insulin Pen) and in Disetronic D-TRON^{®3} or D-TRON^{®3} plus insulin pumps using Disetronic Rapid^{®3} infusion sets.

88 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
89 cartridge or for the cartridge to be refilled with insulin.

90 Always check the carton and cartridge label of the Humalog you receive from your pharmacy
91 to make sure it is the same as prescribed by your doctor.

92 Always check the appearance of Humalog solution in your cartridge before using. When using
93 a Humalog cartridge in an external insulin pump, inspect the cartridge before inserting it in the
94 external insulin pump and periodically during use. Humalog is a clear and colorless liquid with a
95 water-like appearance and consistency.

96 Do not use Humalog:

- 97 • if it appears cloudy, thickened, or slightly colored, or
- 98 • if solid particles are visible.

99 If you see anything unusual in the appearance of the Humalog in your cartridge or notice your
100 insulin requirements changing, talk to your doctor.

101 **Storage**

102 *When used in Reusable Insulin Pen*

103 **Not in-use (unopened):** Humalog cartridges not in-use should be stored in a refrigerator, but
104 not in the freezer.

105 **In-use (opened):** Humalog cartridges in-use should **NOT** be refrigerated but should be kept at
106 room temperature [below 86°F (30°C)] away from direct heat and light. The Humalog cartridge
107 you are currently using must be discarded **28 days** after the first use, even if it still contains
108 Humalog.

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

111 *When used in an External Insulin Pump*

112 **Infusion sets (tubing and catheters) and D-TRON^{®3} or D-TRON^{®3}plus cartridge adapter**
113 **should be discarded every 48 hours or less. Humalog in an external insulin pump should**
114 **not be exposed to temperatures above 98.6°F (37°C) such as in sauna or hot tub, hot**
115 **showers, direct sunlight, or radiant heater. A Humalog 3 mL cartridge used in the**
116 **D-TRON^{®3} or D-TRON^{®3}plus pump should be discarded after 7 days, even if it still**
117 **contains Humalog.**

118 **INSTRUCTIONS FOR INSULIN CARTRIDGE USE**

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

122 **NEVER SHARE INSULIN PENS, EXTERNAL INSULIN PUMPS, INFUSION SETS,**
123 **CARTRIDGES, OR NEEDLES.**

124 **PREPARING FOR AN INJECTION USING REUSABLE INSULIN PEN OR EXTERNAL** 125 **INSULIN PUMP**

- 126 1. Inspect the appearance of Humalog solution before you insert the cartridge into the
127 reusable insulin Pen or external insulin pump. Humalog should look clear and colorless.
128 Do not use Humalog if it appears cloudy, thickened, slightly colored, or if solid particles
129 are visible. Once the cartridge is in-use, inspect the insulin in the insulin Pen before each
130 injection. When using a Humalog cartridge in an external insulin pump, inspect the
131 cartridge before inserting it in the external insulin pump and periodically during use.
- 132 2. *Use in Reusable Insulin Pen* — Follow the reusable insulin Pen manufacturer's
133 instructions carefully for loading the cartridge into the insulin Pen and for use of the

134 insulin Pen. Follow the insulin needle manufacturer's instructions for attaching and
135 changing the needle.

136 3. *Use in an External Insulin Pump* — Follow the external insulin pump manufacturer's
137 instructions carefully for use of Humalog 3 mL cartridges in the D-TRON^{®3} or
138 D-TRON^{®3}plus insulin pump.

139 **GENERAL INSTRUCTIONS**

140 *For use in Reusable Insulin Pen*

- 141 1. Wash your hands.
- 142 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
143 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
- 144 3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
145 injection
- 146 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
147 site for several seconds. **Do not rub the area.**
- 148 5. After the injection, remove the needle from the Humalog Pen. **Do not reuse needles.**
- 149 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
150 the puncture-resistant container as directed by your Health Care Professional.
- 151 7. Use the gauge on the side of the cartridge to help you judge how much insulin remains.
152 The distance between each mark on the 3 mL cartridge is about 20 units.

153 *For use in an External Insulin Pump*

154 Your doctor should train you on intensive insulin therapy including sterile techniques. You
155 should also be trained on the use of your external insulin pump and pump accessories.

156 **You should replace the infusion set (tubing and catheter) and D-TRON^{®3} or
157 D-TRON^{®3}plus cartridge adapter every 48 hours or less.** You should also choose a new
158 infusion site every 48 hours or less. A Humalog 3 mL cartridge used in the pump should be
159 discarded after 7 days, even if it still contains Humalog. Contact your doctor if your infusion
160 sites are red, itching, or thickened, and then choose a new infusion site.

161 Follow the external insulin pump manufacturer's instructions carefully for use of Humalog
162 3 mL cartridges in Disetronic D-TRON^{®3} or D-TRON^{®3}plus insulin pump.

163 **DOSAGE**

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

169 **Illness**

170 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
171 Even if you are not eating, you will still require insulin. You and your doctor should establish a
172 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
173 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

174 **Pregnancy**

175 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
 176 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
 177 are nursing a baby, talk to your doctor. Humalog has not been tested in pregnant or nursing
 178 women.

179 **Geriatric Use**

180 Elderly patients using Humalog had HbA_{1c} values and hypoglycemia rates similar to those
 181 observed in younger patients. The onset of action of Humalog may be different in elderly
 182 patients.

183 **Medication**

184 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 185 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 186 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 187 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
 188 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
 189 Professional may be aware of other medications that may affect your diabetes control. Therefore,
 190 always discuss any medications you are taking with your doctor.

191 **Exercise**

192 Exercise may lower your body's need for insulin during and for some time after the physical
 193 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
 194 involves the area of injection site (for example, the leg should not be used for injection just prior
 195 to running). Discuss with your doctor how you should adjust your insulin regimen to
 196 accommodate exercise.

197 **Travel**

198 When traveling across more than 2 time zones, you should talk to your doctor concerning
 199 adjustments in your insulin schedule.

200 **COMMON PROBLEMS OF DIABETES**

201 **Hypoglycemia (Low Blood Sugar)**

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

- 204 1. **Missing or delaying meals.**
- 205 2. Taking too much insulin.
- 206 3. Exercising or working more than usual.
- 207 4. An infection or illness associated with diarrhea or vomiting.
- 208 5. A change in the body's need for insulin.
- 209 6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver
 210 disease.
- 211 7. Interactions with other drugs that lower blood glucose, such as oral antidiabetic agents,
 212 salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some
 213 kidney and blood pressure medicines.
- 214 8. Consumption of alcoholic beverages.

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

241 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

247 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
248 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
249 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,
250 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose
251 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
252 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
253 of consciousness, or death. Therefore, it is important that you obtain medical assistance
254 immediately.

255 **Lipodystrophy**

256 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
257 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
258 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
259 the problem.

260 **Allergy**

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

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

270 **ADDITIONAL INFORMATION**

271 Information about diabetes may be obtained from your diabetes educator.

272 Additional information about diabetes and Humalog can be obtained by calling The Lilly
273 Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

275 ¹ HumaPen[®], HumaPen MEMOIR[™] and HumaPen LUXURA[™] HD are trademarks of Eli Lilly and Company.

276 ² Autopen[®] is a registered trademark of Owen Mumford, Ltd.

277 ³ Disetronic[®], D-TRON[®], and Rapid[®] are registered trademarks of Roche Diagnostics GMBH.

