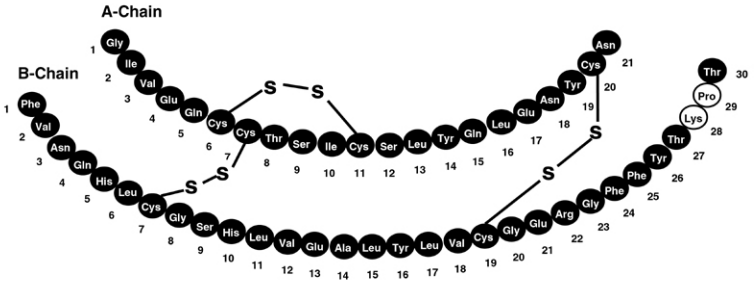
HUMALOG® Mix50/50™
50% INSULIN LISPRO PROTAMINE SUSPENSION AND 50% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

DESCRIPTION

Humalog® Mix50/50™ [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:



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

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

Each milliliter of Humalog Mix50/50 injection contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection. Humalog Mix50/50 has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

CLINICAL PHARMACOLOGY

Antidiabetic Activity

The primary activity of insulin, including Humalog Mix50/50, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

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

Pharmacokinetics

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

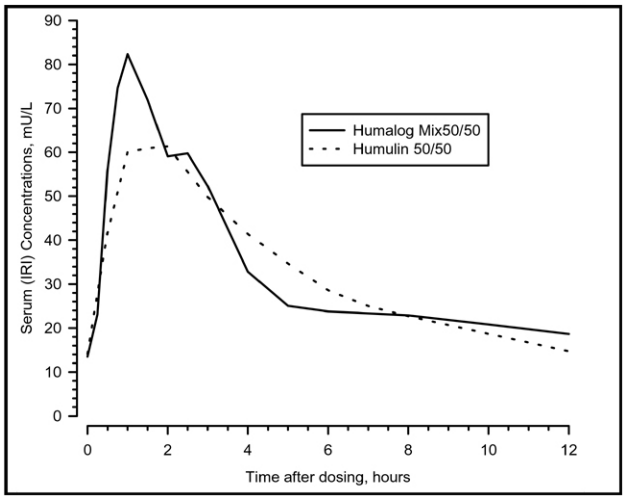


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.

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

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

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

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

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

Pharmacodynamics

Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter duration of glucose-lowering activity than Regular human insulin. The early onset of activity of

Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2 and 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (*see* General *under* PRECAUTIONS).

