

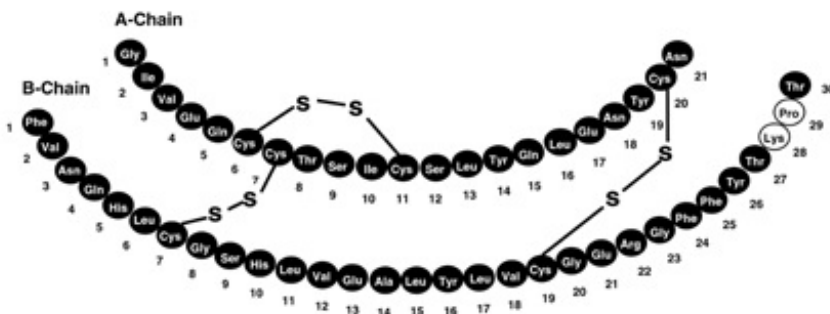
HUMALOG MIX75/25 - insulin lispro injection, suspension
HUMALOG MIX75/25 KWIKPEN - insulin lispro injection, suspension
Eli Lilly and Company

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.

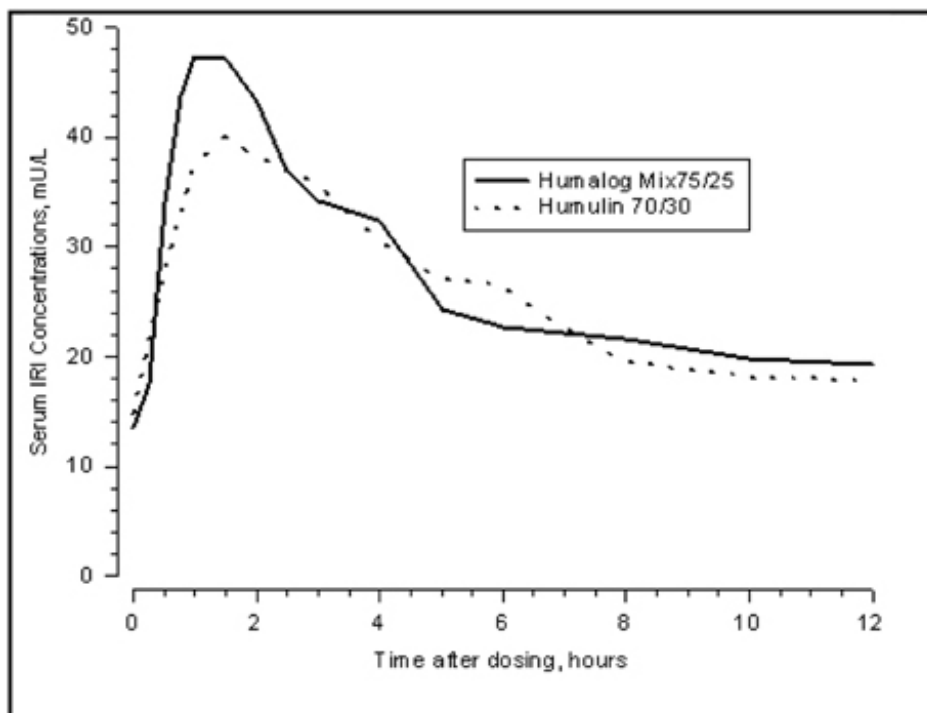


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.

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.