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

279 Patient Information issued/revised Month dd, yyyy

280

281

282

283

284

285

Cartridges manufactured by
Lilly France, F-67640 Fegersheim, France

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

286 A1.0 PA 9380 FSAMP

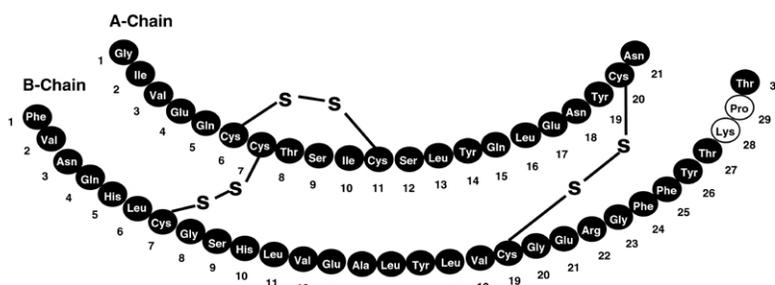
A1.0 NL 3711 AMP
 A1.0 NL 5781 AMP
 A1.0 NL 4841 AMP
 A1.0 PA 9224 FSAMP

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 to produce 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:



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 Pens 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 Metacresol, 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 to 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

38 of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism.
 39 In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits
 40 gluconeogenesis, and promotes the conversion of excess glucose into fat.

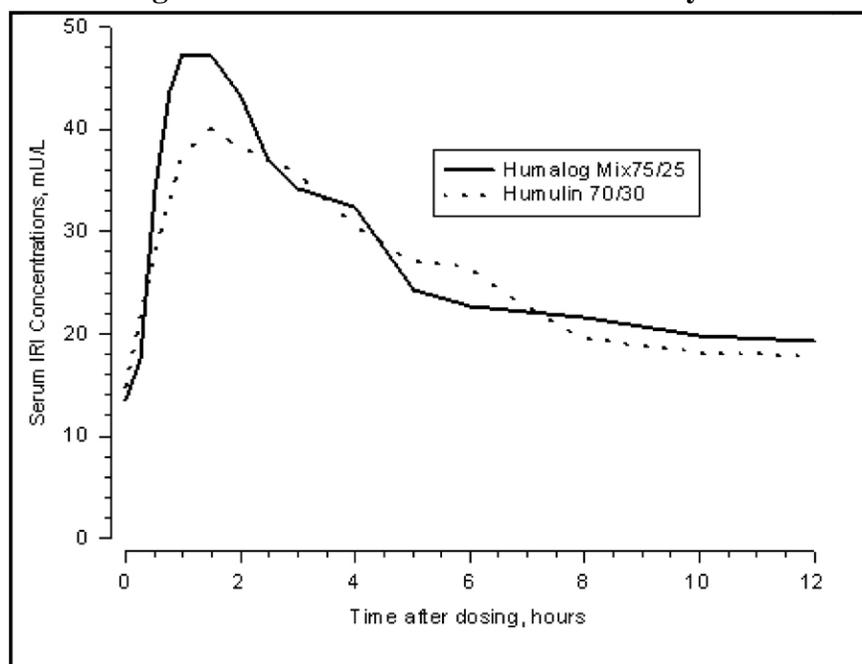
41 Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be
 42 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same
 43 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 44 shorter duration.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

46 Pharmacokinetics

47 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
 48 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix75/25, is
 49 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
 50 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
 51 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
 52 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
 53 results were seen in patients with type 1 diabetes.

54

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



57

58

59 Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and
 60 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
 61 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous doses
 62 (0.3 U/kg) of Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes
 63 (median, 60 minutes) after dosing (*see* Figure 1). Identical results were found in patients with
 64 type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with
 65 Humalog Mix75/25 (*see* Figure 1).

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

69 *Distribution* — Radiolabeled distribution studies of Humalog Mix75/25 have not been
70 conducted. However, the volume of distribution following injection of Humalog is identical to
71 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

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

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

80 **Pharmacodynamics**

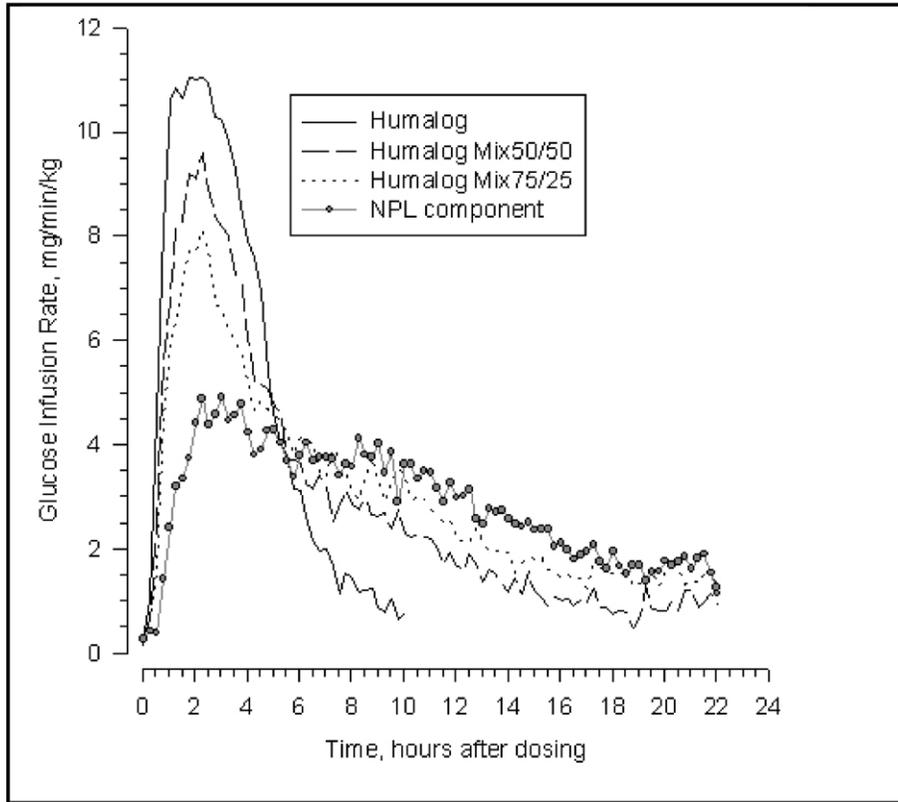
81 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
82 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
83 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
84 Humalog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

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

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

100

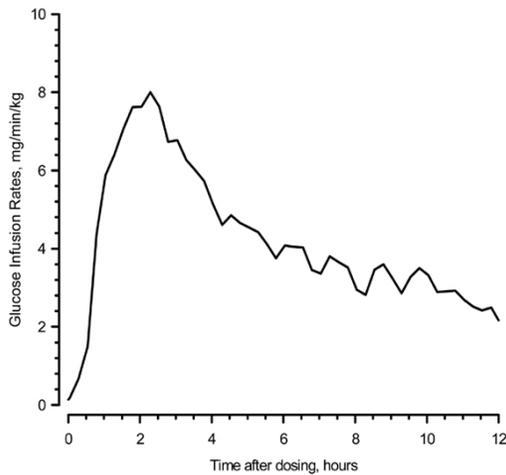
101 **Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog**
102 **Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic**
103 **Subjects.**



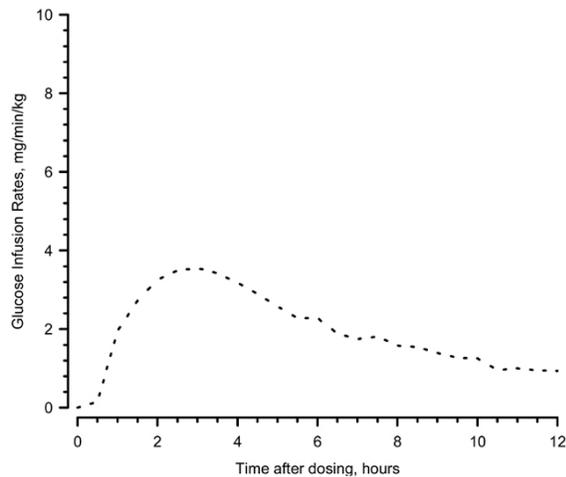
104
105
106
107
108
109
110

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

**Figure 3a
Humalog Mix75/25**



**Figure 3b
Humulin 70/30**



111
112
113
114

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

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

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

119 Special Populations

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

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

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

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

135 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
136 pharmacodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with
137 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
138 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the
139 patients to insulin did change, with an increased response to insulin as the renal function
140 declined. Careful glucose monitoring and dose reductions of insulin, including
141 Humalog Mix75/25, may be necessary in patients with renal dysfunction.