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

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

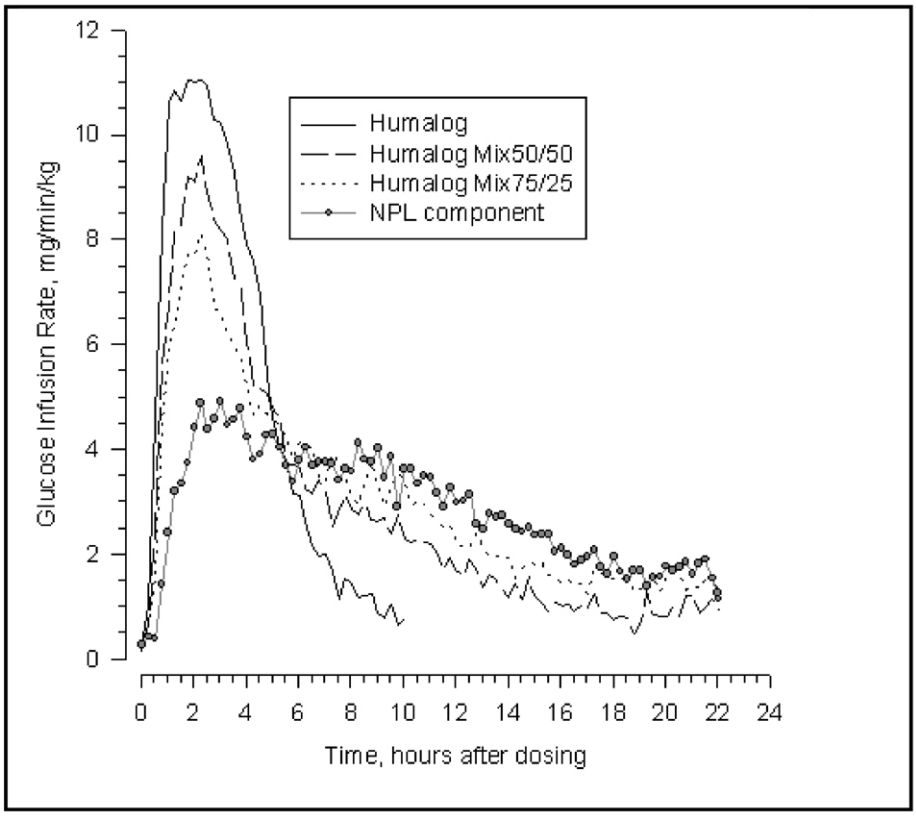


Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

Figure 3a
Humalog Mix50/50

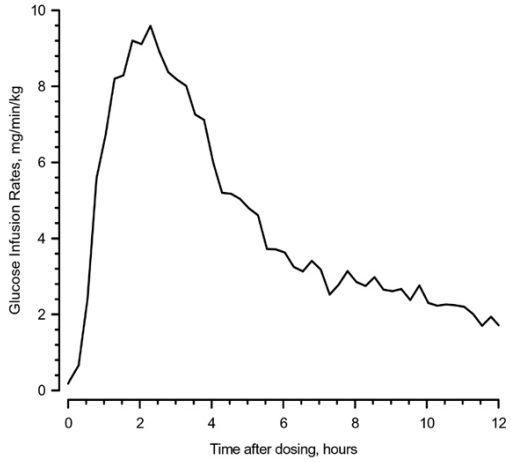


Figure 3b
Humulin 50/50

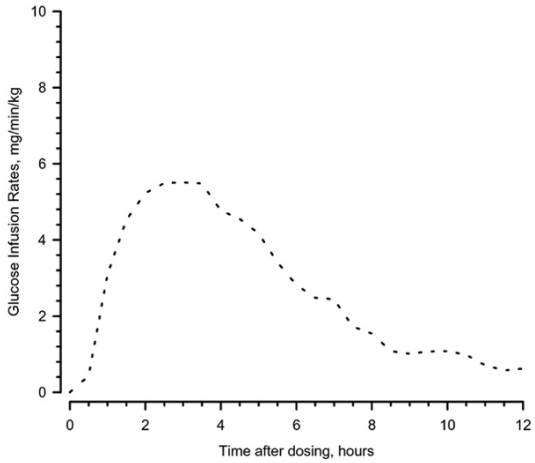


Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

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

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

Special Populations

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

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

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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 Mix50/50, 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 Mix50/50 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

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

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

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

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

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

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

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

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

Information for Patients

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

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

Refer patients to the 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 Mix50/50 should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the monitoring of long-term glycemic control.

Drug Interactions

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

Insulin requirements may be decreased in the presence of drugs 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 Mix50/50 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog Mix50/50 dose, meal plan, or both.

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

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

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

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

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of Humalog Mix50/50 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

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

HOW SUPPLIED

Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7512-01 (VL-7512)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8793-59 (HP-8793)

5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8798-59 (HP-8798)

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

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	**Not In-Use (Unopened) Refrigerated**	**In-Use (Opened) Room Temperature [Below 30°C (86°F)]**
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. **Do not refrigerate.**

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

www.humalog.com

Patient Information

Humalog® (HU-ma-log) Mix50/50™
50% insulin lispro protamine suspension and 50% 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 Mix50/50 before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have questions about managing your diabetes.

What is Humalog Mix50/50?
Humalog Mix50/50 is a mixture of fast-acting and longer-acting man-made insulins. Humalog Mix50/50 is used to control high blood sugar (glucose) in people with diabetes.

