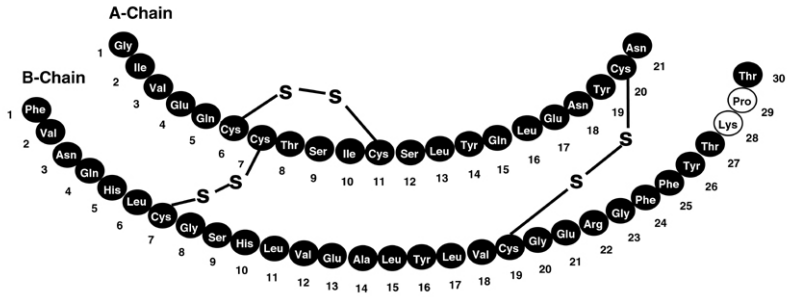
AAD_0025 NL 5532 AMP

HUMALOG®
INSULIN LISPRO INJECTION, USP (rDNA ORIGIN) 100 UNITS PER ML (U-100)

DESCRIPTION

Humalog® [insulin lispro injection, USP (rDNA origin)] is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it 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. Humalog is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro.

Humalog 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.

The vials, cartridges, and Pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

Each milliliter of Humalog injection contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

Antidiabetic Activity

The primary activity of insulin, including Humalog, 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.

Humalog has been shown to be equipotent to 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 glucose-lowering activity of Humalog and Regular human insulin is comparable when administered to nondiabetic subjects by the intravenous route.

Pharmacokinetics

Absorption and Bioavailability — Humalog is as bioavailable as Regular human insulin, with absolute bioavailability ranging between 55% to 77% with doses between 0.1 to 0.2 U/kg, inclusive. Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog is absorbed faster than Regular human insulin (U-100) (*see* Figure 1). 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. The pharmacokinetic profiles of Humalog and Regular human insulin are comparable to one another when administered to nondiabetic subjects by the intravenous route. Humalog was absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human insulin or Humalog at abdominal, deltoid, or femoral subcutaneous sites, the three sites often used by patients with diabetes. After abdominal administration of Humalog, serum drug levels are higher and the duration of action is slightly shorter than after deltoid or thigh administration (*see* DOSAGE AND ADMINISTRATION). Humalog has less intra- and inter-patient variability compared with Regular human insulin.

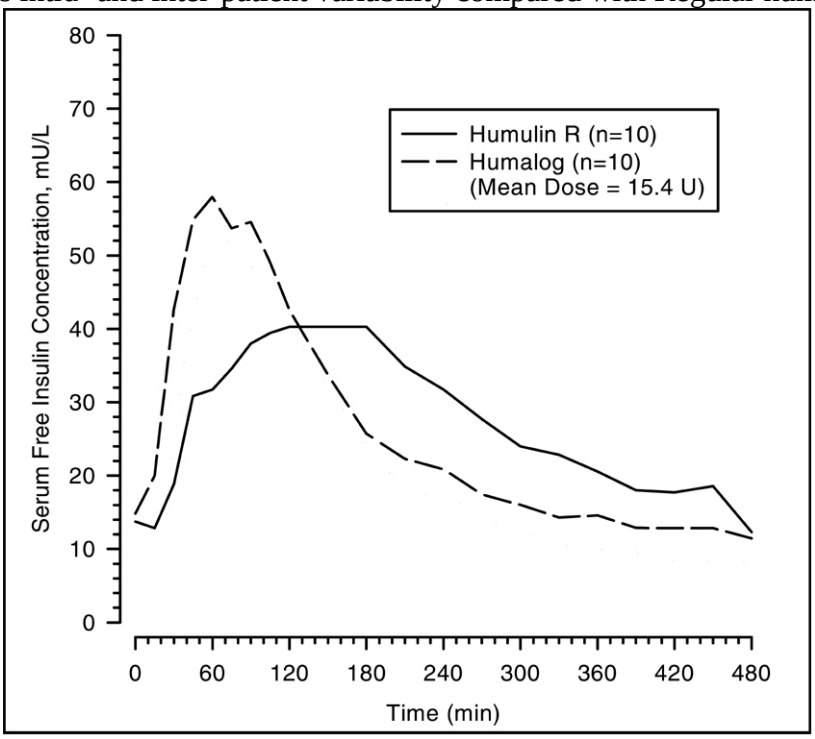


Figure 1: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes. *

* Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Distribution — 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 have not been conducted. However, animal studies indicate that the metabolism of Humalog is identical to that of Regular human insulin.

Elimination — When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of Regular human insulin (1 versus 1.5 hours, respectively). When given intravenously, Humalog and Regular human insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 and 52 minutes at 0.1 U/kg and 0.2 U/kg, respectively.