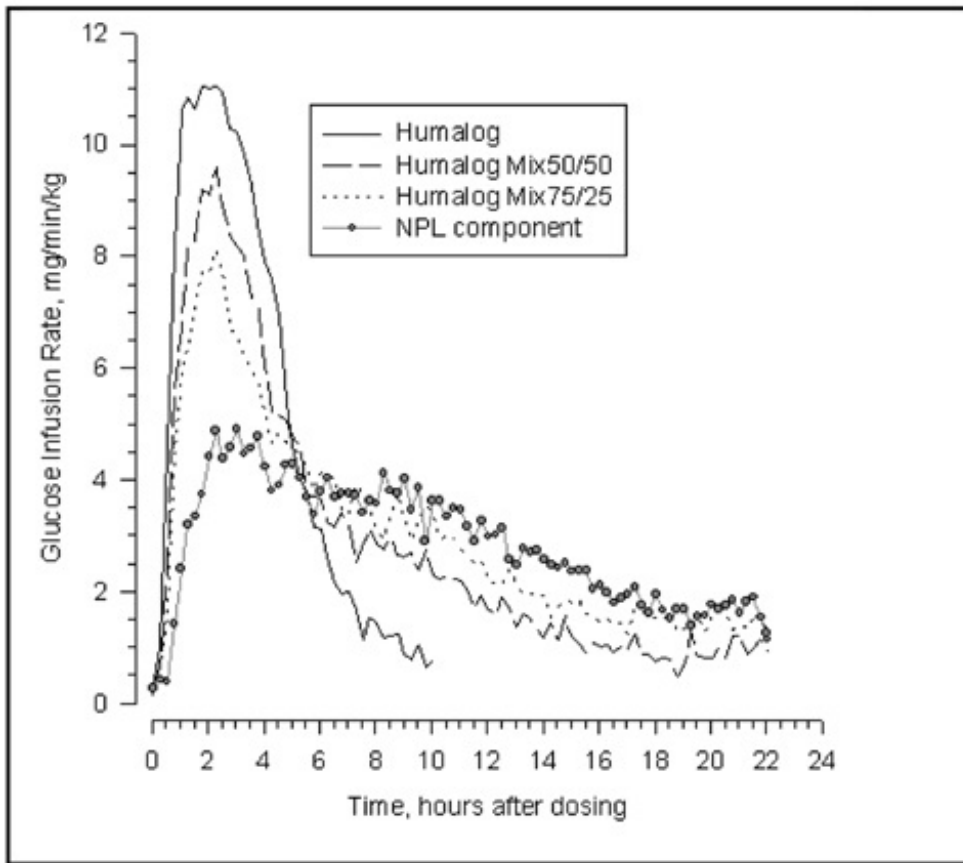
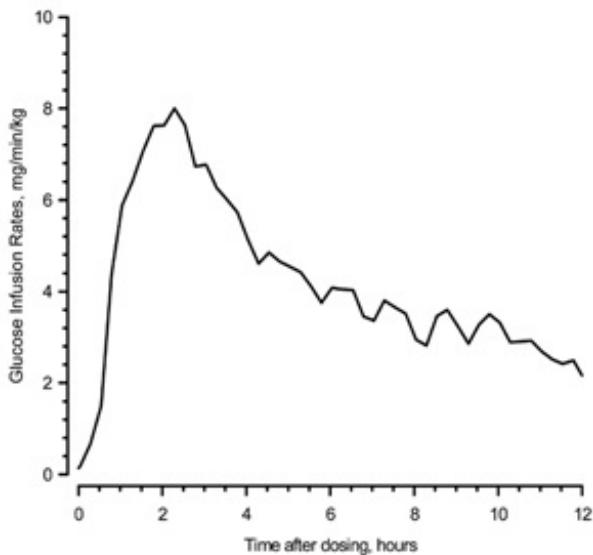


Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

**Figure 3a
Humalog Mix75/25**



**Figure 3b
Humulin 70/30**

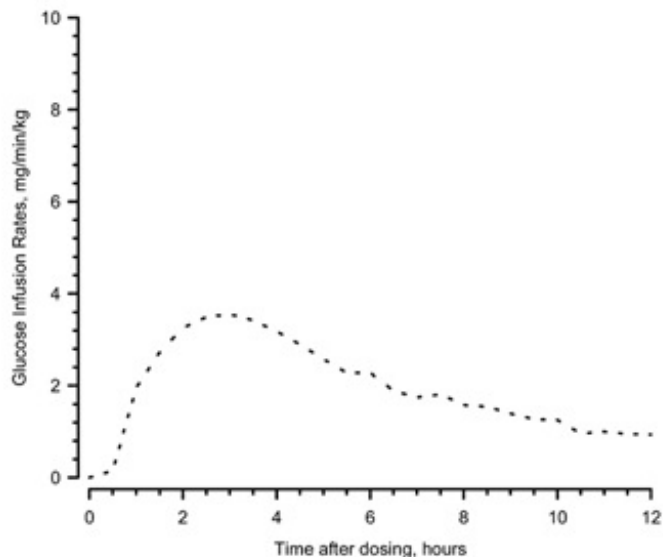


Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in Nondiabetic Subjects.

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/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.

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[®] Mix75/25[™] KwikPens[®] must never be shared between patients, even if the needle is changed. Patients using Humalog Mix75/25 vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

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.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists :

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including Humalog Mix75/25, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

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 (KwikPen®)	NDC 0002-8797-59 (HP-8797)

Each prefilled Humalog Mix75/25 KwikPen is for use by a single patient. Humalog Mix75/25 KwikPens must never be shared between patients, even if the needle is changed. Patients using Humalog Mix75/25 vials must never share needles or syringes with another person.

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)] 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 KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

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www.humalog.com

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Patient Information

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

Important:

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

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

Do not share your Humalog Mix75/25 KwikPen or syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

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.

What should I tell my healthcare provider before taking Humalog Mix75/25?