Humalog Mix50/50 comes in:
- 10 mL vials (bottles) for use with a syringe
- Prefilled pens

Who should not take Humalog Mix50/50?
Do not take Humalog Mix50/50 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 Mix50/50.
- you are allergic to anything in Humalog Mix50/50. See the end of this leaflet for a complete list of ingredients in Humalog Mix50/50.

What should I tell my healthcare provider before taking Humalog Mix50/50?
Before you use Humalog Mix50/50, 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 Mix50/50.
- 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 Mix50/50.
- **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 Mix50/50 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 Mix50/50 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 Mix50/50?
Talk to your healthcare provider if you have any questions. Your healthcare provider will tell you the right syringes to use with Humalog Mix50/50 vials. Your healthcare provider should

show you how to inject Humalog Mix50/50 before you start using it. **Read the User Manual that comes with your Humalog Mix50/50 prefilled pen.**

- **Use Humalog Mix50/50 exactly as prescribed by your healthcare provider.**
- **Humalog Mix50/50 starts working faster than other insulins that contain regular human insulin.** Inject Humalog Mix50/50 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 Mix50/50 well before each use.** For Humalog Mix50/50 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 Mix50/50 should be cloudy or milky after mixing well.
- Look at your Humalog Mix50/50 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 Mix50/50.
- **Inject your dose of Humalog Mix50/50 under the skin of your stomach area, upper arm, upper leg, or buttocks. Never inject Humalog Mix50/50 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 Mix50/50 in the same syringe with other insulin products.**
- **Never use Humalog Mix50/50 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 Mix50/50?

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 Mix50/50 may cause serious side effects, including:

- **swelling of your hands and feet**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with Humalog Mix50/50 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 Mix50/50. Your healthcare provider should monitor you closely while you are taking TZDs with Humalog Mix50/50. 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 Mix50/50 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 Mix50/50. Ask your healthcare provider or pharmacist for more information.

How should I store Humalog Mix50/50?

- **Store all unopened (unused) Humalog Mix50/50 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 Mix50/50 that has been frozen.
- Do not use after the expiration date printed on the carton and label.
- Protect Humalog Mix50/50 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 Mix50/50

Use Humalog Mix50/50 only to treat your diabetes. Do not share it with anyone else, even if they also have diabetes. It may harm them.
This leaflet summarized the most important information about Humalog Mix50/50. If you would like more information about Humalog Mix50/50 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Humalog Mix50/50 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 Mix50/50?

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.

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

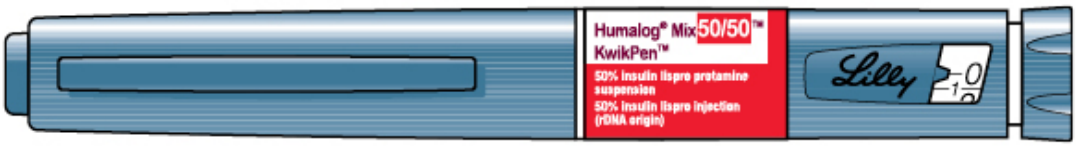
www.humalog.com

Instructions for Use

HUMALOG® Mix50/50™ KwikPen™

50% insulin lispro protamine suspension and

50% insulin lispro injection (rDNA origin)