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

151 **INDICATIONS AND USAGE**

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

158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

General

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

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

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

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

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

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

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

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

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

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

210 **Information for Patients**

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

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

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

222 For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read
223 the “INFORMATION FOR THE PATIENT” insert that accompanies the drug product and the
224 User Manual that accompanies the delivery device and re-read them each time the prescription
225 is renewed. Patients should be instructed on how to properly use the delivery device, prime the
226 Pen, and properly dispose of needles. Patients should be advised not to share their Pens with
227 others.

228 **Laboratory Tests**

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

232 **Drug Interactions**

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

236 Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity,
237 such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine
238 oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking
239 agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.
240 Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

241 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

242 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
243 Humalog, Humalog Mix75/25 or Humalog Mix50/50. Insulin lispro was not mutagenic in a
244 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
245 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).

246 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

247 **Pregnancy**

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

255 **Nursing Mothers**

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

260 **Pediatric Use**

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

263 **Geriatric Use**

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

269 **ADVERSE REACTIONS**

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

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

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

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

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

276 **OVERDOSAGE**

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

283 **DOSAGE AND ADMINISTRATION**

284 **Table 1***

285 **Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study
 286 Comparison)**
 287

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 with 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 to 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

Humalog Mix75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] vials are available in the following package size:

100 units per mL (U-100)

10 mL vials

NDC 0002-7511-01 (VL-7511)

317 Humalog Mix75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection,
 318 (rDNA origin)] Pen, a disposable insulin delivery device, is available in the following package
 319 size:

320 5 x 3 mL disposable insulin delivery devices
 321 NDC 0002-8794-59 (HP-8794)

322 *Storage* — Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 323 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated
 324 [below 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 325 Humalog Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens must be used within 10 days or be
 326 discarded, even if they still contain Humalog Mix75/25. Protect from direct heat and light. See
 327 table below:
 328

	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	10 days	Until expiration date	10 days. Do not refrigerate.

329

330 Literature issued/revised Month dd, yyyy

331 **Pens manufactured by**
 332 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 333 **Lilly France, F-67640 Fegersheim, France**

334 **Vials manufactured by**
 335 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 336 **Lilly France, F-67640 Fegersheim, France**

337
 338 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

339

Copyright © 1999, yyyy, Eli Lilly and Company. All rights reserved.

340 A1.0 NL 3711 AMP
 341 A1.0 NL 5781 AMP
 342 A1.0 NL 4841 AMP
 343 A1.0 PA 9224 FSAMP

PRINTED IN USA

A1.0 NL 5771 AMP
A1.0 NL 4851 AMP

INFORMATION FOR THE PATIENT
10 mL Vial (1000 Units per vial)

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

WARNINGS

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.

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

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.

DIABETES

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.

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

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

45 **HUMALOG Mix75/25**

46 **Description**

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

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

61 **Identification**

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

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

67 Always check the carton and bottle label of the Humalog Mix75/25 you receive from your
68 pharmacy to make sure it is the same as prescribed by your doctor.

69 Always check the appearance of your bottle of Humalog Mix75/25 before withdrawing each
70 dose. Before each injection the Humalog Mix75/25 bottle must be carefully shaken or rotated
71 several times to completely mix the insulin. Humalog Mix75/25 suspension should look
72 uniformly cloudy or milky after mixing. If not, repeat the above step until contents are mixed.

73 Do not use Humalog Mix75/25:

- 74 • if the insulin substance (the white material) remains at the bottom of the bottle after
75 mixing or
- 76 • if there are clumps in the insulin after mixing, or
- 77 • if solid white particles stick to the bottom or wall of the bottle, giving a frosted
78 appearance.

79 If you see anything unusual in the appearance of Humalog Mix75/25 suspension in your bottle
80 or notice your insulin requirements changing, talk to your doctor.

81 **Storage**

82 **Not in-use (unopened):** Humalog Mix75/25 bottles not in-use should be stored in a
83 refrigerator, but not in the freezer.

84 **In-use (opened):** The Humalog Mix75/25 bottle you are currently using can be kept
85 unrefrigerated, for **up to 28 days**, as long as it is kept at room temperature [below 86°F (30°C)]
86 away from direct heat and light. The Humalog Mix75/25 bottle you are currently using must be
87 discarded **28 days** after the first use, even if it still contains Humalog Mix75/25.

88 **Do not use Humalog Mix75/25 after the expiration date stamped on the label or if it has**
 89 **been frozen.**

90 INSTRUCTIONS FOR INSULIN VIAL USE

91 *Use with Syringes*

92 **NEVER SHARE NEEDLES AND SYRINGES.**

93 **Correct Syringe Type**

94 Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL=1 cc).
 95 With Humalog Mix75/25, it is important to use a syringe that is marked for U-100 insulin
 96 preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious
 97 problems for you, such as a blood glucose level that is too low or too high.

98 **Syringe Use**

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

100 Disposable syringes and needles should be used only once and then discarded by placing the
 101 used needle in a puncture-resistant disposable container. Properly dispose of the puncture-
 102 resistant container as directed by your Health Care Professional.

103 **Preparing the Dose**

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

123 **Injection Instructions**

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

134 **DOSAGE**

135 Your doctor has told you which insulin to use, how much, and when and how often to inject it.
 136 Because each patient's diabetes is different, this schedule has been individualized for you. Your

137 usual dose of Humalog Mix75/25 may be affected by changes in your diet, activity, or work
 138 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things
 139 that may affect your Humalog Mix75/25 dose are:

140 **Illness**

141 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
 142 Even if you are not eating, you will still require insulin. You and your doctor should establish a
 143 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
 144 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

145 **Pregnancy**

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

150 **Medication**

151 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 152 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 153 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 154 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
 155 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
 156 Professional may be aware of these and other medications that may affect your diabetes control.
 157 Therefore, always discuss any medications you are taking with your doctor.

158 **Exercise**

159 Exercise may lower your body's need for insulin during and for some time after the physical
 160 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
 161 involves the area of injection site (for example, the leg should not be used for injection just prior
 162 to running). Discuss with your doctor how you should adjust your insulin regimen to
 163 accommodate exercise.

164 **Travel**

165 When traveling across more than 2 time zones, you should talk to your doctor concerning
 166 adjustments in your insulin schedule.

167 **COMMON PROBLEMS OF DIABETES**

168 **Hypoglycemia (Low Blood Sugar)**

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

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

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

208 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

214 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
215 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
216 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,
217 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose

218 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
219 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
220 of consciousness, or death. Therefore, it is important that you obtain medical assistance
221 immediately.

222 **Lipodystrophy**

223 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
224 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
225 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
226 the problem.

227 **Allergy**

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

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

237 **ADDITIONAL INFORMATION**

238 Information about diabetes may be obtained from your diabetes educator.

239 Additional information about diabetes and Humalog Mix75/25 can be obtained by calling The
240 Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

241 Patient Information issued/revised Month dd, yyyy

242 **Vials manufactured by**
243 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
244 **Lilly France, F-67640 Fegersheim, France**

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

246

247 Copyright © 1999, yyyy, Eli Lilly and Company. All rights reserved.

248 A1.0 NL 5771 AMP

249 A1.0 NL 4851 AMP

PRINTED IN USA

1
2
3
4

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

5
6
7
8
9

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

10

WARNINGS

11
12
13
14
15
16

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.

17
18
19
20
21

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

22
23
24
25

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.

26
27
28

TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE USER MANUAL AND THIS “INFORMATION FOR THE PATIENT” INSERT BEFORE USING THIS PRODUCT.

29
30
31
32
33
34
35

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 TOO MUCH OR TOO LITTLE INSULIN (*see also* INSTRUCTIONS FOR INSULIN PEN USE section).

36

DIABETES

37
38
39

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.

40
41
42
43

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 your 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

44 is maintained as close to normal as possible. The American Diabetes Association recommends
45 that if your pre-meal glucose levels are consistently above 130 mg/dL, bedtime glucose levels
46 are consistently above 160 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, you should
47 talk to your doctor. A change in your diabetes therapy may be needed. If your blood tests
48 consistently show below-normal glucose levels, you should also let your doctor know. Proper
49 control of your diabetes requires close and constant cooperation with your doctor. Despite
50 diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and
51 take your insulin injections as prescribed by your doctor.