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 (*see* Figure 2). The earlier onset of activity of Humalog is directly related to its more rapid rate of absorption. The time course of action of insulin and insulin analogs, such as Humalog, may vary considerably in different individuals or within the same individual. The parameters of Humalog activity (time of onset, peak time, and duration) as presented in Figure 2 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).

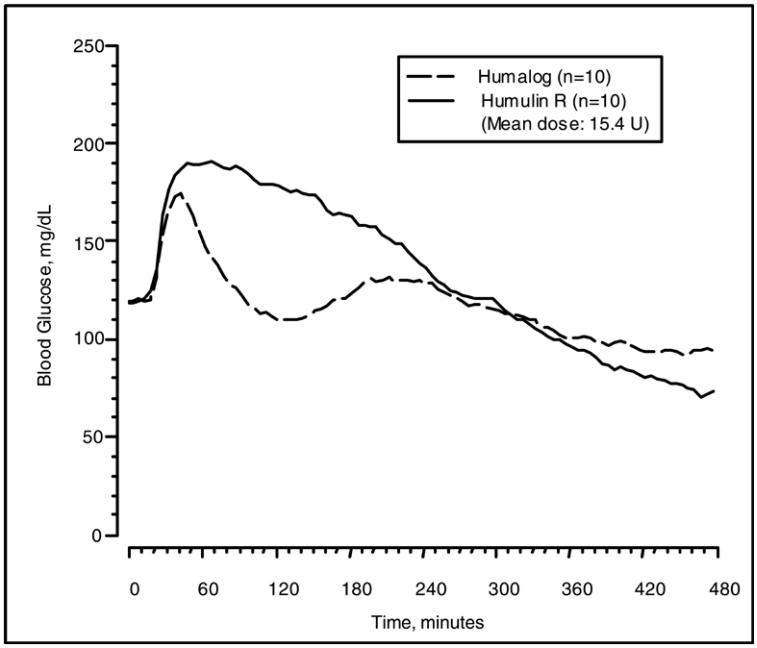


Figure 2: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes. *

* Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Special Populations

Age and Gender — Information on the effect of age and gender on the pharmacokinetics of Humalog is unavailable. However, in large clinical trials, sub-group analysis based on age and gender did not indicate any difference in postprandial glucose parameters between Humalog and Regular human insulin.

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

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

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of Humalog 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 — Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. 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, 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. 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, may be necessary in patients with hepatic dysfunction.

CLINICAL STUDIES

In open-label, cross-over studies of 1008 patients with type 1 diabetes and 722 patients with type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with Regular human insulin (*see* Table 1). The clinical significance of improvement in postprandial hyperglycemia has not been established.

Table 1: Comparison of Means of Glycemic Parameters at the End of Combined Treatment Periods. All Randomized Patients in Cross-Over Studies (3 Months for Each Treatment)

Type 1, N=1008 Glycemic Parameter, (mg/dL)	Humalog[a]	Humulin R[a*]
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA_{1c} (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722 Glycemic Parameter, (mg/dL)	Humalog[a]	Humulin R[a]
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA_{1c} (%)	8.2 ± 1.3	8.2 ± 1.4

[a] Mean ± Standard Deviation.
[*] REGULAR insulin human injection, USP (rDNA origin).

In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA_{1c} did not differ between patients treated with Regular human insulin and those treated with Humalog.

Hypoglycemia — While the overall rate of hypoglycemia did not differ between patients with type 1 and type 2 diabetes treated with Humalog compared with Regular human insulin, patients

with type 1 diabetes treated with Humalog had fewer hypoglycemic episodes between midnight and 6 a.m. The lower rate of hypoglycemia in the Humalog-treated group may have been related to higher nocturnal blood glucose levels, as reflected by a small increase in mean fasting blood glucose levels.

Humalog in Combination with Sulfonylurea Agents — In a two-month study in patients with fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were randomized to one of three treatment regimens; Humulin® NPH at bedtime plus SU, Humalog three times a day before meals plus SU, or Humalog three times a day before meals and Humulin NPH at bedtime. The combination of Humalog and SU resulted in an improvement in HbA_{1c} accompanied by a weight gain (*see* Table 2).

Table 2: Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone

	Humulin N h.s. + SU[a]	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA_{1c} (%) at baseline	9.9	10.0	10.0
HbA_{1c} (%) at 2-months	8.7	8.4	8.5
HbA_{1c} (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia[*] (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

[a] a.c.-three times a day before meals. h.s.-at bedtime. SU-oral sulfonylurea agent.
[*] blood glucose ≤36 mg/dL or needing assistance from third party.