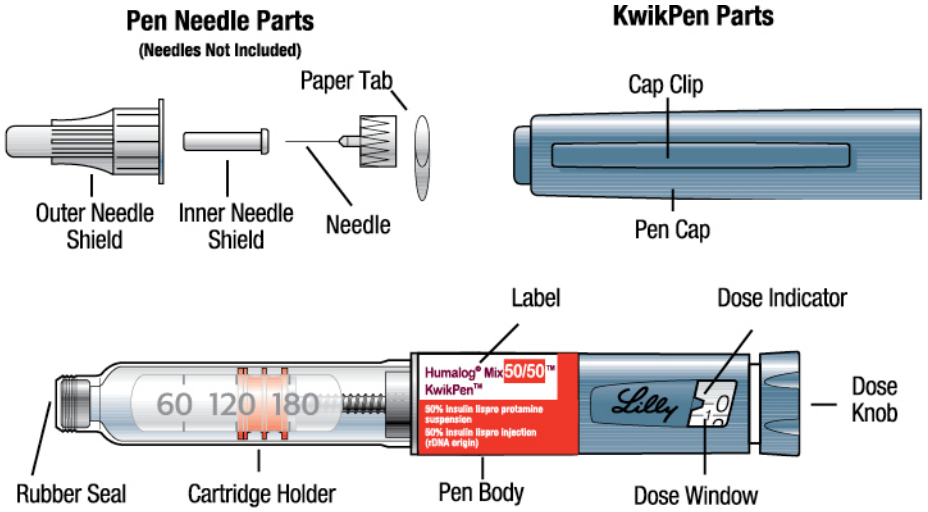


Read the Instructions for Use before you start taking HUMALOG Mix50/50 and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

HUMALOG® Mix50/50™ KwikPen™ ("Pen") is a disposable pen containing 3 mL (300 units) of U-100 HUMALOG® Mix50/50™ [50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)] insulin. You can inject from 1 to 60 units in a single injection.

Do not share your HUMALOG Mix50/50 KwikPen or needles with anyone else. You may give an infection to them or get an infection from them.

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

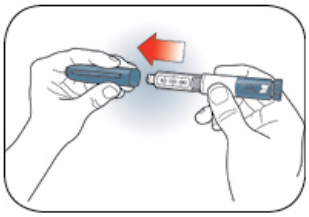
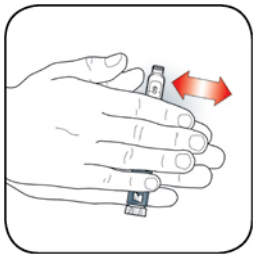
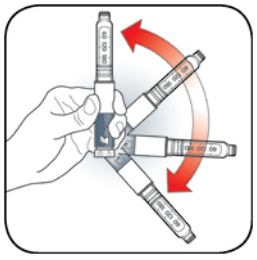


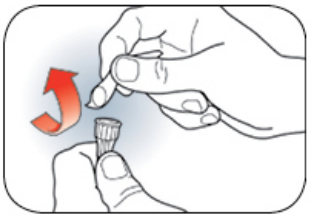
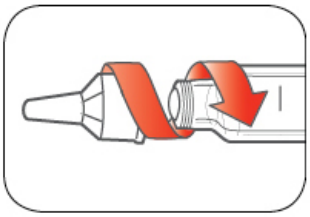
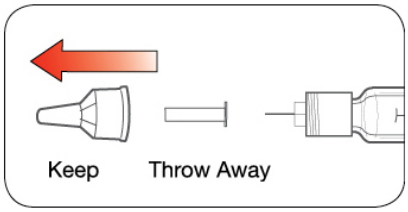
Supplies you will need to give your HUMALOG Mix50/50 injection:

- HUMALOG Mix50/50 KwikPen
- HUMALOG Mix50/50 KwikPen compatible needle (Becton, Dickinson and Company Pen Needles recommended)
- Alcohol swab

Preparing HUMALOG Mix50/50 KwikPen:

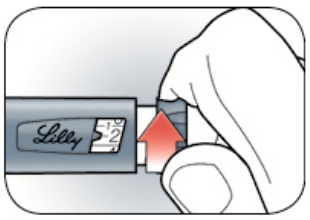
- Wash your hands with soap and water.
- Check the HUMALOG Mix50/50 KwikPen Label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use HUMALOG Mix50/50 past the expiration date printed on the Label.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles.