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

55 HUMALOG Mix75/25

56 Description

57 Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special
58 non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically
59 altered to produce this human insulin analog. Humalog Mix75/25 is a mixture of 75% insulin
60 lispro protamine suspension and 25% insulin lispro injection (rDNA origin). It is a longer-acting
61 insulin combined with the more rapid onset of action of Humalog. The duration of activity is
62 similar to that of Humulin[®] 70/30 and may last up to 24 hours following injection. The time
63 course of Humalog Mix75/25 action, like that of other insulins, may vary in different individuals
64 or at 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 only. 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 to 60 minutes before a meal.

71 Identification

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

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

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

80 Always check the carton and Pen label of the Humalog Mix75/25 you receive from your
81 pharmacy to make sure it is the same as prescribed by your doctor.

82 Always check the appearance of Humalog Mix75/25 suspension in your insulin Pen before
83 using. A cartridge of Humalog Mix75/25 contains a small glass bead to assist in mixing. Roll the
84 Pen between the palms 10 times (*see* Figure 1). Holding the Pen by one end, invert it
85 180° slowly 10 times to allow the small glass bead to travel the full length of the cartridge with
86 each inversion (*see* Figure 2).

87

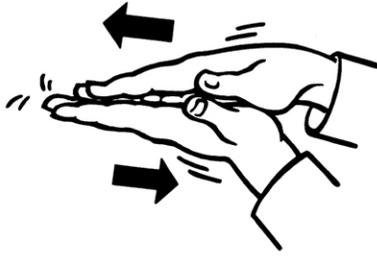


Figure 1.

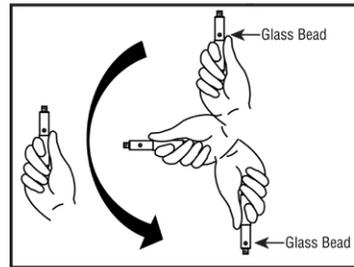


Figure 2.

88
89

90 Humalog Mix75/25 suspension should look uniformly cloudy or milky after mixing. If not,
91 repeat the above steps until contents are mixed. Pens containing Humalog Mix75/25 suspension
92 should be examined frequently.

93 Do not use Humalog Mix75/25:

- 94 • if the insulin substance (the white material) remains visibly separated from the liquid
- 95 after mixing or
- 96 • if there are clumps in the insulin after mixing, or
- 97 • if solid white particles stick to the bottom or wall of the cartridge, giving a frosted
- 98 appearance.

99 If you see anything unusual in the appearance of the Humalog Mix75/25 suspension in your
100 Pen or notice your insulin requirements changing, talk to your doctor.

101 Never attempt to remove the cartridge from the Humalog Mix75/25 Pen. Inspect the cartridge
102 through the clear cartridge holder.

103 **Storage**

104 **Not in-use (unopened):** Humalog Mix75/25 Pens not in-use should be stored in a refrigerator,
105 but not in the freezer.

106 **In-use (opened):** Humalog Mix75/25 Pens in-use should **NOT** be refrigerated but should be
107 kept at room temperature [below 86°F (30°C)] away from direct heat and light. The
108 Humalog Mix75/25 Pen you are currently using must be discarded **10 days** after the first use,
109 even if it still contains Humalog Mix75/25.

110 **Do not use Humalog Mix75/25 after the expiration date stamped on the label or if it has**
111 **been frozen.**

112

112 **INSTRUCTIONS FOR INSULIN PEN USE**

113 **It is important to read, understand, and follow the instructions in the Insulin Delivery**
114 **Device User Manual before using. Failure to follow instructions may result in getting too**
115 **much or too little insulin. The needle must be changed and the Pen must be primed before**
116 **each injection to make sure the Pen is ready to dose. Performing these steps before each**
117 **injection is important to confirm that insulin comes out when you push the injection**
118 **button, and to remove air that may collect in the insulin cartridge during normal use.**

119 **Every time you inject:**

- 120 • Use a new needle.
- 121 • Prime to make sure the Pen is ready to dose.
- 122 • Make sure you got your full dose.

123 **NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.**

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. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
 129 injection.
 130 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
 131 site for several seconds. **Do not rub the area.**
 132 5. After the injection, remove the needle from the Humalog Mix75/25 Pen. **Do not reuse**
 133 **needles.**
 134 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
 135 the puncture-resistant container as directed by your Health Care Professional.

136 **DOSAGE**

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

142 **Illness**

143 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
 144 Even if you are not eating, you will still require insulin. You and your doctor should establish a
 145 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
 146 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

147 **Pregnancy**

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

152 **Medication**

153 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 154 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 155 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 156 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
 157 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
 158 Professional may be aware of these and other medications that may affect your diabetes control.
 159 Therefore, always discuss any medications you are taking with your doctor.

160 **Exercise**

161 Exercise may lower your body's need for insulin during and for some time after the physical
 162 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
 163 involves the area of injection site (for example, the leg should not be used for injection just prior
 164 to running). Discuss with your doctor how you should adjust your insulin regimen to
 165 accommodate exercise.

166 **Travel**

167 When traveling across more than 2 time zones, you should talk to your doctor concerning
 168 adjustments in your insulin schedule.

169 **COMMON PROBLEMS OF DIABETES**

170 **Hypoglycemia (Low Blood Sugar)**

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

- 173 1. **Missing or delaying meals.**

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

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

210 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

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

224 **Lipodystrophy**

225 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
226 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
227 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
228 the problem.

229 **Allergy**

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

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

239 **ADDITIONAL INFORMATION**

240 Information about diabetes may be obtained from your diabetes educator.

241 Additional information about diabetes and Humalog Mix75/25 can be obtained by calling The
242 Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

243 Patient Information issued/revised Month dd, yyyy

244 **Pens manufactured by**

245 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
246 **Lilly France, F-67640 Fegersheim, France**

247
248 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

249

Copyright © 1999, yyyy, Eli Lilly and Company. All rights reserved.

250 A1.0 NL 3721 AMP
251 A1.0 PA 9235 FSAMP

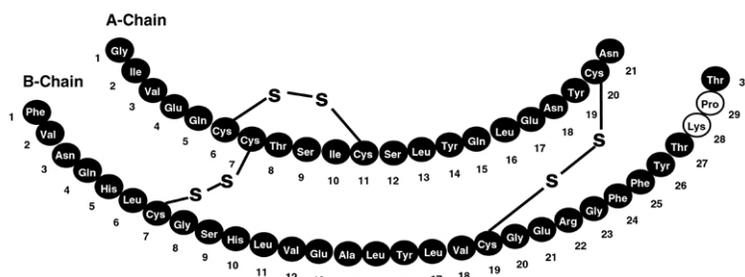
PRINTED IN USA

HUMALOG[®] Mix50/50[™]
50% INSULIN LISPRO PROTAMINE SUSPENSION AND
50% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] Mix50/50[™] [50% insulin lispro protamine suspension and 50% 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 to produce 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:



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 Mix50/50 vials and Pens contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of Humalog Mix50/50 injection contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection. Humalog Mix50/50 has a pH of 7.0 to 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 Mix50/50, 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.

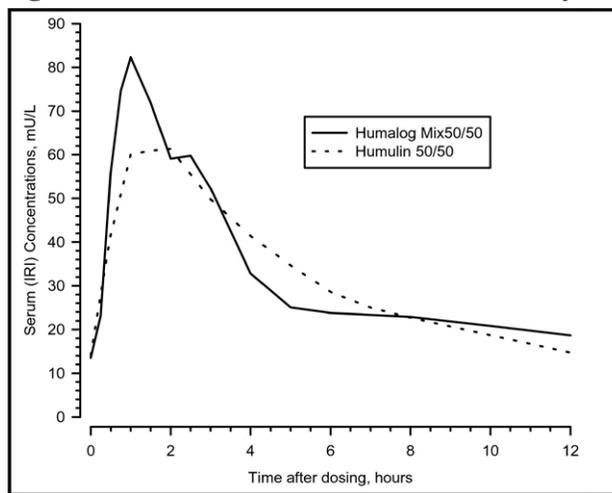
37 In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits
38 gluconeogenesis, and promotes the conversion of excess glucose into fat.