Humalog in External Insulin Pumps — To evaluate the administration of Humalog via external insulin pumps, two open-label cross-over design studies were performed in patients with type 1 diabetes. One study involved 39 patients treated for 24 weeks with Humalog or Regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.8% to 7.2% in the Humalog-treated patients and from 7.8% to 7.5% in the Regular human insulin-treated patients. Another study involved 60 patients treated for 24 weeks with either Humalog or Regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.7% to 7.4% in the Humalog-treated patients and remained unchanged from 7.7% in the Regular human insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in both studies. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

INDICATIONS AND USAGE

Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than Regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump.

CONTRAINDICATIONS

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or any of its excipients.

WARNINGS

This human insulin analog differs from Regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a meal-time insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump). Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Hypoglycemia is the most common adverse effect associated with insulins, including Humalog. 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.

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the Patient Information leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in this Humalog physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (*see* PRECAUTIONS, *For Patients Using External Insulin Pumps, and* DOSAGE AND ADMINISTRATION).

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 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 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. 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 — The requirements for insulin 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, 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. In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and 30 patients receiving Humalog (N=2944) (p=0.053). Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production — In large clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage in External Insulin Pumps — The infusion set (reservoir syringe, tubing, and catheter), Disetronic® D-TRON®[2,3] or D-TRON®[2,3]plus cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

In the D-TRON®[2,3] or D-TRON®[2,3]plus pump, Humalog 3 mL cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients Using External Insulin Pumps, Mixing of Insulins,* DOSAGE AND ADMINISTRATION, *and Storage*).

Information for Patients

Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients 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 timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing insulin, 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, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps: Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog was also tested in Disetronic®[2] H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-TRON®[2,3] and D-TRON®[2,3]plus insulin pumps (with Humalog 3 mL cartridges) using Disetronic Rapid®[2] infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON®[2,3] or D-TRON®[2,3]plus cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external pump should not be exposed to temperatures above 37°C (98.6°F). A Humalog 3 mL cartridge used in the D-TRON®[2,3] or D-TRON®[2,3]plus pump should be discarded after 7 days, even if it still contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

Laboratory Tests

As with all insulins, the therapeutic response to Humalog 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 (*see* CLINICAL PHARMACOLOGY).

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.

Mixing of Insulins — Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately." Mixing Humalog with Humulin N or Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with Regular human insulin.

The effects of mixing Humalog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (*see* WARNINGS).

If Humalog is mixed with a longer-acting insulin, such as Humulin N or Humulin U, Humalog should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge, for the Humalog in the cartridge to be diluted or for the cartridge to be refilled with insulin. Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

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 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 Humalog. 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.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers

It is unknown whether Humalog 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 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use

In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group: Regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group: Regular human insulin 30 to 45 minutes before meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all

three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND ADMINISTRATION).

Geriatric Use

Of the total number of subjects (n=2834) in eight clinical studies of Humalog, twelve percent (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes. HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of Humalog action have not been performed.

ADVERSE REACTIONS

Clinical studies comparing Humalog with Regular human insulin 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

Humalog is intended for subcutaneous administration, including use in select external insulin pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage regimens of Humalog 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. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to Regular human insulin (i.e., one unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent pre-meal hyperglycemia.

When used as a meal-time insulin, Humalog should be given within 15 minutes before or immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

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. Humalog was absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with Regular human insulin (*see* PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of

action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog in a vial may be diluted with STERILE DILUENT for Humalog®, Humulin® N, Humulin® R, Humulin® 70/30, and Humulin® R U-500 to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog contained in a cartridge or Humalog used in an external insulin pump.

Parenteral drug products should be inspected visually before use whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date.

The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be refilled with insulin.

External Insulin Pumps — Humalog was tested in MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog was also tested in the Disetronic®[2] H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the Disetronic D-TRON®[2,3] and D-TRON®[2,3]plus pumps (with Humalog 3 mL cartridges) using Disetronic Rapid®[2] infusion sets.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED

Humalog [insulin lispro injection, USP (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7510-01 (VL-7510)
5 x 3 mL cartridges[3]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL disposable insulin delivery devices (Pen)	NDC 0002-8725-59 (HP-8725)
5 x 3 mL disposable insulin delivery devices (KwikPen™)	NDC 0002-8799-59 (HP-8799)

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1 MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

2 Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

3 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device and Disetronic D-TRON® and D-TRON®plus pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®, HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

Other product and company names may be the trademarks of their respective owners.

