Important information on discontinuation of original Prefilled Pen containing Humalog® Mix75/25™

As of January 1, 2011, Eli Lilly and Company will no longer make the original Prefilled Pen containing Humalog® Mix75/25™. However, your same Humalog Mix75/25 insulin is currently available in another pen option, Humalog® Mix75/25™ KwikPen™. This is a different pen device only. The insulin inside remains the same.

Availability of the original Prefilled Pen containing Humalog Mix75/25 will depend on the amount your pharmacy has in stock. We anticipate that the pens will start to become unavailable in some areas beginning in summer 2010.

Eli Lilly and Company is honored that you and your doctor have trusted Humalog Mix75/25 insulin to help in the management of diabetes. We want to make every effort to continue to keep you up-to-date on all changes and advances in diabetes care.

Original Prefilled Pen containing Humalog® Mix75/25™ to be discontinued
(75% insulin lispro protamine suspension,
25% insulin lispro injection [rDNA origin])

Humalog® Mix75/25™ KwikPen™ available
(75% insulin lispro protamine suspension,
25% insulin lispro injection [rDNA origin])

Why is Eli Lilly and Company no longer making the original Prefilled Pen containing Humalog Mix75/25?

We introduced Humalog Mix75/25 KwikPen in early 2008 and have since decided to stop making the original Prefilled Pen containing Humalog Mix75/25. Humalog Mix75/25 remains available in Humalog Mix75/25 KwikPen and other delivery options.

How long will the original Prefilled Pen containing Humalog Mix75/25 be available?

Availability of the pen will depend on the amount your pharmacy has in stock. We anticipate that the pens will start to become unavailable in some areas beginning in summer 2010. You will need to talk to your pharmacist or your doctor to determine whether or not you will need a new prescription for Humalog Mix75/25 KwikPen.

What should I do with the original Prefilled Pens containing Humalog Mix75/25 I still have?

If stored properly, you can continue to use the original Prefilled Pen containing Humalog Mix75/25 until the expiration date stamped on the carton and pen.

What is Humalog Mix75/25 KwikPen?

Just like the original Prefilled Pen containing Humalog Mix75/25, Humalog Mix75/25 KwikPen is a prefilled insulin delivery device (“insulin pen”) containing 3 mL (300 units) of U-100 Humalog Mix75/25.

How does Humalog Mix75/25 KwikPen work?

You can inject from 1 to 60 units of insulin in one injection—you simply dial your dose one unit at a time. If you dial too many units, you can dial backward to correct the dose without wasting any insulin. Visit **www.Humalog.com/PenInfo** to view a demonstration of how a KwikPen works.

Will Humalog Mix75/25 KwikPen be covered by my insurance?

For most insurance plans, Humalog Mix75/25 KwikPen is available for the same co-pay as the original Prefilled Pen containing Humalog Mix75/25. Since plans may vary, it is important to check with your plan if you have additional questions about your coverage.

How do I store Humalog Mix75/25 KwikPen?

Just like the original Prefilled Pen containing Humalog Mix75/25, there is no refrigeration needed after the first use. Please refer to the Patient Information accompanying this document for complete information regarding storage.

What needles can be used with Humalog Mix75/25 KwikPen?

You can continue to use the same BD (Becton Dickinson) needles with Humalog Mix75/25 KwikPen that you used with the original Prefilled Pen containing Humalog Mix75/25.

What should I do if I have questions about my Humalog Mix75/25 options?

If you have questions or concerns about the discontinuation of the original Prefilled Pen containing Humalog Mix75/25 or about Humalog Mix75/25 KwikPen, please talk to your doctor or pharmacist, visit **www.Humalog.com/PenInfo**, or contact Eli Lilly and Company at **1-800-LillyRx (1-800-545-5979)**.

Indication

Humalog Mix75/25 is for use in patients with diabetes to control high blood sugar.