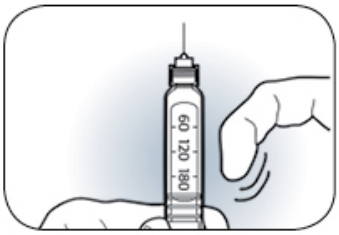
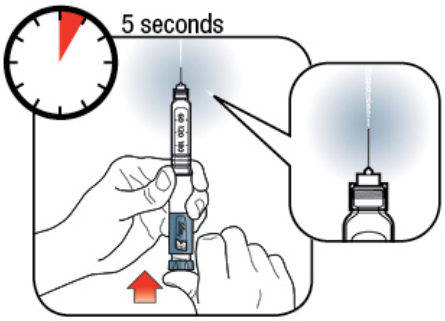
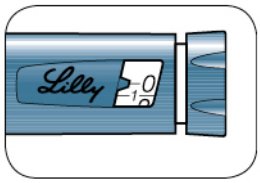
Step 1: Pull the Pen Cap straight off. Wipe the Rubber Seal with an alcohol swab. • **Do not** twist the cap. • **Do not** remove the KwikPen Label.	
Step2: Gently roll the Pen ten times. Invert the Pen ten times. HUMALOG Mix50/50 should look white and cloudy after mixing. **Do not** use if it looks clear or contains any lumps or particles.	 

Step 3: Pull off the Paper Tab from Outer Needle Shield.	
Step 4: Push the capped Needle straight onto the Pen and turn the Needle forward until it is tight.	
Step 5: Pull off the Outer Needle Shield. **Do not** throw it away. Pull off the Inner Needle Shield and throw it away.	

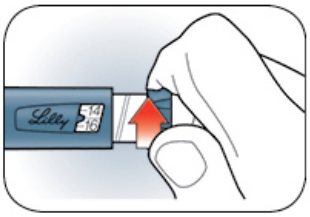
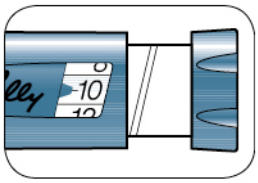
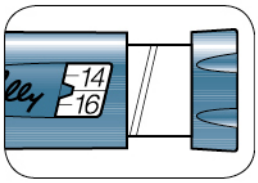
Priming your HUMALOG Mix50/50 KwikPen:

Prime before each injection. Priming ensures the Pen is ready to dose and removes air that may collect in the cartridge during normal use. If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6: Turn the Dose Knob to select 2 units.	

Step 7: Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.	
Step 8: Hold 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**. • A stream of insulin should be seen from the needle. - If you **do not** see a stream of insulin, repeat steps 6 to 8, no more than 4 times. - If you **still do not** see a stream of insulin, change the needle and repeat steps 6 to 8.	 

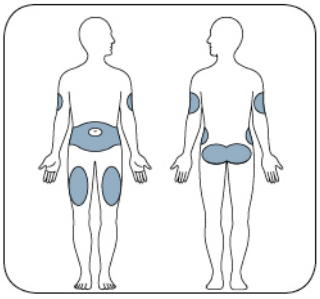
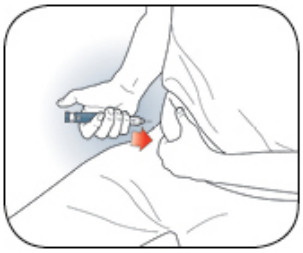
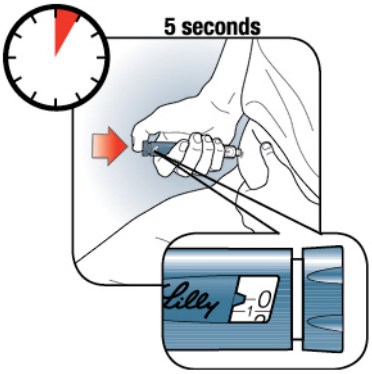
Selecting your dose:

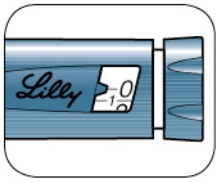
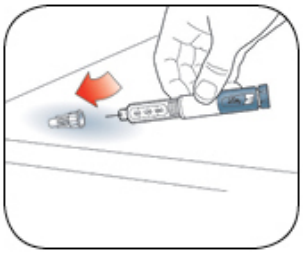
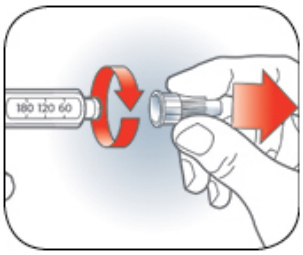
Step 9: Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose. • The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator. • The **even** numbers are printed on the dial. The **odd** numbers, after the number 1, are shown as full lines.	  (10 units shown)  (15 units shown)