Before you use Humalog Mix75/25, tell your healthcare provider if you:

- **have liver or kidney problems or any other medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog Mix75/25.
- take any other medicines, especially ones commonly called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with Humalog Mix75/25.
- **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.
- **take other medicines, 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.**

- **Do not share your Humalog Mix75/25 KwikPen or syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.**
- **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.

Humalog Mix75/25 may cause serious side effects, including:

- **swelling of your hands and feet**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with Humalog Mix75/25 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with Humalog Mix75/25. Your healthcare provider should monitor you closely while you are taking TZDs with Humalog Mix75/25. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
 - shortness of breath
 - swelling of your ankles or feet
 - sudden weight gain

Treatment with TZDs and Humalog Mix75/25 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

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 other people, 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 healthcare providers.

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.

Patient Information revised: February 25, 2015

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

www.humalog.com

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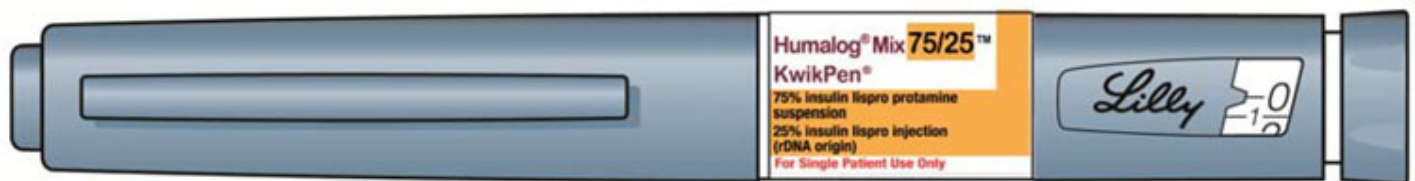
LOG7525-0001-PPI-20150225

Instructions for Use

HUMALOG[®] Mix75/25[™] KwikPen[®]

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

100 units/mL, 3 mL pen



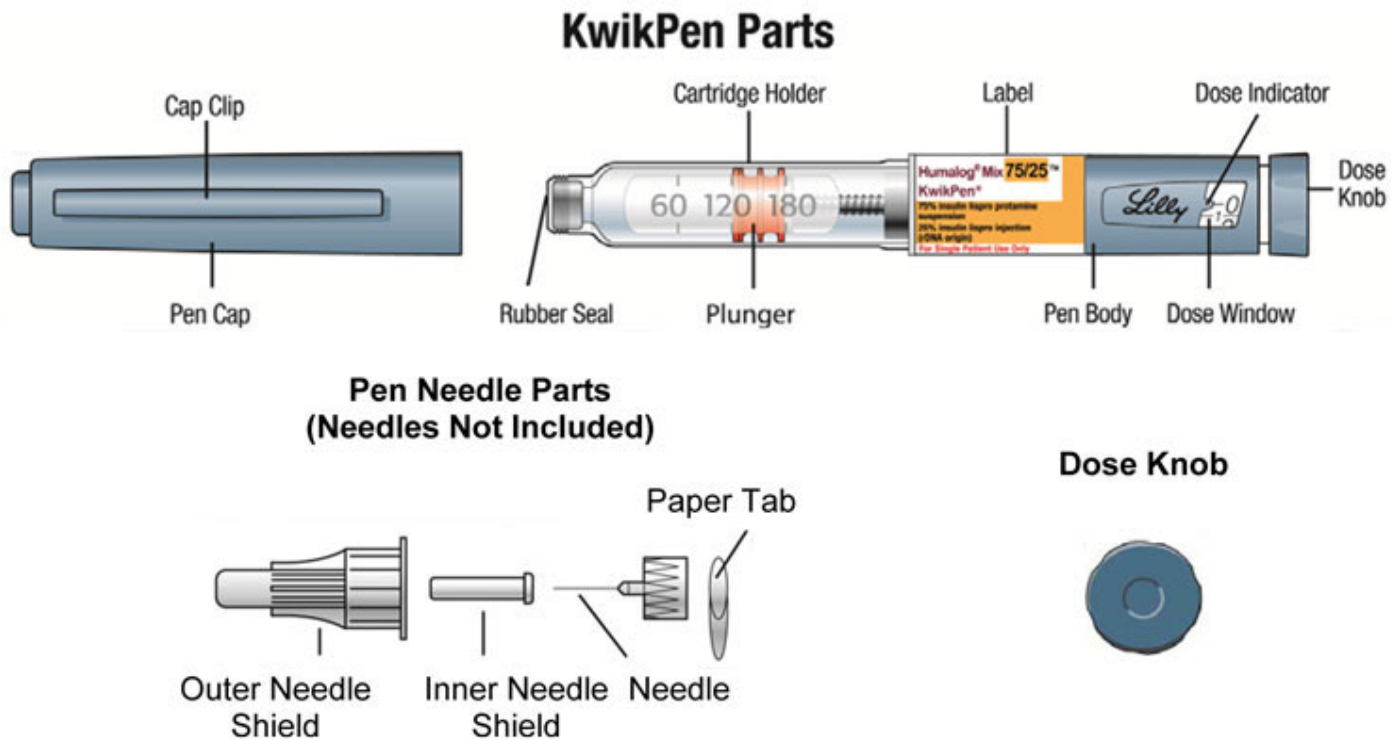
Read the Instructions for Use before you start taking HUMALOG Mix75/25 and each time you get another KwikPen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your HUMALOG Mix75/25 KwikPen with other people, even if the needle has been