39 Insulin lispro, the rapid-acting component of Humalog Mix50/50, has been shown to be
40 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same
41 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
42 shorter duration.

43 Pharmacokinetics

44 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
45 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix50/50, is
46 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
47 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
48 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
49 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
50 results were seen in patients with type 1 diabetes.

51
52 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
53 **Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.**



54
55
56 Humalog Mix50/50 has two phases of absorption. The early phase represents insulin lispro and
57 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
58 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous
59 doses (0.3 U/kg) of Humalog Mix50/50, peak serum concentrations were observed 45 minutes to
60 13.5 hours (median, 60 minutes) after dosing (*see* Figure 1). In patients with type 1 diabetes,
61 peak serum concentrations were observed 45 minutes to 120 minutes (median, 60 minutes) after
62 dosing. The rapid absorption characteristics of Humalog are maintained with Humalog Mix50/50
63 (*see* Figure 1).

64 Direct comparison of Humalog Mix50/50 and Humulin 50/50 was not performed. However, a
65 cross-study comparison shown in Figure 1 suggests that Humalog Mix50/50 has a more rapid
66 absorption than Humulin 50/50.

67 *Distribution* — Radiolabeled distribution studies of Humalog Mix50/50 have not been
68 conducted. However, the volume of distribution following injection of Humalog is identical to
69 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

70 *Metabolism* — Human metabolism studies of Humalog Mix50/50 have not been conducted.
71 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of
72 Humalog Mix50/50, is identical to that of Regular human insulin.

73 *Elimination* — Humalog Mix50/50 has two absorption phases, a rapid and a prolonged phase,
74 representative of the insulin lispro and insulin lispro protamine suspension components of the
75 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
76 be calculated after administration of Humalog Mix50/50 because of the prolonged insulin lispro
77 protamine suspension absorption.

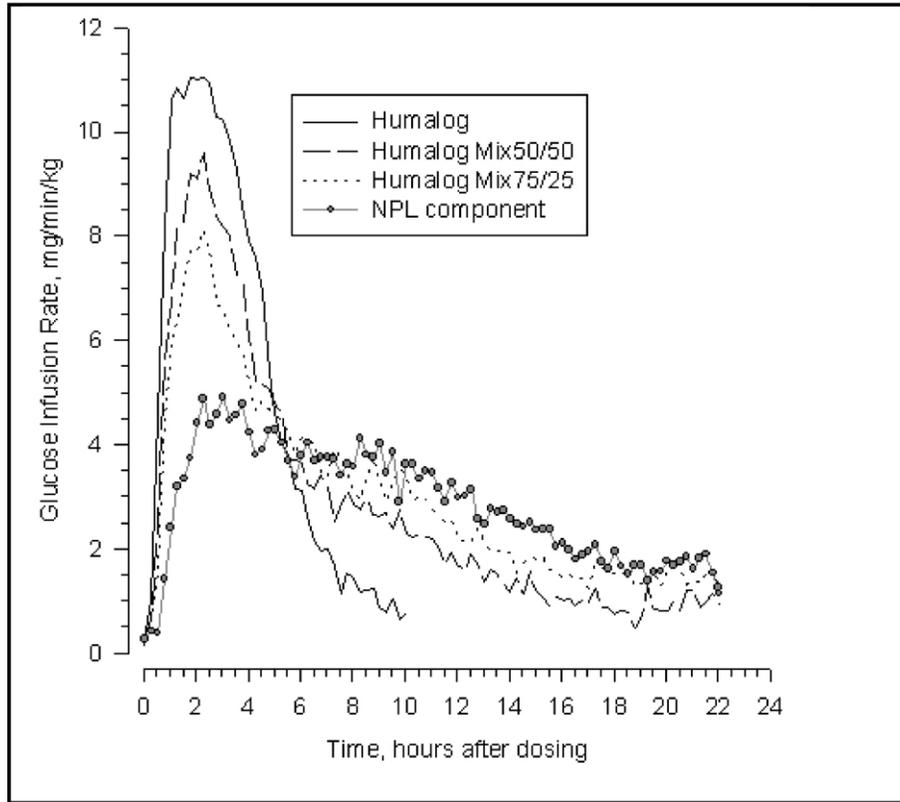
78 **Pharmacodynamics**

79 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
80 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
81 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
82 Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of
83 action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may
84 vary considerably in different individuals or within the same individual. The parameters of
85 Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in
86 Figures 2 and 3 should be considered only as general guidelines. The rate of insulin absorption
87 and consequently the onset of activity is known to be affected by the site of injection, exercise,
88 and other variables (*see General under PRECAUTIONS*).

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

95 Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed.
96 However, a cross-study comparison shown on Figure 3 suggests that Humalog Mix50/50 has a
97 duration of activity that is similar to Humulin 50/50.

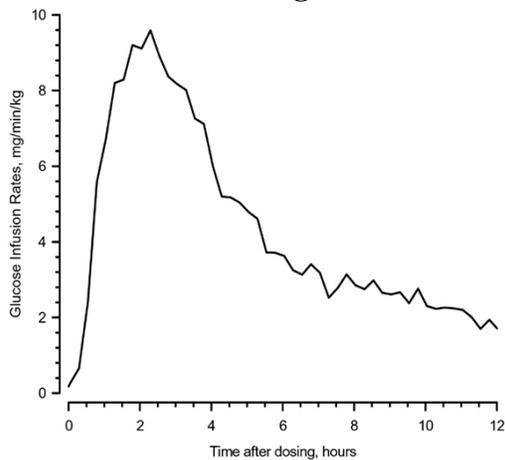
98
99 **Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection**
100 **of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine**
101 **Suspension (NPL Component) in 30 Nondiabetic Subjects.**



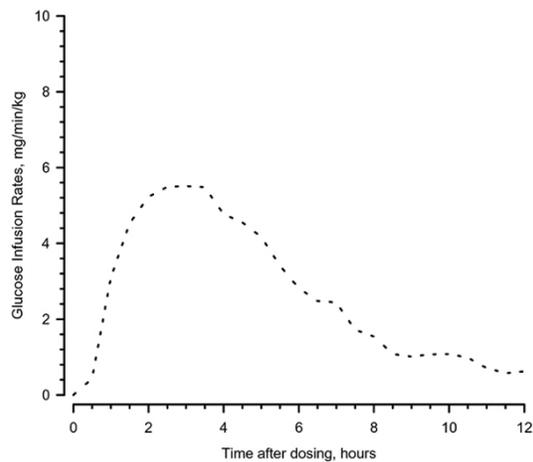
102
103
104
105
106
107
108

Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

**Figure 3a
Humalog Mix50/50**



**Figure 3b
Humulin 50/50**



109
110
111
112
113
114

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

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

115 Figure 3 is a comparison of the time activity profiles of Humalog Mix50/50 (*see* Figure 3a) and
116 of Humulin 50/50 (*see* Figure 3b) from two different studies.

117 Special Populations

118 *Age and Gender* — Information on the effect of age on the pharmacokinetics of
119 Humalog Mix50/50 is unavailable. Pharmacokinetic and pharmacodynamic comparisons
120 between men and women administered Humalog Mix50/50 showed no gender differences. In
121 large Humalog clinical trials, sub-group analysis based on age and gender demonstrated that
122 differences between Humalog and Regular human insulin in postprandial glucose parameters are
123 maintained across sub-groups.

124 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
125 Humalog Mix50/50 has not been studied.

126 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
127 Humalog Mix50/50 has not been studied.

128 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and
129 pharmacodynamics of Humalog Mix50/50 has not been studied. In large clinical trials, which
130 included patients with Body Mass Index up to and including 35 kg/m², no consistent differences
131 were observed between Humalog and Humulin[®] R with respect to postprandial glucose
132 parameters.

