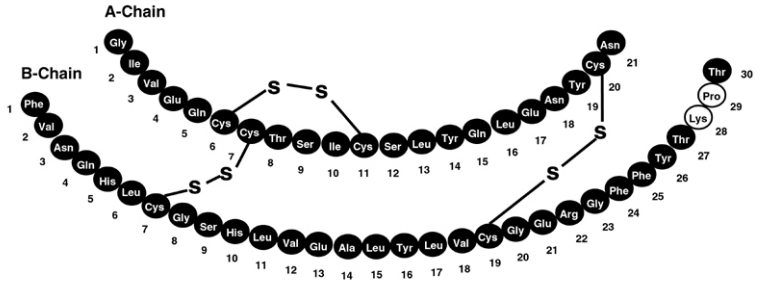
A1.0 NL 5791 AMP
A1.0 NL 4502 AMP

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.

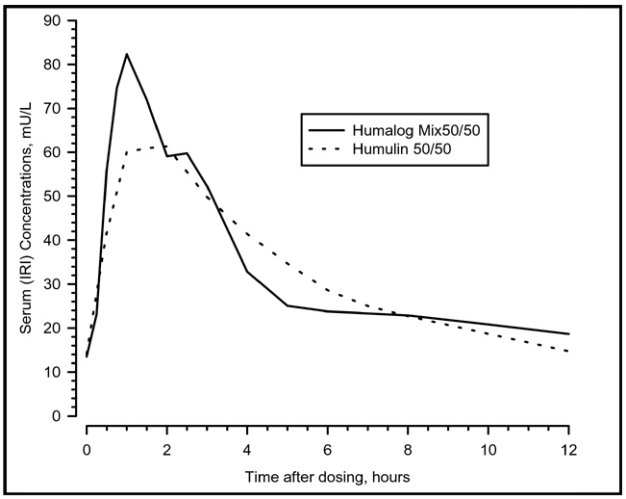
In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Insulin lispro, the rapid-acting component of Humalog Mix50/50, 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.

Pharmacokinetics

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

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



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

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

Distribution — Radiolabeled distribution studies of Humalog Mix50/50 have not been conducted. However, 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 of Humalog Mix50/50 have not been conducted. Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of Humalog Mix50/50, is identical to that of Regular human insulin.

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

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. The early onset of activity of Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2 and 3 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).

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

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

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

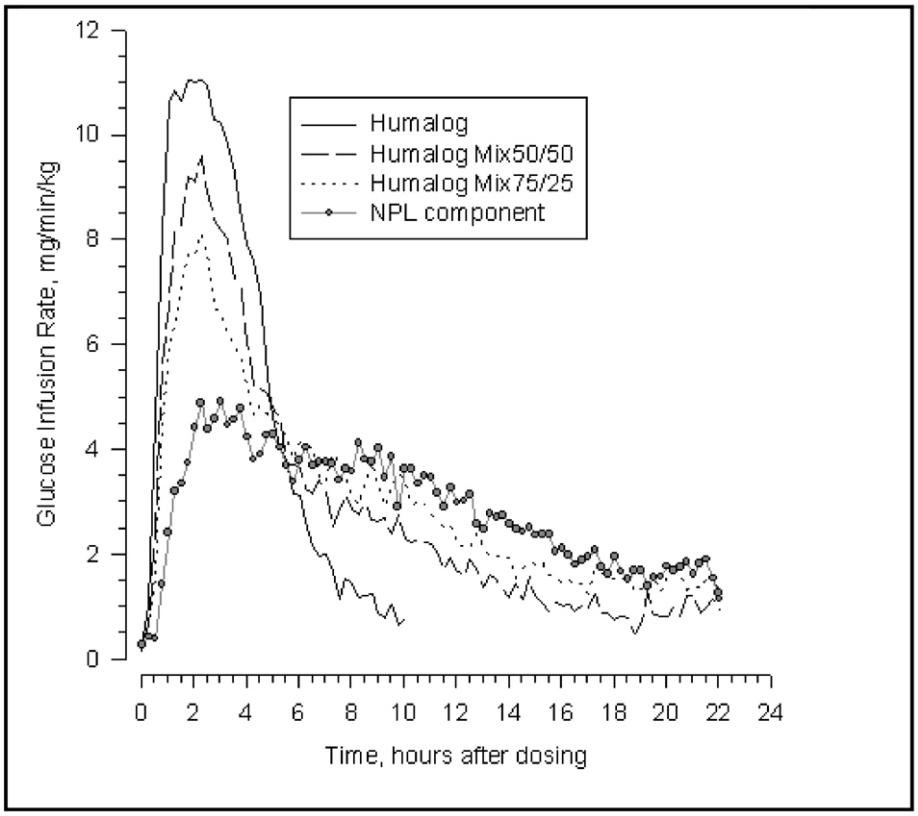


Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

Figure 3a
Humalog Mix50/50

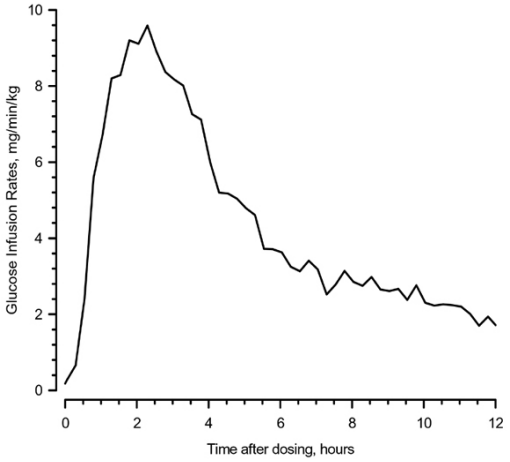
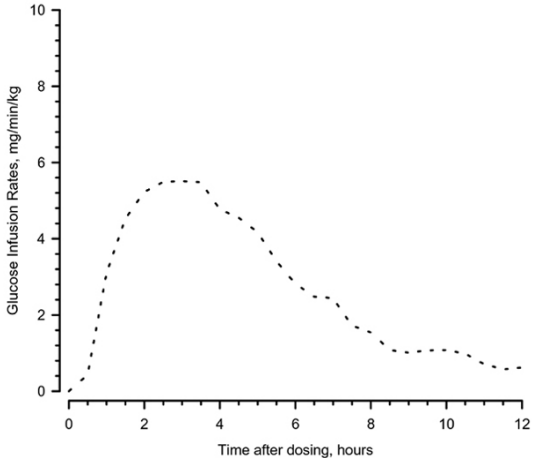


Figure 3b
Humulin 50/50



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).

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

Special Populations

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

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

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

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. In large clinical trials, which included patients with Body Mass Index up to and including 35 kg/m^2, no consistent differences were observed between Humalog and Humulin® R with respect to postprandial glucose parameters.

Renal Impairment — The effect of renal impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. 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 Mix50/50, 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. The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. However, 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 Mix50/50, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Humalog Mix50/50 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 Mix50/50 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix50/50. 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 Mix50/50 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 Mix50/50 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 Mix50/50. 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 Mix50/50 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 Mix50/50, 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.

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

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

Information for Patients

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

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

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

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

Laboratory Tests

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

Drug Interactions

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Table 1*
Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study Comparison)

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)

Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

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

Humalog 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

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

	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.**

Literature issued/revised Month dd, yyyy

Pen manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France
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Lilly France, F-67640 Fegersheim, France

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