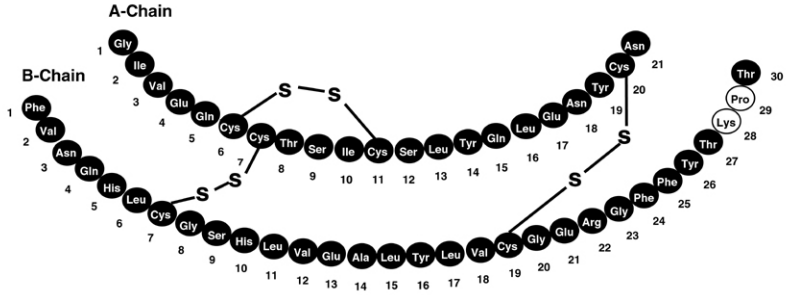
HUMALOG® Mix75/25™
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

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.

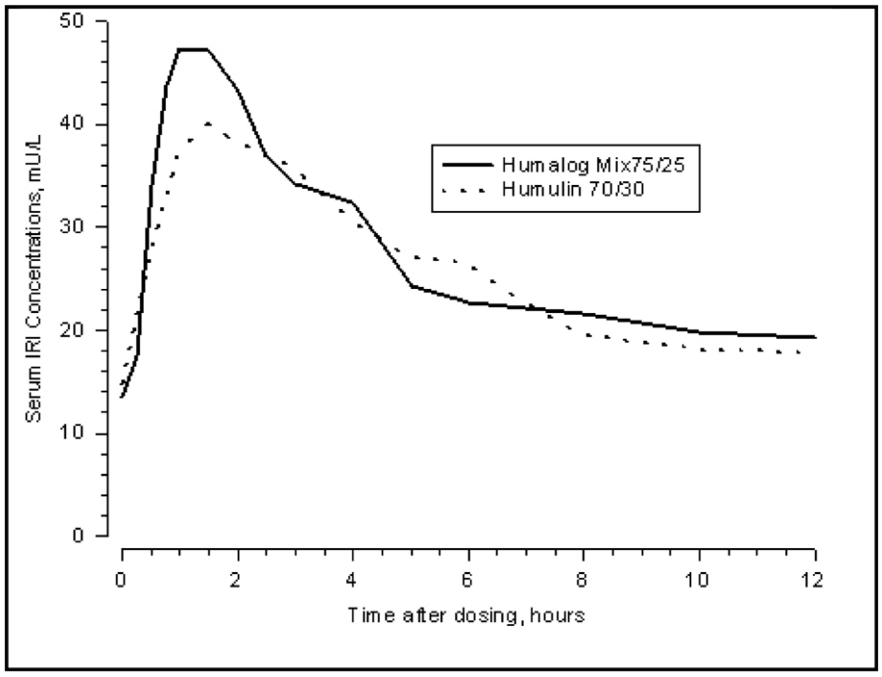


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.

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.