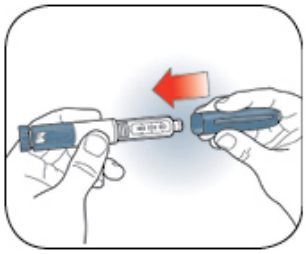
- The HUMALOG Mix50/50 KwikPen will not let you dial more than the number of units left in the Pen.
- If your dose is more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose, **or**
  - get a new Pen and inject the full dose.
- The Pen is designed to deliver a total of 300 units of insulin. The cartridge contains an additional small amount of insulin that can't be delivered.

Giving your HUMALOG Mix50/50 injection:

- Inject your HUMALOG Mix50/50 as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting HUMALOG Mix50/50.

Step 10: Choose your injection site. HUMALOG Mix50/50 is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.	
Step 11: Insert the Needle into your skin.	
Step 12: Put your thumb on the Dose Knob and push the Dose Knob in until it stops. Hold the Dose Knob in and **slowly count to 5**.	

Step 13: Pull the Needle out of your skin. You should see “0” in the Dose Window. If you do not see “0” in the Dose Window, you did not receive your full dose. 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. A drop of insulin at the needle tip is normal. It will not affect your dose. **If you do not think you received your full dose, do not take another dose.** Call Lilly or your healthcare provider for assistance.	
Step 14: Carefully replace the Outer Needle Shield.	
Step 15: Unscrew the capped Needle and throw it away. Do not store the Pen with the Needle attached to prevent leaking, blocking of the Needle, and air from entering the Pen.	

Step 16: Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.	

After your injection:

- Put your used needles and pens in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens 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 pens. 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

How should I store my HUMALOG Mix50/50 KwikPen?

- Store unused HUMALOG Mix50/50 Pens in the refrigerator at 36°F to 46°F (2°C to 8°C). The Pen you are currently using can be stored out of the refrigerator below 86°F (30°C).
- **Do not** freeze HUMALOG Mix50/50. **Do not** use HUMALOG Mix50/50 if it has been frozen.
- Unused HUMALOG Mix50/50 Pens may be used until the expiration date printed on the Label, if kept in the refrigerator.
- The HUMALOG Mix50/50 Pen you are using should be thrown away after 10 days, even if it still has insulin left in it.
- Keep HUMALOG Mix50/50 away from heat and out of the light.

General information about the safe and effective use of HUMALOG Mix50/50 KwikPen

- **Keep HUMALOG Mix50/50 KwikPen 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.
- If you can not remove the Pen Cap, gently twist the Pen Cap back and forth, and then pull the Pen Cap straight off.
- If it is hard to push the Dose Knob or the Pen is not working the right way:
  - 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 one.
  - It may help to push the Dose Knob more slowly during your injection.
- Use the space below to keep track of how long you should use each HUMALOG Mix50/50 KwikPen.
  - Write down the date you start using your HUMALOG Mix50/50 KwikPen. Count forward 10 days.
  - Write down the date you should throw it away.

Example:

Pen 1 - First used on _____ + 10 days = Throw out on _____
Date Date

Pen 1 - First used on _____ Throw out on _____
Date Date

Pen 2 - First used on _____ Throw out on _____
Date Date

Pen 3 - First used on _____ Throw out on _____
Date Date

Pen 4 - First used on _____ Throw out on _____
Date Date

Pen 5 - First used on _____ Throw out on _____
Date Date

If you have any questions or problems with your HUMALOG Mix50/50 KwikPen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMALOG Mix50/50 KwikPen and insulin, go to www.humalog.com.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

Humalog® Mix50/50™ and Humalog® Mix50/50™ KwikPen™ are trademarks of Eli Lilly and Company.

Marketed by: Lilly USA, LLC

Indianapolis, IN 46285, USA

Humalog Mix50/50 KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2000.

Revised: Month Day, Year