changed. You may give other people a serious infection or get a serious infection from them.

HUMALOG® Mix75/25™ KwikPen® (“Pen”) is a disposable prefilled pen containing 300 units of HUMALOG Mix75/25. You can give yourself more than 1 dose from the Pen. Each turn (click) of the Dose Knob dials 1 unit of insulin. You can give from 1 to 60 units in a single injection. **If your dose is more than 60 units, you will need to give yourself more than 1 injection.** The Plunger only moves a little with each injection, and you may not notice that it moves. The Plunger will only reach the end of the cartridge when you have used all 300 units in the Pen.

This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.



How to recognize your HUMALOG Mix75/25 KwikPen

- Pen color: Dark blue
- Dose Knob: Dark blue
- Labels: White label with yellow stripe

Supplies you will need to give your injection

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

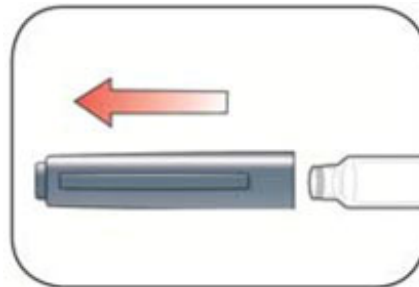
Preparing your Pen

- Wash your hands with soap and water.
- Check your Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the Label or for more than 10 days after you first start using the Pen.
- **Always use a new needle for each injection to help prevent infections and blocked needles. Do not reuse or share your needles with other people. You may give other people a serious**

infection or get a serious infection from them.

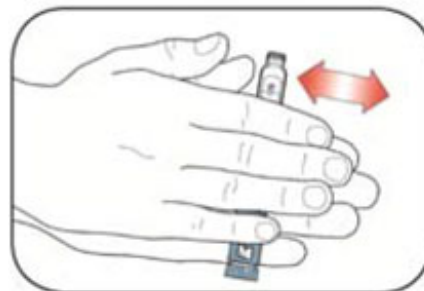
Step 1:

- Pull the Pen Cap straight off.
 - **Do not** remove the Pen Label.
- Wipe the Rubber Seal with an alcohol swab.
 - **Do not** attach the Needle before mixing.



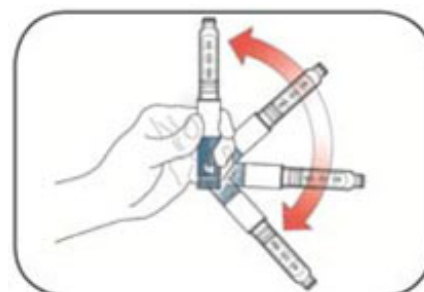
Step 2:

- Gently roll the Pen between your hands 10 times.



Step 3:

- Move the Pen up and down (invert) 10 times.
Mixing by rolling and inverting the Pen is important to make sure you get the right dose.



Step 4:

- **Check the liquid in the Pen.**
HUMALOG Mix75/25 should look white and cloudy after mixing. **Do not** use if it looks clear or has any lumps or particles in it.

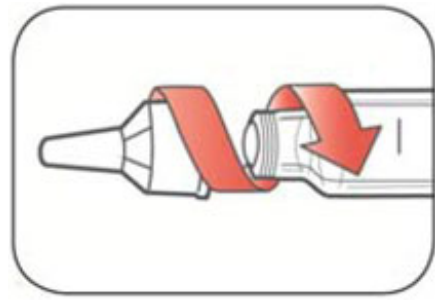
Step 5:

- **Select a new Needle.**
- Pull off the Paper Tab from the Outer Needle Shield.