Select Safety Information:

- Starting or changing insulin therapy should be done cautiously and only under medical supervision
- Low blood sugar is the most common adverse effect associated with insulins, including Humalog Mix75/25
- Humalog Mix75/25 is a mixture of fast-acting and longer-acting insulin. Humalog Mix75/25 starts working faster than other insulins that contain regular human insulin. Humalog Mix75/25 should be taken within 15 minutes before a meal

Please see additional Important Safety Information on back and full Prescribing Information, including Patient Information attached.

Humalog® mix 75/25™

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

Lilly

Important Safety Information About Humalog® Mix75/25™

Who should use Humalog Mix75/25?

Humalog Mix75/25 (75% insulin lispro protamine suspension, 25% insulin lispro injection [rDNA origin]) is for use in patients with diabetes to control high blood sugar.

What is some important safety information I should know about Humalog Mix75/25?

Starting or changing insulin therapy should be done cautiously and only under medical supervision.

Humalog Mix75/25 should not be used during episodes of low blood sugar (hypoglycemia) or if you are allergic to anything in Humalog Mix75/25.

Humalog Mix75/25 is a mixture of fast-acting and longer-acting insulin. Humalog Mix75/25 starts working faster than other insulins that contain regular human insulin. Humalog Mix75/25 should be taken within 15 minutes before a meal. Check your blood sugar levels as told by your healthcare professional.

The safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not been established. There are no adequate and well-controlled clinical studies of the use of Humalog Mix75/25 in pregnant or nursing women.

Low Blood Sugar

Low blood sugar is the most common adverse effect associated with insulins, including Humalog Mix75/25. Low blood sugar can happen suddenly, and symptoms may be different for each person and may change from time to time. Know your symptoms of low blood sugar. Severe low blood sugar can cause seizures and be life threatening. Follow your healthcare professional's instructions for treating low blood sugar. Talk to your healthcare professional if low blood sugar is a problem for you.

Other Side Effects

Other potential side effects associated with the use of insulins include: low blood potassium, weight gain, changes in fat tissue at the injection site, and allergic reactions. Allergic reactions can happen at the site of injection and over the whole body. Whole-body allergic reactions are less common, but may be life threatening.

For other important information, see accompanying full Prescribing Information, including Patient Information attached.

Humalog mix 75/25™ KwikPen™

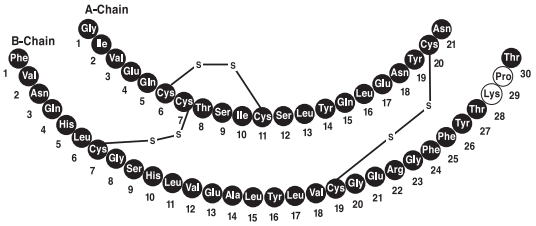
75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)

HI65277 0610 PRINTED IN USA

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.

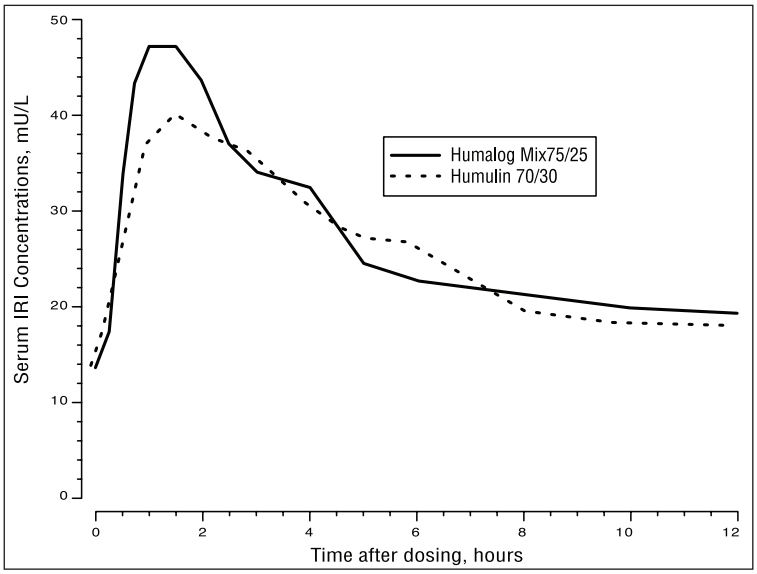
Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 units, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg Metacresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and Water for Injection. Humalog Mix75/25 has a 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 of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

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

Pharmacokinetics—*Absorption*—Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix75/25, is absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1 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 Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.