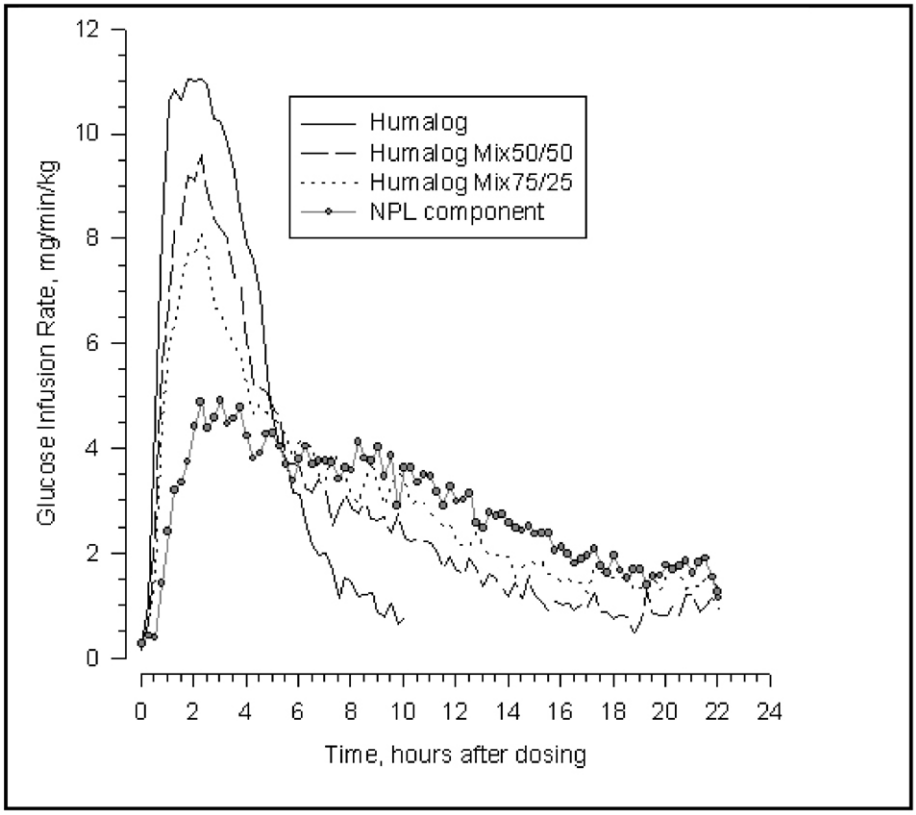


Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

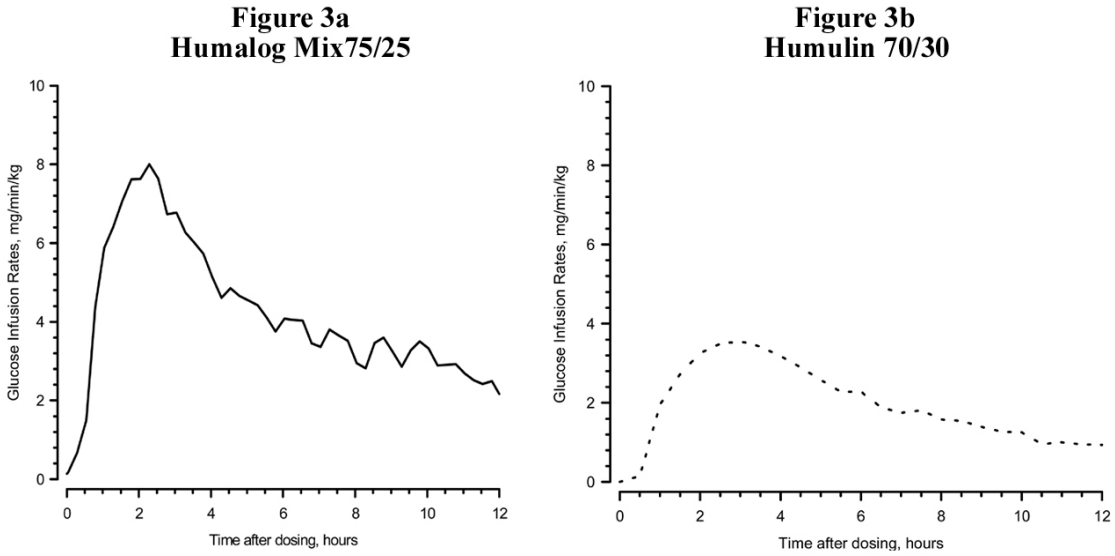


Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in Nondiabetic Subjects.

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/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 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.