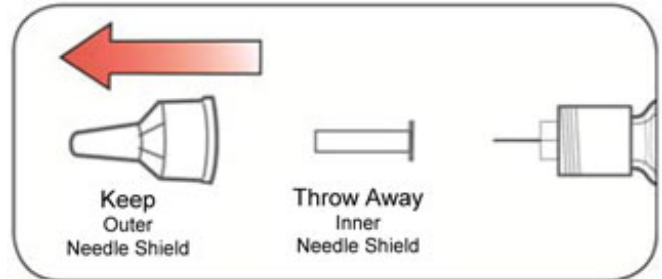
Step 6:

- Push the capped Needle straight onto the Pen and twist the Needle on until it is tight.



Step 7:

- Pull off the Outer Needle Shield. **Do not** throw it away.
- Pull off the Inner Needle Shield and throw it away.

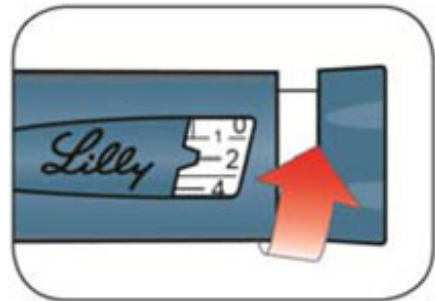


Priming your Pen**Prime before each injection.**

- Priming your Pen means removing the air from the Needle and Cartridge that may collect during normal use and ensures that the Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

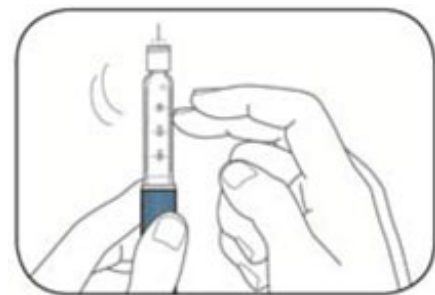
Step 8:

- To prime your Pen, turn the Dose Knob to select 2 units.



Step 9:

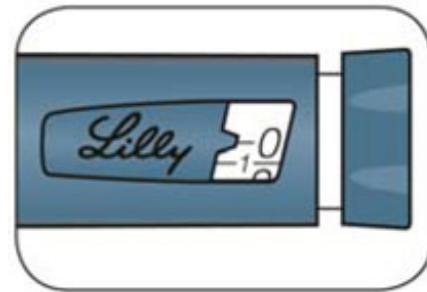
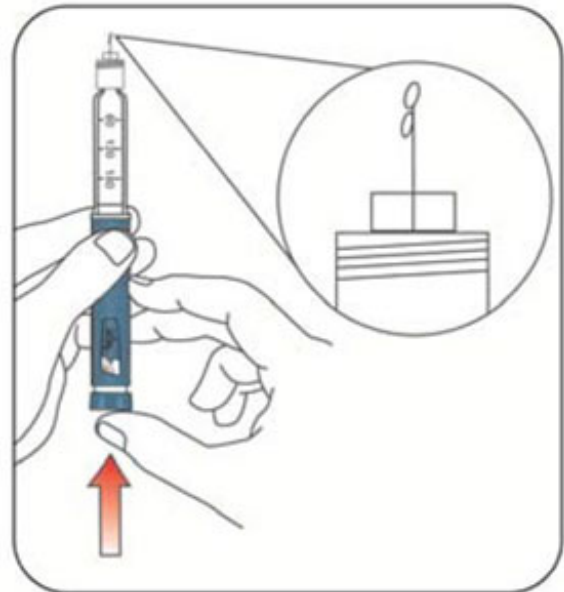
- Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.



Step 10:

- Continue holding your Pen with Needle pointing up. Push the Dose Knob in until it stops, and “0” is seen in the Dose Window. Hold the Dose Knob in and **count to 5 slowly**.
- You should see insulin at the tip of the Needle.
 - If you **do not** see insulin, repeat priming steps 8 to 10, no more than 4 times.
 - If you **still do not** see insulin, change the Needle and repeat priming steps 8 to 10.

Small air bubbles are normal and will not affect your dose.

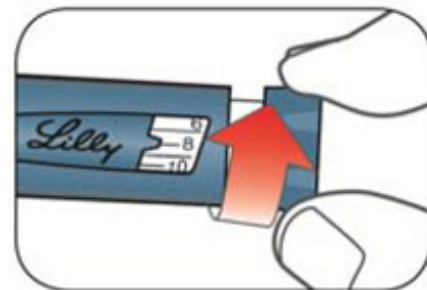


Selecting your dose

- You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give more than one injection.
 - If you need help with dividing up your dose the right way, ask your healthcare provider.
 - Use a new Needle for each injection and repeat the priming step.