133 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
134 pharmacodynamics of Humalog Mix50/50 has not been studied. In a study of 25 patients with
135 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
136 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the
137 patients to insulin did change, with an increased response to insulin as the renal function
138 declined. Careful glucose monitoring and dose reductions of insulin, including
139 Humalog Mix50/50, may be necessary in patients with renal dysfunction.

140 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
141 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the
142 pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. However,
143 in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the
144 subcutaneous absorption or general disposition of Humalog when compared with patients with
145 no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption
146 and elimination when compared with Regular human insulin. Careful glucose monitoring and
147 dose adjustments of insulin, including Humalog Mix50/50, may be necessary in patients with
148 hepatic dysfunction.

149 INDICATIONS AND USAGE

150 Humalog Mix50/50, a mixture of 50% insulin lispro protamine suspension and 50% insulin
151 lispro injection (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for
152 the control of hyperglycemia. Based on cross-study comparisons of the pharmacodynamics of
153 Humalog Mix50/50 and Humulin 50/50, it is likely that Humalog Mix50/50 has a more rapid
154 onset of glucose-lowering activity compared with Humulin 50/50 while having a similar duration
155 of action. This profile is achieved by combining the rapid onset of Humalog with the
156 intermediate action of insulin lispro protamine suspension.

157 CONTRAINDICATIONS

158 Humalog Mix50/50 is contraindicated during episodes of hypoglycemia and in patients
159 sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS

160
161 **Humalog differs from Regular human insulin by its rapid onset of action as well as a**
162 **shorter duration of activity. Therefore, the dose of Humalog Mix50/50 should be given**
163 **within 15 minutes before a meal.**

164 **Hypoglycemia is the most common adverse effect associated with the use of insulins,**
165 **including Humalog Mix50/50. As with all insulins, the timing of hypoglycemia may differ**
166 **among various insulin formulations. Glucose monitoring is recommended for all patients**
167 **with diabetes.**

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

PRECAUTIONS

General

172
173 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
174 with the use of all insulins. Because of differences in the action of Humalog Mix50/50 and other
175 insulins, care should be taken in patients in whom such potential side effects might be clinically
176 relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using
177 potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).
178 Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated
179 with the use of all insulins.

180 As with all insulin preparations, the time course of Humalog Mix50/50 action may vary in
181 different individuals or at different times in the same individual and is dependent on site of
182 injection, blood supply, temperature, and physical activity.

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

186 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
187 with the administration of Humalog Mix50/50. Rapid changes in serum glucose concentrations
188 may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value.
189 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
190 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
191 beta-blockers, or intensified diabetes control.

192 **Renal Impairment** — As with other insulins, the requirements for Humalog Mix50/50 may be
193 reduced in patients with renal impairment.

194 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
195 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
196 Humalog Mix50/50, may be necessary.

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

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

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

209 **Information for Patients**

210 Patients should be informed of the potential risks and advantages of Humalog Mix50/50 and
211 alternative therapies. Patients should not mix Humalog Mix50/50 with any other insulin. They
212 should also be informed about the importance of proper insulin storage, injection technique,
213 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
214 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
215 hyperglycemia, and periodic assessment for diabetes complications.

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

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

221 For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read
222 the “INFORMATION FOR THE PATIENT” insert that accompanies the drug product and the
223 User Manual that accompanies the delivery device and re-read them each time the prescription is
224 renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen,
225 and properly dispose of needles. Patients should be advised not to share their Pens with others.

226 **Laboratory Tests**

227 As with all insulins, the therapeutic response to Humalog Mix50/50 should be monitored by
228 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
229 monitoring of long-term glycemic control.

230 **Drug Interactions**

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

234 Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity,
235 such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine
236 oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking
237 agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.
238 Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

239 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

245 **Pregnancy**

246 Teratogenic Effects — *Pregnancy Category B* — Reproduction studies with insulin lispro have
247 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
248 respectively, the average human dose (40 units/day) based on body surface area. The results have
249 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
250 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25 or

251 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
252 predictive of human response, this drug should be used during pregnancy only if clearly needed.

253 **Nursing Mothers**

254 It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many
255 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
256 exercised when Humalog Mix50/50 is administered to a nursing woman. Patients with diabetes
257 who are lactating may require adjustments in Humalog Mix50/50 dose, meal plan, or both.

258 **Pediatric Use**

259 Safety and effectiveness of Humalog Mix50/50 in patients less than 18 years of age have not
260 been established.

261 **Geriatric Use**

262 Clinical studies of Humalog Mix50/50 did not include sufficient numbers of patients
263 aged 65 and over to determine whether they respond differently than younger patients. In
264 general, dose selection for an elderly patient should take into consideration the greater frequency
265 of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
266 in this population.

267 **ADVERSE REACTIONS**

268 Clinical studies comparing Humalog Mix50/50 with human insulin mixtures did not
269 demonstrate a difference in frequency of adverse events between the two treatments.

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

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

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

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

274 **OVERDOSAGE**

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

281 **DOSAGE AND ADMINISTRATION**

282 **Table 1***

283 **Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study
284 Comparison)**
285

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 Mix50/50 is intended only for subcutaneous administration. Humalog Mix50/50 should not be administered intravenously. Dosage regimens of Humalog Mix50/50 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. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed. However, a cross-study comparison shown in Figure 3 suggests that Humalog Mix50/50 has a duration of activity that is similar to Humulin 50/50.

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 Mix50/50 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix50/50 should be inspected visually before use. Humalog Mix50/50 should be used only if it appears uniformly cloudy after mixing. Humalog Mix50/50 should not be used after its expiration date.

HOW SUPPLIED

Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] vials are available in the following package size:

100 units per mL (U-100)

10 mL vials

NDC 0002-7512-01 (VL-7512)

Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] Pen, a disposable insulin delivery device, is available in the following package size:

5 x 3 mL disposable insulin delivery devices

NDC 0002-8793-59 (HP-8793)

Storage — Humalog Mix50/50 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but not in the freezer. Do not use Humalog Mix50/50 if it has been frozen. Unrefrigerated [below 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain Humalog Mix50/50. Unrefrigerated [below 30°C (86°F)] Pens must be used within 10 days or be

321 discarded, even if they still contain Humalog Mix50/50. Protect from direct heat and light. See
 322 table below:
 323

	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	10 days	Until expiration date	10 days. Do not refrigerate.

324

325 Literature issued/revised Month dd, yyyy

326

Pen manufactured by

327

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

328

329

Vials manufactured by

330

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

331

332

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

333

334

Copyright © 2006, yyyy, Eli Lilly and Company. All rights reserved.

A1.0 NL PV 5791 AMP

PRINTED IN USA

335

A1.0 NL 4502 AMP

336

1
2
3

INFORMATION FOR THE PATIENT
10 mL Vial (1000 Units per vial)

4
5
6
7
8

HUMALOG[®] Mix50/50[™]
50% INSULIN LISPRO PROTAMINE SUSPENSION AND
50% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

9

WARNINGS

10
11
12
13
14
15

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[®] Mix50/50[™] [50% INSULIN LISPRO PROTAMINE SUSPENSION AND 50% INSULIN LISPRO INJECTION, (rDNA ORIGIN)] WITHIN 15 MINUTES BEFORE YOU EAT.

16
17
18
19
20

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG Mix50/50.

21
22
23
24

PATIENTS TAKING HUMALOG Mix50/50 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.

25

DIABETES

26
27
28

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.

29
30
31
32
33
34
35
36
37
38
39
40

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

41
42
43

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

HUMALOG Mix50/50

44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88

Description

Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce this human insulin analog. Humalog Mix50/50 is a mixture of 50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin). It is a longer-acting insulin combined with the more rapid onset of action of Humalog. The duration of activity is similar to that of Humulin[®] 50/50 and may last up to 16 hours following injection. The time course of Humalog Mix50/50 action, like that of other insulins, may vary in different individuals or at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity. Humalog Mix50/50 is a sterile suspension and is for subcutaneous injection only. It should not be used intravenously. The concentration of Humalog Mix50/50 is 100 units/mL (U-100).