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

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

Distribution—Radiolabeled distribution studies of Humalog Mix75/25 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 Mix75/25 have not been conducted. Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of Humalog Mix75/25, is identical to that of Regular human insulin.

Elimination—Humalog Mix75/25 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 Mix75/25 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 Mix75/25 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 Mix75/25), may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix75/25 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 Mix75/25.

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

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

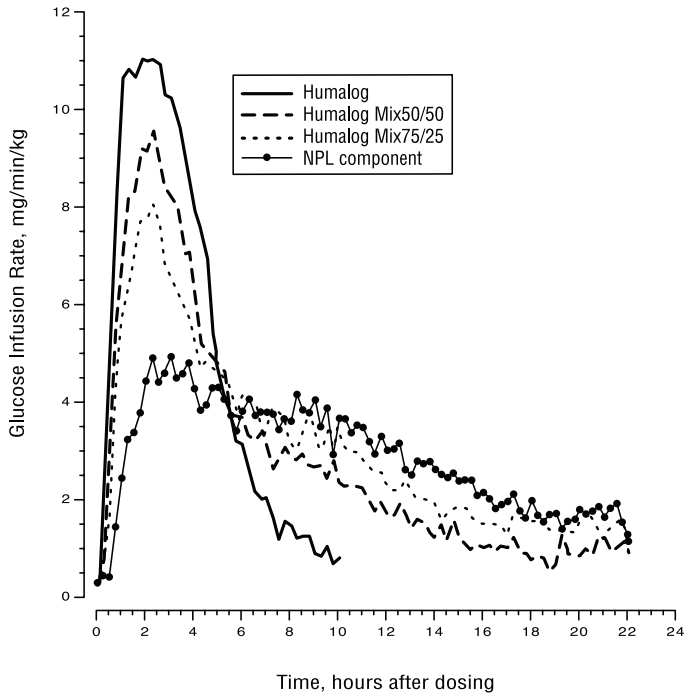


Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in Nondiabetic Subjects.

Figure 3a
Humalog Mix75/25

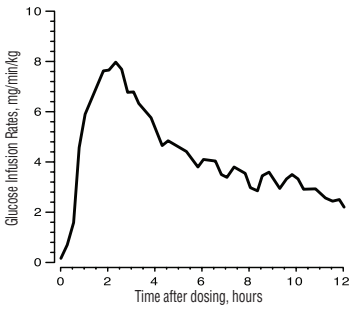
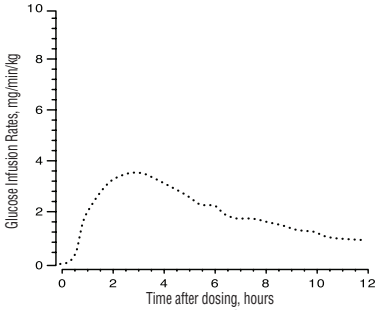


Figure 3b
Humulin 70/30



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 Mix50/50, Humalog Mix75/25, and insulin lispro protamine suspension (NPL component).

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

Special Populations—*Age and Gender*—Information on the effect of age on the pharmacokinetics of Humalog Mix75/25 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and women administered Humalog Mix75/25 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 Mix75/25 has not been studied.

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

Obesity—The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of Humalog Mix75/25 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— The effect of renal impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix75/25 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 Mix75/25, may be necessary in patients with renal dysfunction.