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 Month dd, yyyy

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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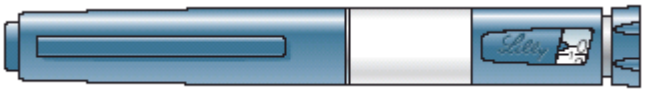


Disposable Insulin Delivery Device
User Manual

Lilly

Introduction

Humalog® Mix75/25™ KwikPen™ ("Pen") is designed for ease of use. It is a disposable insulin delivery device ("insulin Pen") containing 3 mL (300 units) of U-100 Humalog® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)] insulin. You can inject from 1 to 60 units of Humalog Mix75/25 in one injection. You can dial your dose one unit at a time. If you dial too many units, you can dial backwards to correct the dose without wasting any insulin.

Before using Humalog Mix75/25 KwikPen, read the entire manual completely and follow the directions carefully. If you do not follow these directions completely, you may get too much or too little insulin.

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

DO NOT USE your KwikPen if any part appears broken or damaged. Contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or your healthcare professional for a replacement Pen. Always carry an extra Pen in case yours is lost or damaged.

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

Preparing Humalog Mix75/25 KwikPen

Important Notes

- Read and follow the directions provided in the *Patient Information Leaflet*.
- Check the label on your Pen before each injection for the expiration date and to make sure you are using the correct type of insulin.

- Your healthcare professional has prescribed the best type of insulin for you. **Any changes in insulin therapy should be made only under medical supervision.**
- **KwikPen** is recommended for use with Becton, Dickinson and Company pen needles.
- Be sure the needle is completely attached to the Pen before use.
- Do not share your Pen or needles.
- Keep these directions for future reference.

Frequently Asked Questions about Preparing Humalog Mix75/25 KwikPen

- **What should my insulin look like?** Humalog Mix75/25 should be cloudy or milky after mixing well. If your Humalog Mix75/25 has solid particles or clumps in it, return it to your pharmacy for a replacement. Be sure to refer to your *Patient Information Leaflet* for the appearance of your specific insulin.
- **Why should I use a new needle for each injection?** This will help ensure sterility. If needles are reused, you may get the wrong amount of insulin, a clogged needle or a jammed Pen.
- **What should I do if I am not sure how much insulin remains in my cartridge?** Hold the Pen with the needle end pointing down. The scale on the clear Cartridge Holder shows an estimate of the number of units remaining. **These numbers should NOT be used for measuring an insulin dose.**

Priming Humalog Mix75/25 KwikPen

Important Notes

- **Prime every time.** The Pen must be primed to a stream of insulin before each injection to make sure the Pen is ready to dose.
- **If you do not prime, you may get too much or too little insulin.**

Frequently Asked Questions about Priming

- **Why should I prime my KwikPen before each dose?**
    1. Ensures that the Pen is ready to dose.
    2. Confirms that a stream of insulin comes out of the tip of the needle when you push the Dose Knob in.
    3. Removes air that may collect in the needle or insulin cartridge during normal use.

- **What should I do if I cannot completely push in the Dose Knob when priming the KwikPen?**
    1. Attach a new needle.
    2. Prime the Pen.

- **What should I do if I see an air bubble in the cartridge?** You need to prime the Pen. Remember, do not store the Pen with the needle attached as this may cause air bubbles to collect in the insulin cartridge. A small air bubble will not affect your dose and you can continue to take your dose as usual.

Injecting Your Dose

Important Notes

- Follow the instructions for sanitary injection technique recommended by your healthcare professional.
- Make sure you receive your complete dose by pushing and holding the dose knob in and **count to 5 slowly** before removing the needle. If insulin is leaking from the Pen you may not have held it in your skin long enough.
- The Pen will not allow you to dial more than the number of units left in the Pen.
- If your dose is greater than the number of units left in the Pen, you may either inject the amount remaining in your current Pen and then use a new Pen to complete your dose OR inject the full dose with a new Pen.
- Do not attempt to inject your insulin by *turning* the Dose Knob. You will NOT receive your insulin by turning the Dose Knob. **You must PUSH the Dose Knob straight in for the dose to be delivered.**
- Do not attempt to change the dose while injecting.
- The directions regarding needle handling are not intended to replace local, healthcare professional or institutional policies.
- Remove the needle after completing each injection.