Storage — Unopened Humalog should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated [below 30°C (86°F)] vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they still contain Humalog. 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 Cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Pen and KwikPen (disposable)	28 days	Until expiration date	28 days, **Do not refrigerate.**

Use in an External Insulin Pump — A Humalog 3 mL cartridge used in the D-TRON®[2,3] or D-TRON®[2,3]plus should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON®[2,3] and D-TRON®[2,3]plus cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

Literature issued/revised Month DD, YYYY

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Patient Information

Humalog® (HU-ma-log)
insulin lispro injection, USP (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 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?
Humalog is an injectable fast-acting man-made insulin. Humalog is used to control high blood sugar (glucose) in people with diabetes.

Humalog comes in:
- 10 mL vials (bottles) for use with a syringe or external insulin pump
- Prefilled pens
- 3 mL cartridges for use with a reusable pen or external insulin pump

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

Tell your healthcare provider:
- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog has not been studied in pregnant or nursing women.

- **about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.** Many medicines can affect your blood sugar levels and insulin needs. Your Humalog 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?

Humalog can be used with a syringe, prefilled pen, reusable pen or external insulin pump. Talk to your healthcare provider if you have any questions. Your healthcare provider will tell you the right syringes to use with Humalog vials. Your healthcare provider should show you how to inject Humalog before you start using it.

- **Read the User Manual that comes with your Humalog prefilled pen and the manufacturer's instructions that comes with your external insulin pump. Use Humalog exactly as prescribed by your healthcare provider.**
- **If you have type 1 diabetes, you need to take a longer-acting insulin in addition to Humalog (except when using an external insulin pump).**
- **If you have type 2 diabetes, you may be taking diabetes pills and/or a longer-acting insulin in addition to Humalog.**
- **Humalog starts working faster than other insulins that contain regular human insulin.** Inject Humalog within fifteen minutes before eating or right after eating a meal.
- **Check your blood sugar levels as told by your healthcare provider.**
- Look at your Humalog before using. Humalog should be clear, have no color and look like water. If your Humalog is cloudy, thickened, even slightly colored, or has solid particles or clumps in it, do not use. Return it to your pharmacy for new Humalog.
- Humalog can be mixed with a longer-acting human insulin, but only if you are told to do so by your healthcare provider. If you are mixing two types of insulin, always draw Humalog into the syringe first. Talk with your healthcare provider about how to properly mix Humalog with a different insulin.
- Humalog can be used in an external insulin pump either by withdrawing Humalog from a vial or using a 3 mL Humalog cartridge that is inserted into the pump.
- Humalog was tested with MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed Polyfin®[1] infusion sets. Humalog was also tested with the Disetronic®[2] H-TRONplus®[2] V100 insulin pump (with plastic 3.15 mL insulin reservoir), using the Disetronic Rapid®[2] infusion set.
- A Humalog cartridge used in the D-TRON[2] or D-TRONplus[2] pump, may be used for up to 7 days. Humalog in the external insulin pump reservoir and the complete infusion set should be replaced and a new infusion site selected every 48 hours or less.
- Humalog in an external insulin pump should not be exposed to temperature above 98.6°F (37°C), such as in a sauna or hot tub, hot showers, direct sunlight, or radiant heaters.

- **Inject your dose of Humalog under the skin of your stomach area, upper arm, upper leg, or buttocks. Never inject Humalog 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 dilute or mix Humalog with another insulin in the same prefilled pen, cartridge or external 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?

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

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

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

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

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

How should I store Humalog?

- **Store all unopened (unused) Humalog 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 that has been frozen.
- Do not use after the expiration date printed on the carton and label.
- Protect Humalog 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.
- **Cartridge and Prefilled Pens:** Do not store a cartridge or prefilled pen that you are using in the refrigerator. Keep at room temperature below 86°F (30°C) for up to 28 days. Throw away a cartridge or prefilled pen 28 days after first use, even if there is insulin left in the cartridge or the pen.

General information about Humalog

Use Humalog 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. If you would like more information about Humalog or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Humalog that is written for health professionals.

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

What are the ingredients in Humalog?

Active ingredient: insulin lispro.

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

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[1] MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

[2] Disetronic®, H-TRONplus®, D-TRON®, D-TRONplus and Rapid® are registered trademarks of Roche Diagnostics GMBH.

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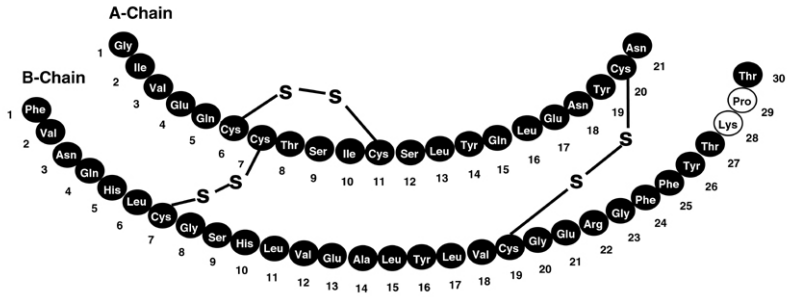
HUMALOG® Mix75/25™
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

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.