HUMALOG® Mix75/25™ 75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) PV 5551 AMP

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 Mix75/25 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 Mix75/25, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE: Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering activity compared with Humulin 70/30 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 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.

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 Mix75/25 and alternative therapies. Patients should not mix Humalog Mix75/25 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 Patient Information leaflet for information on normal appearance, 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 Patient Information leaflet 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 to a stream of insulin, 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 Mix75/25 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 that increase insulin sensitivity or have 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 Mix75/25 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog Mix75/25 dose, meal plan, or both.

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

Geriatric Use—Clinical studies of Humalog Mix75/25 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 Mix75/25 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 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 healthcare provider 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)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

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

Storage—Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but not in the freezer. Do not use Humalog Mix75/25 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 Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used within 10 days or be discarded, even if they still contain Humalog Mix75/25. 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 and KwikPen (prefilled)	10 days	Until expiration date	10 days. **Do not refrigerate.**

Literature revised March 16, 2009

PV 5551 AMP PRINTED IN USA

Lilly

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

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

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HUMALOG® Mix75/25™ 75% INSULIN LISPRO PROTAMINE
SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) PV 5551 AMP

Patient Information

Humalog® (HU-ma-log) Mix75/25™

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

Important

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

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

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

What is Humalog Mix75/25?

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

Humalog Mix75/25 comes in:

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

Who should not take Humalog Mix75/25?

Do not take Humalog Mix75/25 if:

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

Tell your healthcare provider:

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

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

How should I use Humalog Mix75/25?

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

- **Use Humalog Mix75/25 exactly as prescribed by your healthcare provider.**
- **Humalog Mix75/25 starts working faster than other insulins that contain regular human insulin.** Inject Humalog Mix75/25 fifteen minutes or less before a meal. If you do not plan to eat within 15 minutes, delay the injection until the correct time (15 minutes before eating).
- **Check your blood sugar levels as told by your healthcare provider.**
- **Mix Humalog Mix75/25 well before each use.** For Humalog Mix75/25 in a vial, carefully shake or rotate the vial until completely mixed. For prefilled pens, carefully follow the User Manual for instructions on mixing the pen. Humalog Mix75/25 should be cloudy or milky after mixing well.
- Look at your Humalog Mix75/25 before each injection. If it is not evenly mixed or has solid particles or clumps in it, do not use. Return it to your pharmacy for new Humalog Mix75/25.
- **Inject your dose of Humalog Mix75/25 under the skin of your stomach area, upper arm, upper leg, or buttocks. Never inject Humalog Mix75/25 into a muscle or vein.**
- **Change (rotate) your injection site with each dose.**
- **Your insulin needs may change because of:**
  - illness
  - stress
  - other medicines you take
  - changes in eating
  - physical activity changes

Follow your healthcare provider's instructions to make changes in your insulin dose.

- **Never mix Humalog Mix75/25 in the same syringe with other insulin products.**
- **Never use Humalog Mix75/25 in an insulin pump.**
- **Always carry a quick source of sugar to treat low blood sugar, such as glucose tablets, hard candy, or juice.**

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

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

- hunger
- dizziness
- feeling shaky or shakiness
- lightheadedness
- sweating
- irritability
- headache
- fast heartbeat
- confusion

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

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

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

How should I store Humalog Mix75/25?

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

After starting use (open):

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

General information about Humalog Mix75/25

Use Humalog Mix75/25 only to treat your diabetes. Do not share it with anyone else, even if they also have diabetes. It may harm them.

This leaflet summarized the most important information about Humalog Mix75/25. If you would like more information about Humalog Mix75/25 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Humalog Mix75/25 that is written for health professionals.

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

What are the ingredients in Humalog Mix75/25?

Active ingredients: insulin lispro protamine suspension and insulin lispro.

Inactive ingredients: protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, zinc oxide (zinc ion), phenol and water for injection.

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