Step 11:

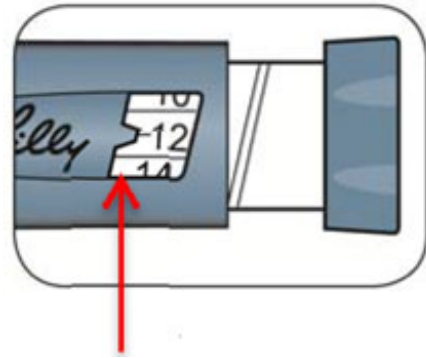
- Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.
 - The Pen dials 1 unit at a time.
 - The Dose Knob clicks as you turn it.
 - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to you getting too much insulin



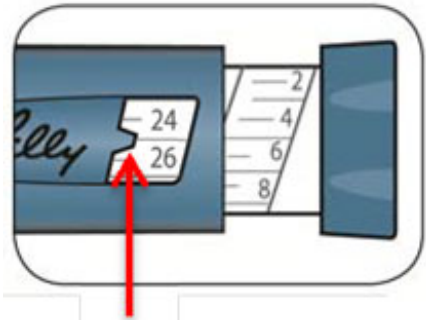
may lead to you getting too much insulin or not enough insulin.

- The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator.
- The **even** numbers (for example, 12) are printed on the dial.
- The **odd** numbers, (for example, 25) after the number 1, are shown as full lines.

- **Always check the number in the Dose Window to make sure you have dialed the correct dose.**



(Example: 12 units shown in the Dose Window)



(Example: 25 units shown in the Dose Window)

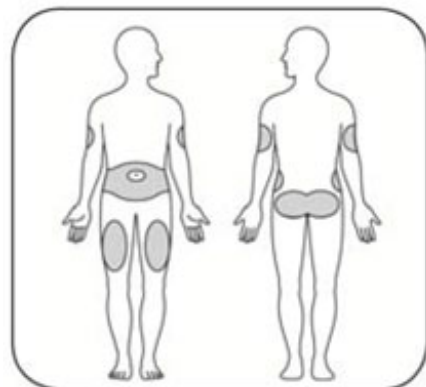
- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
 - inject the amount left in your Pen and then use a new Pen to give the rest of your dose, **or**
 - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you can not inject.

Giving your injection

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

Step 12:

- Choose your injection site.
HUMALOG Mix75/25 is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.
- Wipe your skin with an alcohol swab, and let your skin dry before you inject your dose.



Step 13:

- Insert the Needle into your skin.
- Push the Dose Knob all the way in.
- Continue to hold the Dose Knob in and **slowly**

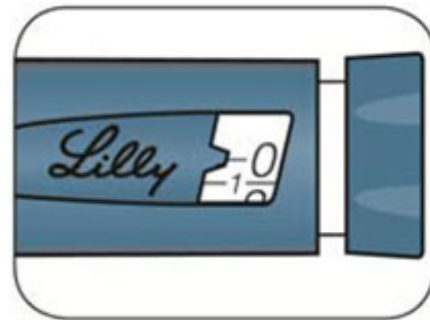
count to 5 before removing the Needle.



Do not try to inject your insulin by turning the Dose Knob. You will **not** receive your insulin by turning the Dose Knob.

Step 14:

- Pull the Needle out of your skin.
A drop of insulin at the Needle tip is normal. It will not affect your dose.
- Check the number in the Dose Window.
 - If you see “0” in the Dose Window, you have received the full amount you dialed.
 - If you do not see “0” in the Dose Window, do not redial. Insert the Needle into your skin and finish your injection.
 - If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat the injection.** Monitor your blood glucose as instructed by your healthcare provider.
 - If you normally need to give 2 injections for your full dose, be sure to give your second injection.



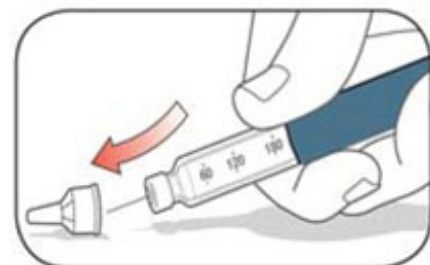
The Plunger only moves a little with each injection, and you may not notice that it moves.

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

After your injection

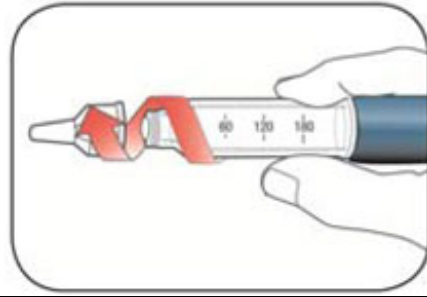
Step 15:

- Carefully replace the Outer Needle Shield.