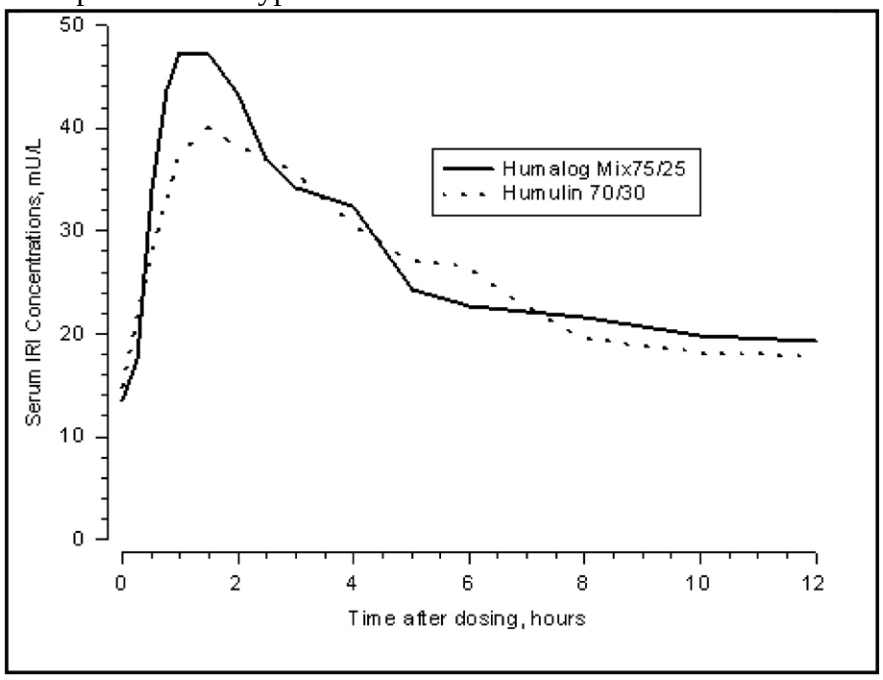


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.

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.