Humalog Mix50/50 starts lowering blood glucose more quickly than Regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing Regular human insulin should be given 30 to 60 minutes before a meal.

Identification

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

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION. YOU SHOULD NOT MIX HUMALOG Mix50/50 WITH ANOTHER INSULIN.

Always check the carton and bottle label of the Humalog Mix50/50 you receive from your pharmacy to make sure it is the same as prescribed by your doctor.

Always check the appearance of your bottle of Humalog Mix50/50 before withdrawing each dose. Before each injection the Humalog Mix50/50 bottle must be carefully shaken or rotated several times to completely mix the insulin. Humalog Mix50/50 suspension should look uniformly cloudy or milky after mixing. If not, repeat the above step until contents are mixed.

Do not use Humalog Mix50/50:

- if the insulin substance (the white material) remains at the bottom of the bottle after mixing or
- if there are clumps in the insulin after mixing, or
- if solid white particles stick to the bottom or wall of the bottle, giving a frosted appearance.

If you see anything unusual in the appearance of Humalog Mix50/50 suspension in your bottle or notice your insulin requirements changing, talk to your doctor.

Storage

Not in-use (unopened): Humalog Mix50/50 bottles not in-use should be stored in a refrigerator, but not in the freezer.

In-use (opened): The Humalog Mix50/50 bottle you are currently using can be kept unrefrigerated, for **up to 28 days**, as long as it is kept at room temperature [below 86°F (30°C)] away from direct heat and light. The Humalog Mix50/50 bottle you are currently using must be discarded **28 days** after the first use, even if it still contains Humalog Mix50/50.

Do not use Humalog Mix50/50 after the expiration date stamped on the label or if it has been frozen.

INSTRUCTIONS FOR INSULIN VIAL USE

89

90 *Use with Syringes*91 **NEVER SHARE NEEDLES AND SYRINGES.**92 **Correct Syringe Type**93 Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL=1 cc).94 With Humalog Mix50/50, it is important to use a syringe that is marked for U-100 insulin
95 preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious
96 problems for you, such as a blood glucose level that is too low or too high.97 **Syringe Use**

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

99 Disposable syringes and needles should be used only once and then discarded by placing the
100 used needle in a puncture-resistant disposable container. Properly dispose of the puncture-
101 resistant container as directed by your Health Care Professional.102 **Preparing the Dose**

- 103 1. Wash your hands.
- 104 2. Carefully shake or rotate the bottle of insulin several times to completely mix the insulin.
- 105 3. Inspect the insulin. Humalog Mix50/50 suspension should look uniformly cloudy or
106 milky. Do not use Humalog Mix50/50 if you notice anything unusual in its appearance.
- 107 4. If using a new Humalog Mix50/50 bottle, flip off the plastic protective cap, but **do not**
108 remove the stopper. Wipe the top of the bottle with an alcohol swab.
- 109 5. Draw an amount of air into the syringe that is equal to the Humalog Mix50/50 dose. Put
110 the needle through rubber top of the Humalog Mix50/50 bottle and inject the air into the
111 bottle.
- 112 6. Turn the Humalog Mix50/50 bottle and syringe upside down. Hold the bottle and syringe
113 firmly in one hand and shake gently.
- 114 7. Making sure the tip of the needle is in the Humalog Mix50/50 suspension, withdraw the
115 correct dose of Humalog Mix50/50 into the syringe.
- 116 8. Before removing the needle from the Humalog Mix50/50 bottle, check the syringe for air
117 bubbles. If bubbles are present, hold the syringe straight up and tap its side until the
118 bubbles float to the top. Push the bubbles out with the plunger and then withdraw the
119 correct dose.
- 120 9. Remove the needle from the bottle and lay the syringe down so that the needle does not
121 touch anything.

122 **Injection Instructions**

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

133

DOSAGE

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

135 Because each patient's diabetes is different, this schedule has been individualized for you. Your

136 usual dose of Humalog Mix50/50 may be affected by changes in your diet, activity, or work

137 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things
138 that may affect your Humalog Mix50/50 dose are:

139 **Illness**

140 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
141 Even if you are not eating, you will still require insulin. You and your doctor should establish a
142 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
143 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

144 **Pregnancy**

145 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
146 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
147 are nursing a baby, talk to your doctor. Humalog Mix50/50 has not been tested in pregnant or
148 nursing women.

149 **Medication**

150 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
151 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
152 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
153 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
154 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
155 Professional may be aware of these and other medications that may affect your diabetes control.
156 Therefore, always discuss any medications you are taking with your doctor.

157 **Exercise**

158 Exercise may lower your body's need for insulin during and for some time after the physical
159 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
160 involves the area of injection site (for example, the leg should not be used for injection just prior
161 to running). Discuss with your doctor how you should adjust your insulin regimen to
162 accommodate exercise.

163 **Travel**

164 When traveling across more than 2 time zones, you should talk to your doctor concerning
165 adjustments in your insulin schedule.

166 **COMMON PROBLEMS OF DIABETES**

167 **Hypoglycemia (Low Blood Sugar)**

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

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

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

207 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

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

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

213 In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in
 214 DKA (a life-threatening emergency). The first symptoms of DKA usually come on gradually,
 215 over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite,

216 and fruity odor on the breath. With DKA, blood and urine tests show large amounts of glucose
217 and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected,
218 prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss
219 of consciousness, or death. Therefore, it is important that you obtain medical assistance
220 immediately.

221 **Lipodystrophy**

222 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
223 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
224 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
225 the problem.

226 **Allergy**

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

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

236 **ADDITIONAL INFORMATION**

237 Information about diabetes may be obtained from your diabetes educator.

238 Additional information about diabetes and Humalog Mix50/50 can be obtained by calling The
239 Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

240 Patient Information issued/revised Month dd, yyyy

241 **Vials manufactured by**
242 **Eli Lilly and Company, Indianapolis, IN 46285, USA**

243

Copyright © 2006, yyyy, Eli Lilly and Company. All rights reserved.

A1.0 NL 5801 AMP

PRINTED IN USA

244

1
2
3

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

4
5
6
7
8

**HUMALOG[®] Mix50/50[™] Pen
50% INSULIN LISPRO PROTAMINE SUSPENSION AND
50% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)**

9

WARNINGS

10
11
12
13
14
15

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[®] Mix50/50[™] [50% INSULIN LISPRO PROTAMINE SUSPENSION AND 50% INSULIN LISPRO INJECTION, (rDNA ORIGIN)] WITHIN 15 MINUTES BEFORE YOU EAT.

16
17
18
19
20

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG Mix50/50.

21
22
23
24

PATIENTS TAKING HUMALOG Mix50/50 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.

25
26
27

TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE INSULIN DELIVERY DEVICE USER MANUAL AND THIS “INFORMATION FOR THE PATIENT” INSERT BEFORE USING THIS PRODUCT.

28
29
30
31
32
33
34

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 TOO MUCH OR TOO LITTLE INSULIN (*see also* INSTRUCTIONS FOR INSULIN PEN USE section).

35

DIABETES

36
37
38

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.

39
40
41
42
43

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 your 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

44 that if your pre-meal glucose levels are consistently above 130 mg/dL, bedtime glucose levels
45 are consistently above 160 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, you should
46 talk to your doctor. A change in your diabetes therapy may be needed. If your blood tests
47 consistently show below-normal glucose levels, you should also let your doctor know. Proper
48 control of your diabetes requires close and constant cooperation with your doctor. Despite
49 diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and
50 take your insulin injections as prescribed by your doctor.