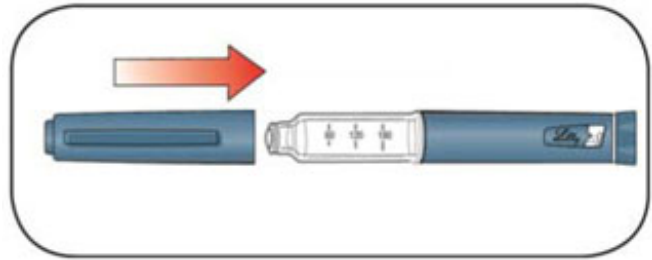
Step 16:

- Unscrew the capped Needle and throw it away (see **Disposing of Pens and Needles** section).
- **Do not** store the Pen with the Needle attached to prevent leaking, blocking the Needle, and air from entering the Pen.



Step 17:

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



Disposing of Pens and Needles

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

Storing your Pen**Unused Pens**

- Store unused Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze your insulin. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the Label, if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature [up to 86°F (30°C)]. Keep away from heat and light.
- Throw away the HUMALOG Mix75/25 Pen you are using after 10 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you can not remove the Pen Cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the Dose Knob is hard to push:
 - Pushing the Dose Knob more slowly will make it easier to inject.
 - Your Needle may be blocked. Put on a new Needle and prime the Pen.
 - You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

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



Scan this code to launch
www.humalog.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

HUMALOG[®] Mix75/25[™] and HUMALOG[®] Mix75/25[™] KwikPen[®] are trademarks of Eli Lilly and Company.

Revised: January 6, 2017

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

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HUMALOG Mix75/25 KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2014.
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LOG7525KP-0002-IFU-20170106

PACKAGE CARTON – HUMALOG Mix75/25 10 mL vial

NDC 0002-7511-01

10 mL

VL-7511

100 units per mL

Humalog[®]

Mix75/25™

75% insulin lispro

protamine suspension

25% insulin lispro injection

(rDNA origin)

For subcutaneous use only.

Rx only

U-100

www.humalog.com

Lilly



PACKAGE CARTON – HUMALOG Mix75/25 KwikPen

NDC 0002-8797-59

Humalog® Mix75/25™

KwikPen®

75% insulin lispro protamine suspension

25% insulin lispro injection (rDNA origin)

For Single Patient Use Only

HP-8797

U-100

Rx only

100 units per mL

Needles not included

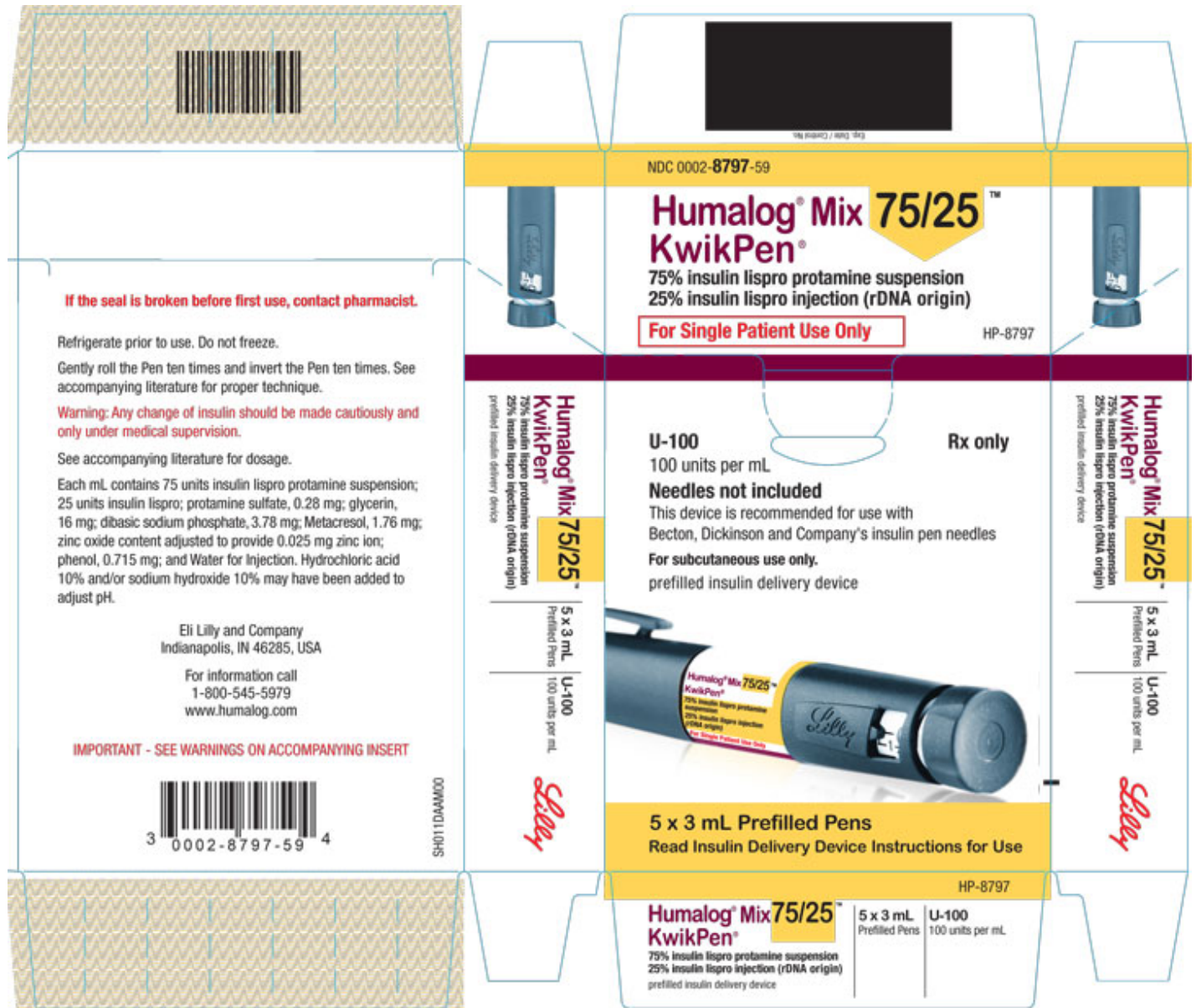
This device is recommended for use with Becton, Dickinson and Company's insulin pen needles