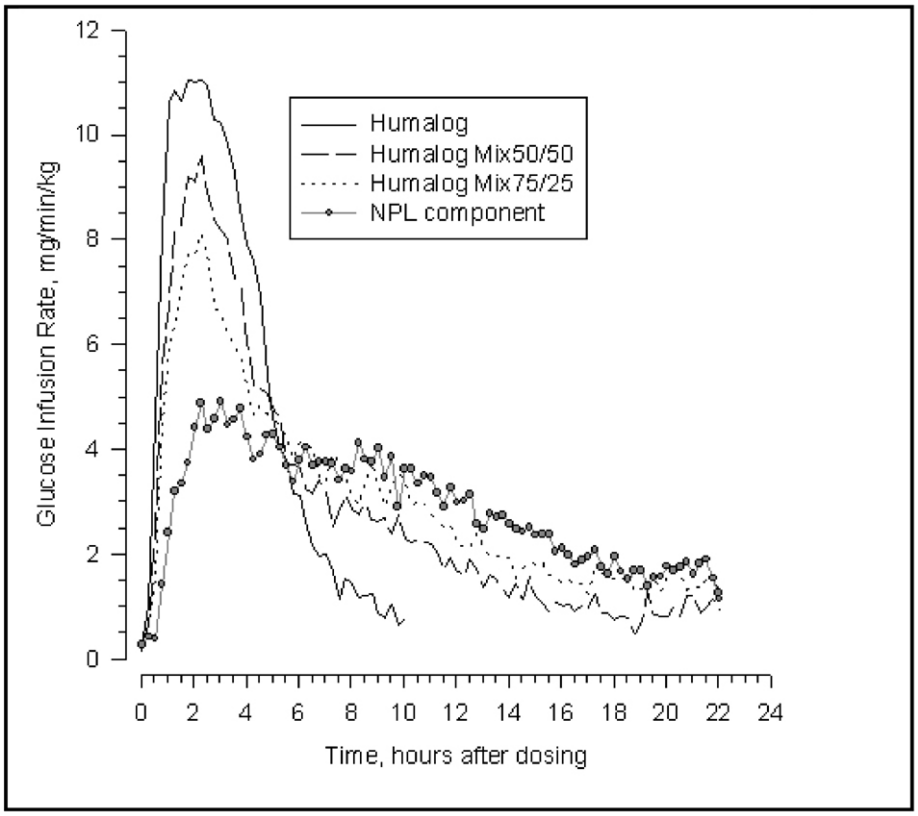


Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

Figure 3a
Humalog Mix75/25

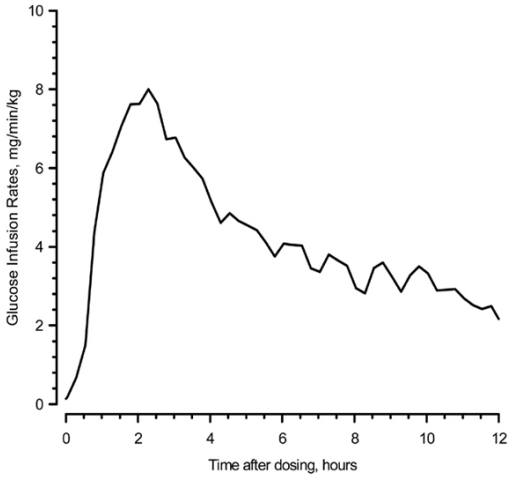


Figure 3b
Humulin 70/30

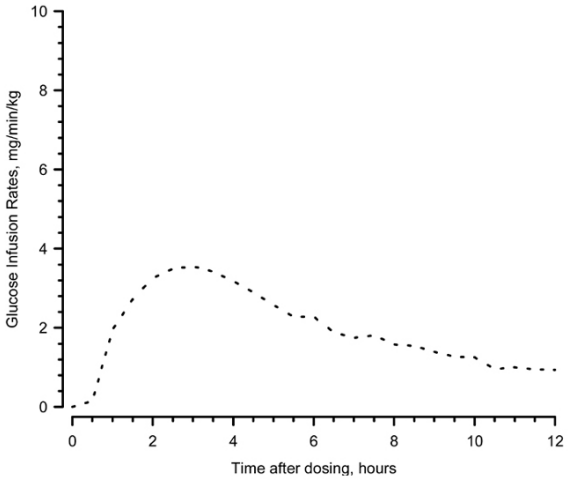


Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in Nondiabetic Subjects.

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/m^2, no consistent differences were observed between Humalog and Humulin® R with respect to postprandial glucose parameters.

Renal Impairment — The effect of renal impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and Regular human insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose reductions of insulin, including Humalog Mix75/25, may be necessary in patients with renal dysfunction.

Hepatic Impairment — Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix75/25 has not been studied. However, in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of Humalog when compared with patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared with Regular human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE

Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering activity compared with Humulin 70/30 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension.

CONTRAINDICATIONS

Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS

Humalog differs from Regular human insulin by its rapid onset of action as well as a shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix75/25. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

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

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog Mix75/25 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog Mix75/25 action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

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

Hypoglycemia — As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment — As with other insulins, the requirements for Humalog Mix75/25 may be reduced in patients with renal impairment.

Hepatic Impairment — Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary.

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

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

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

Information for Patients

Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

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

Refer patients to the Patient Information leaflet for information on normal appearance, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the Patient Information leaflet that accompanies the drug product and the User Manual that accompanies the delivery device and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen, 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 disposable insulin delivery devices (Pen)	NDC 0002-8794-59 (HP-8794)
5 x 3 mL disposable insulin delivery devices (KwikPen™)	NDC 0002-8797-59 (HP-8797)

Storage — Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated [below 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain Humalog Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect from direct heat and light. See table below:

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

Literature issued/revised Month DD, YYYY

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

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

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Patient Information

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

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

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

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

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

Humalog Mix75/25 comes in:
- 10 mL vials (bottles) for use with a syringe
- Prefilled pens

Who should not take Humalog Mix75/25?
Do not take Humalog Mix75/25 if:
- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog Mix75/25.
- you are allergic to anything in Humalog Mix75/25. See the end of this leaflet for a complete list of ingredients in Humalog Mix75/25.

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

sugar levels and insulin needs. Your Humalog Mix75/25 dose may need to change if you take other medicines.

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

How should I use Humalog Mix75/25?

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

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

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

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

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

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

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

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

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

How should I store Humalog Mix75/25?

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

After starting use (open):

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

General information about Humalog Mix75/25

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

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

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

What are the ingredients in Humalog Mix75/25?

Active ingredients: insulin lispro protamine suspension and insulin lispro.