Frequently Asked Questions about Injecting Your Dose

- **Why is it difficult to push the Dose Knob when I try to inject?**
    1. Your needle may be clogged. Try attaching a new needle. When you do this you may see insulin come out of the needle. Then prime the Pen.
    2. Pressing the Dose Knob quickly may make the Dose Knob harder to push. Pressing the Dose Knob more slowly may make it easier.
    3. Using a larger diameter needle will make it easier to push the Dose Knob during your injection. See your healthcare professional to determine which needle size is best for you.
    4. If the Dose Knob continues to be difficult to push after following the steps above, try the steps below under “What should I do if my **KwikPen** is jammed?”.

- **What should I do if my KwikPen is jammed?** Your Pen may be jammed if it is difficult to inject a dose or dial a dose. To clear the jam:
    1. Attach a new needle. When you do this you may see insulin come out of the needle.
    2. Prime the Pen.
    3. Dial your dose and inject.
    4. If the Dose Knob is still difficult to push, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979).

- **Why is insulin leaking from the needle after I finished injecting my dose?** You may have removed the needle from your skin too quickly.
    1. Make sure you see a 0 in the Dose Window to confirm you received the complete dose.
    2. For the next dose, **push and hold** the Dose Knob in and **count to 5 slowly** before removing the needle.

- **What should I do if my dose is dialed and the Dose Knob is accidentally pushed in without a needle attached?**
    1. Dial back to zero.
    2. Attach a new needle. When you do this you may see insulin come out of the needle.
    3. Prime the Pen.
    4. Dial your dose and inject.

- **What should I do if I dial a wrong dose (too high or too low)?** Turn the Dose Knob backward or forward to correct the dose before injecting.

- **What should I do if I see insulin leaking from the KwikPen needle while dialing the dose or correcting the dose?** Do not inject the dose because you may not get your complete dose. Dial the Pen down to zero and prime the Pen again (see "Priming **Humalog Mix75/25 KwikPen**" steps 2 B-D). Dial your dose and inject.

- **What should I do if my full dose cannot be dialed?** The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the cartridge you will not be able to dial past 25. Do not attempt to dial past this point. You may either:
    1. Inject the partial dose and then inject the remaining dose using a new Pen.
       or
    2. Inject the full dose with a new Pen.

- **Why can I not dial the dose to use the small amount of insulin that remains in my cartridge?** The Pen is designed to deliver at least 300 units of insulin. The Pen design prevents the cartridge from being completely emptied because the small amount of insulin that remains in the cartridge cannot be delivered.

Storage and Disposal

Important Notes

- Refer to the *Patient Information Leaflet* for complete insulin storage instructions.
- Pens that have not been used should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen.

- Do not store the Pen with the needle attached. If the needle remains attached, insulin may leak from the Pen, insulin may dry inside the needle causing the needle to clog, or air bubbles may form inside the cartridge.
- The Pen you are currently using should be kept at room temperature and away from heat and light.
- Keep the Pen out of the reach of children.
- Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.
- Dispose of used Pens as instructed by your healthcare professional and without the needle attached.

Use the space below to keep track of how long you should use each Pen in the carton. Once you start using a **KwikPen** it must be thrown out after the number of days listed in your *Patient Information Leaflet*, even if there is insulin remaining in the Pen. Record the date you start using a Pen, find the number of days that **KwikPen** should be used in the *Patient Information Leaflet* and determine the date the Pen should be thrown out. Record the dates in the space provided below.

Example:

Pen 1 - First used on _____ (Date) + Number of days you should use **KwikPen** (from *Patient Information Leaflet*) = Throw out on _____ (Date)

Pen 1 - First used on _____ (Date) Throw out on _____ (Date)
Pen 2 - First used on _____ (Date) Throw out on _____ (Date)
Pen 3 - First used on _____ (Date) Throw out on _____ (Date)
Pen 4 - First used on _____ (Date) Throw out on _____ (Date)
Pen 5 - First used on _____ (Date) Throw out on _____ (Date)

If you have any questions or problems with your Humalog Mix75/25 KwikPen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or your healthcare professional for assistance.