For subcutaneous use only.

prefilled insulin delivery device

5 x 3 mL Prefilled Pens

Read Insulin Delivery Device Instructions for Use



HUMALOG MIX75/25

insulin lispro injection, suspension

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:0002-7511

Route of Administration	SUBCUTANEOUS			
Active Ingredient/Active Moiety				
	Ingredient Name	Basis of Strength	Strength	
	Insulin lispro (UNII: GFX7QIS1II) (Insulin lispro - UNII:GFX7QIS1II)	Insulin lispro	100 [iU] in 1 mL	
Inactive Ingredients				
	Ingredient Name	Strength		
	Protamine sulfate (UNII: 0DE9724IHC)	0.28 mg in 1 mL		
	Glycerin (UNII: PDC6A3C0OX)	16 mg in 1 mL		
	sodium phosphate, dibasic (UNII: GR686LBA74)	3.78 mg in 1 mL		
	Metacresol (UNII: GGO4Y809LO)	1.76 mg in 1 mL		
	Zinc (UNII: J41CSQ7QDS)	.025 mg in 1 mL		
	Phenol (UNII: 339NCG44TV)	.715 mg in 1 mL		
	Water (UNII: 059QF0KO0R)			
	Hydrochloric acid (UNII: QTT17582CB)			
	Sodium hydroxide (UNII: 55X04QC32I)			
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-7511-01	1 in 1 CARTON	10/10/2000	
1		10 mL in 1 VIAL; Type 0: Not a Combination Product		
2	NDC:0002-7511-99	1 in 1 CARTON	12/07/2007	
2		10 mL in 1 VIAL; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA021017	12/22/1999		

HUMALOG MIX75/25 KWIKPEN

insulin lispro injection, suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0002-8797
Route of Administration	SUBCUTANEOUS		
Active Ingredient/Active Moiety			
	Ingredient Name	Basis of Strength	Strength
	Insulin lispro (UNII: GFX7QIS1II) (Insulin lispro - UNII:GFX7QIS1II)	Insulin lispro	100 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Protamine sulfate (UNII: 0DE9724IHC)	0.28 mg in 1 mL
Glycerin (UNII: PDC6A3C0OX)	16 mg in 1 mL
sodium phosphate, dibasic (UNII: GR686LBA74)	3.78 mg in 1 mL
Metacresol (UNII: GGO4Y809LO)	1.76 mg in 1 mL
Zinc (UNII: J41CSQ7QDS)	.025 mg in 1 mL
Phenol (UNII: 339NCG44TV)	.715 mg in 1 mL
Water (UNII: 059QF0KO0R)	
Hydrochloric acid (UNII: QTT17582CB)	
Sodium hydroxide (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-8797-59	5 in 1 CARTON	01/16/2008	
1	NDC:0002-8797-01	3 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:0002-8797-99	1 in 1 CARTON	01/16/2008	
2		3 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021017	09/06/2007	

Labeler - Eli Lilly and Company (006421325)

Revised: 1/2017

Eli Lilly and Company