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

Patient Information issued/revised Month DD, YYYY

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

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

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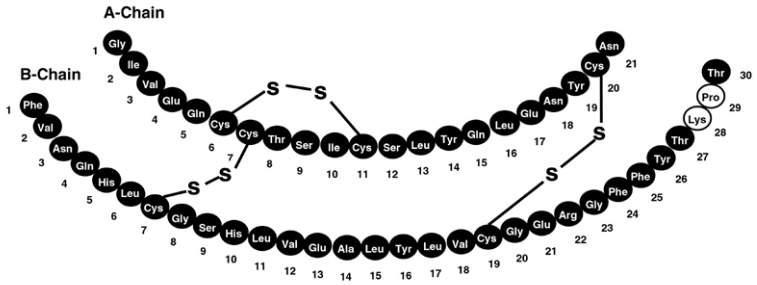
HUMALOG® Mix50/50™
50% INSULIN LISPRO PROTAMINE SUSPENSION AND 50% INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)

DESCRIPTION

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

Insulin lispro has the following primary structure:



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

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

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

CLINICAL PHARMACOLOGY

Antidiabetic Activity

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

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

Pharmacokinetics

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

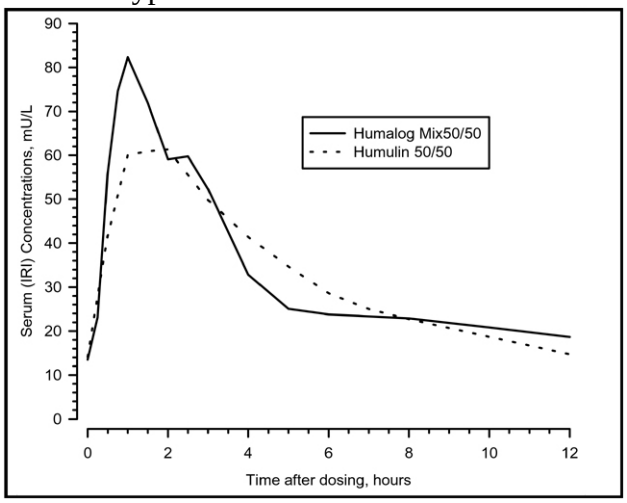


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.

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

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

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

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

Elimination — Humalog Mix50/50 has two absorption phases, a rapid and a prolonged phase, representative of the insulin lispro and insulin lispro protamine suspension components of the

mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot be calculated after administration of Humalog Mix50/50 because of the prolonged insulin lispro protamine suspension absorption.

Pharmacodynamics

Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter duration of glucose-lowering activity than Regular human insulin. The early onset of activity of Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2 and 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (*see* General *under* PRECAUTIONS).