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

54 HUMALOG Mix50/50

55 Description

56 Humalog [insulin lispro injection, USP (rDNA origin)] is made by a special
57 non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically
58 altered to produce this human insulin analog. Humalog Mix50/50 is a mixture of 50% insulin
59 lispro protamine suspension and 50% insulin lispro injection (rDNA origin). It is a longer-acting
60 insulin combined with the more rapid onset of action of Humalog. The duration of activity is
61 similar to that of Humulin 50/50 and may last up to 16 hours following injection. The time
62 course of Humalog Mix50/50 action, like that of other insulins, may vary in different individuals
63 or at different times in the same individual, based on dose, site of injection, blood supply,
64 temperature, and physical activity. Humalog Mix50/50 is a sterile suspension and is for
65 subcutaneous injection only. It should not be used intravenously. The concentration of
66 Humalog Mix50/50 is 100 units/mL (U-100).

67 Humalog Mix50/50 starts lowering blood glucose more quickly than Regular human insulin,
68 allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast,
69 mixtures containing Regular human insulin should be given 30 to 60 minutes before a meal.

70 Identification

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

73 **DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND**
74 **DIRECTION. YOU SHOULD NOT MIX HUMALOG Mix50/50 WITH ANOTHER**
75 **INSULIN.**

76 **The Humalog Mix50/50 Pen is available in boxes of 5 disposable insulin delivery devices**
77 **(“insulin Pens”). The Humalog Mix50/50 Pen is not designed to allow any other insulin to**
78 **be mixed in its cartridge, or for the cartridge to be removed.**

79 Always check the carton and Pen label of the Humalog Mix50/50 you receive from your
80 pharmacy to make sure it is the same as prescribed by your doctor.

81 Always check the appearance of Humalog Mix50/50 suspension in your insulin Pen before
82 using. A cartridge of Humalog Mix50/50 contains a small glass bead to assist in mixing. Roll the
83 Pen between the palms 10 times (*see* Figure 1). Holding the Pen by one end, invert it
84 180° slowly 10 times to allow the small glass bead to travel the full length of the cartridge with
85 each inversion (*see* Figure 2).

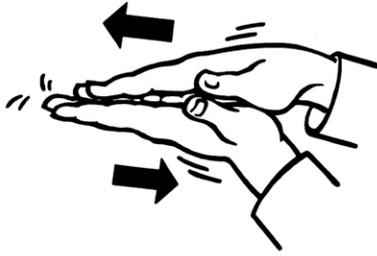


Figure 1.

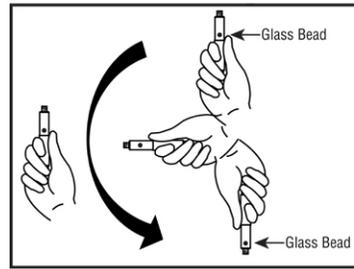


Figure 2.

86 Humalog Mix50/50 suspension should look uniformly cloudy or milky after mixing. If not,
 87 repeat the above steps until contents are mixed. Pens containing Humalog Mix50/50 suspension
 88 should be examined frequently.

89 Do not use Humalog Mix50/50:

- 90 • if the insulin substance (the white material) remains visibly separated from the liquid
- 91 after mixing or
- 92 • if there are clumps in the insulin after mixing, or
- 93 • if solid white particles stick to the bottom or wall of the cartridge, giving a frosted
- 94 appearance.

95 If you see anything unusual in the appearance of the Humalog Mix50/50 suspension in your
 96 Pen or notice your insulin requirements changing, talk to your doctor.

97 Never attempt to remove the cartridge from the Humalog Mix50/50 Pen. Inspect the cartridge
 98 through the clear cartridge holder.

100 Storage

101 **Not in-use (unopened):** Humalog Mix50/50 Pens not in-use should be stored in a refrigerator,
 102 but not in the freezer.

103 **In-use (opened):** Humalog Mix50/50 Pens in-use should **NOT** be refrigerated but should be
 104 kept at room temperature [below 86°F (30°C)] away from direct heat and light. The Humalog
 105 Mix50/50 Pen you are currently using must be discarded **10 days** after the first use, even if it still
 106 contains Humalog Mix50/50.

107 **Do not use Humalog Mix50/50 after the expiration date stamped on the label or if it has**
 108 **been frozen.**

109 INSTRUCTIONS FOR INSULIN PEN USE

110 **It is important to read, understand, and follow the instructions in the Insulin Delivery**
 111 **Device User Manual before using. Failure to follow instructions may result in getting too**
 112 **much or too little insulin. The needle must be changed and the Pen must be primed before**
 113 **each injection to make sure the Pen is ready to dose. Performing these steps before each**
 114 **injection is important to confirm that insulin comes out when you push the injection**
 115 **button, and to remove air that may collect in the insulin cartridge during normal use.**

116 **Every time you inject:**

- 117 • Use a new needle.
- 118 • Prime to make sure the Pen is ready to dose.
- 119 • Make sure you got your full dose.

120 **NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.**

121 PREPARING FOR INJECTION

- 122 1. Wash your hands.

- 123 2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the
 124 previous injection site. The usual sites of injection are abdomen, thighs, and arms.
 125 3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for
 126 injection.
 127 4. After injecting the dose, pull the needle out and apply gentle pressure over the injection
 128 site for several seconds. **Do not rub the area.**
 129 5. After the injection, remove the needle from the Humalog Mix50/50 Pen. **Do not reuse**
 130 **needles.**
 131 6. Place the used needle in a puncture-resistant disposable container and properly dispose of
 132 the puncture-resistant container as directed by your Health Care Professional.

133 **DOSAGE**

134 Your doctor has told you which insulin to use, how much, and when and how often to inject it.
 135 Because each patient's diabetes is different, this schedule has been individualized for you. Your
 136 usual dose of Humalog Mix50/50 may be affected by changes in your diet, activity, or work
 137 schedule. Carefully follow your doctor's instructions to allow for these changes. Other things
 138 that may affect your Humalog Mix50/50 dose are:

139 **Illness**

140 Illness, especially with nausea and vomiting, may cause your insulin requirements to change.
 141 Even if you are not eating, you will still require insulin. You and your doctor should establish a
 142 sick day plan for you to use in case of illness. When you are sick, test your blood glucose
 143 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

144 **Pregnancy**

145 Good control of diabetes is especially important for you and your unborn baby. Pregnancy may
 146 make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or
 147 are nursing a baby, talk to your doctor. Humalog Mix50/50 has not been tested in pregnant or
 148 nursing women.

149 **Medication**

150 Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising
 151 activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin
 152 requirements may be reduced in the presence of drugs with blood-glucose-lowering activity,
 153 such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol,
 154 certain antidepressants and some kidney and blood pressure medicines. Your Health Care
 155 Professional may be aware of these and other medications that may affect your diabetes control.
 156 Therefore, always discuss any medications you are taking with your doctor.

157 **Exercise**

158 Exercise may lower your body's need for insulin during and for some time after the physical
 159 activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise
 160 involves the area of injection site (for example, the leg should not be used for injection just prior
 161 to running). Discuss with your doctor how you should adjust your insulin regimen to
 162 accommodate exercise.

163 **Travel**

164 When traveling across more than 2 time zones, you should talk to your doctor concerning
 165 adjustments in your insulin schedule.

166 **COMMON PROBLEMS OF DIABETES**

167 **Hypoglycemia (Low Blood Sugar)**

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

- 170 1. **Missing or delaying meals.**

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

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

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

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

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

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

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

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

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

207 **Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)**

208 Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

209 Hyperglycemia can be brought about by any of the following:

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

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

221 **Lipodystrophy**

222 Rarely, administration of insulin subcutaneously can result in lipoatrophy (seen as an apparent
 223 depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either
 224 of these conditions, talk to your doctor. A change in your injection technique may help alleviate
 225 the problem.

226 **Allergy**

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

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

236 **ADDITIONAL INFORMATION**

237 Information about diabetes may be obtained from your diabetes educator.

238 Additional information about diabetes and Humalog Mix50/50 can be obtained by calling The
 239 Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

240 Patient Information issued/revised Month dd, yyyy

241 **Pens manufactured by**
 242 **Eli Lilly and Company, Indianapolis, IN 46285, USA**

243

Copyright © 2005, yyyy, Eli Lilly and Company. All rights reserved.

A1.0 NL 4512 AMP

PRINTED IN USA

244