For more information on **Humalog Mix75/25 KwikPen** and insulin, please visit our website at **www.humalog.com**

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

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

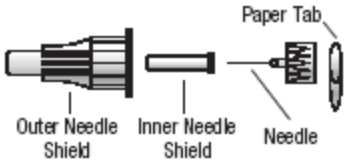
Getting Ready

Make sure you have the following items:

- ❑ **Humalog® Mix75/25™ KwikPen™**
- ❑ **New Pen Needle**
- ❑ **Alcohol Swab**

Pen Parts KwikPen, and Needle∗ Assembly ∗sold separately

Pen Needle Parts (Needles Not Included)



KwikPen Parts

Follow these instructions for each injection

1. Preparing Humalog Mix75/25 KwikPen

A.

Pull Pen Cap to remove.

Be sure to check your insulin for:

- Type
- Expiration date
- Appearance

Use an alcohol swab to wipe the Rubber Seal on the end of the Cartridge Holder.

B.

For Humalog Mix75/25 insulin:

Gently roll the Pen ten times and invert the Pen ten times. The insulin should look evenly mixed.

C.

Remove Paper Tab from Outer Needle Shield.

D.

Push capped needle **straight** onto the Pen.

Screw needle on until secure.

2. Priming Humalog Mix75/25 KwikPen

Caution: If you do not prime before each injection, you may get too much or too little insulin.

A.

Pull off Outer Needle Shield. **Do not** throw away.

Pull off Inner Needle Shield and throw away.

B.

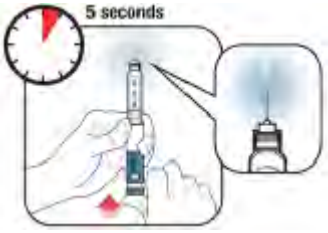
Dial 2 Units by turning the Dose Knob.

C.

Point Pen up.

Tap Cartridge Holder to collect air at top.

D.



With needle pointing up, push Dose Knob in until it stops and 0 is seen in the Dose Window.

Hold Dose Knob in and **count to 5 slowly.**

Priming is complete when a stream of insulin appears from the needle tip **and** you have **counted to 5 slowly.**

If a stream of insulin does not appear, repeat priming steps 2 B-D up to four times. If the Pen still does not prime, change the needle and repeat the priming steps above.

Note: If you do not see a stream of insulin from the tip of the needle and the Dose Knob becomes hard to push, then change the needle and prime the Pen.

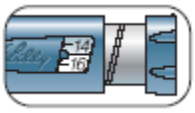
3. Injecting Your Dose

A.

Turn Dose Knob to the number of units you need to inject. If you dial too many units, you can correct the dose by dialing backwards.

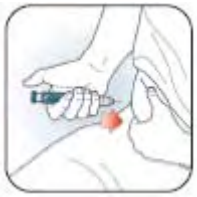
Example: 10 units shown.

Example: 15 units shown.



The **even** numbers are printed on the dial. The **odd** numbers, after the number one, are shown as full lines.

B.



Insert needle into skin using injection technique recommended by your healthcare professional.

Place your thumb on the Dose Knob and push firmly until the Dose Knob stops.

To deliver the full dose, hold Dose Knob in and **count to 5 slowly.** Remove needle from skin.

Note: Check to make sure you see 0 in the Dose Window to confirm you received the complete dose.

Note: The Pen will not allow you to dial more than the number of units left in the Pen.

C.

Carefully replace the Outer Needle Shield.

Note: Remove the needle after each injection to keep air out of the cartridge. Do not store the Pen with the needle attached.

D.

Unscrew the capped needle and dispose of as directed by your healthcare professional.

Replace Pen Cap.

Literature revised October 28, 2011