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

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

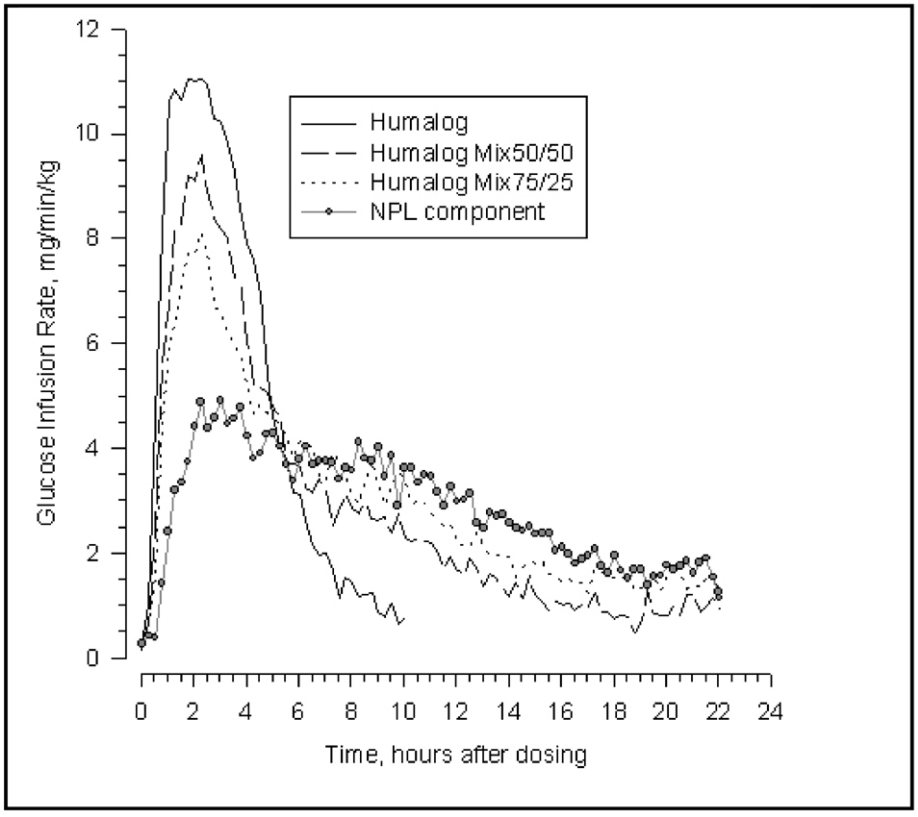


Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

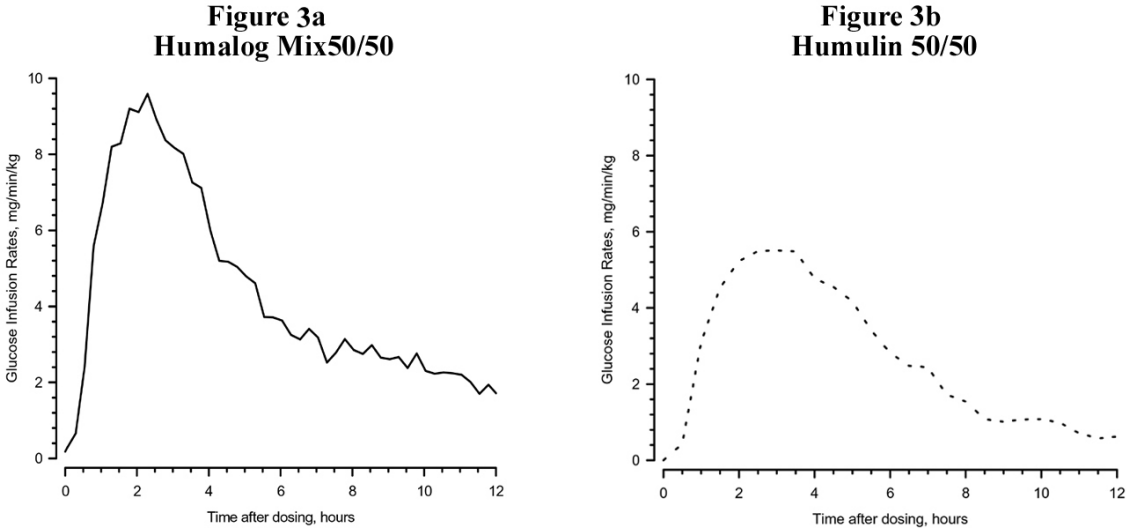


Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in healthy nondiabetic subjects.

Figure 2 shows the time activity profiles of Humalog, Humalog Mix75/25, Humalog Mix50/50, and insulin lispro protamine suspension (NPL component).

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

Special Populations

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

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

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

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

Renal Impairment — The effect of renal impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and Regular human insulin were generally maintained. However, the sensitivity of the

patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose reductions of insulin, including Humalog Mix50/50, may be necessary in patients with renal dysfunction.

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

General

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

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

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

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

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

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

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

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

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

Information for Patients

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

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

Refer patients to the 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, 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 disposable insulin delivery devices (Pen)	NDC 0002-8793-59 (HP-8793)
5 x 3 mL disposable 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 (disposable)	10 days	Until expiration date	10 days. **Do not refrigerate.**

Literature issued/revised Month DD, YYYY

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Pens manufactured by

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

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

www.humalog.com

AAD_0027 NL 5542 AMP PRINTED IN USA

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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.

Tell your healthcare provider:
- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog Mix50/50.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog Mix50/50 has not been studied in pregnant or nursing women.
- **about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.** Many medicines can affect your blood

sugar levels and insulin needs. Your Humalog 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.

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 health professionals.

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

What are the ingredients in Humalog 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.

Patient Information issued/revised Month DD, YYYY

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

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

www.humalog.com

AAD_0018 NL 5573 AMP PRINTED IN USA

KwikPen™

NL 5591 AMP

Disposable Insulin Delivery Device
User Manual

Introduction

The **KwikPen™** is designed for ease of use. It is a disposable insulin delivery device ("insulin Pen") containing 3 mL (300 units) of U-100 insulin. You can inject from 1 to 60 units of insulin in one injection. You can dial your dose one unit at a time. If you dial too many units, you can dial backwards to correct the dose without wasting any insulin.

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

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

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

Preparing the KwikPen

Important Notes

- Read and follow the directions provided in the *Patient Information Sheet*.
- Check the label on your Pen before each injection for the expiration date and to make sure you are using the correct type of insulin.
- Your healthcare professional has prescribed the best type of insulin for you. **Any changes in insulin therapy should be made only under medical supervision.**
- The **KwikPen** is recommended for use with Becton, Dickinson and Company pen needles.
- Be sure the needle is completely attached to the Pen before use.
- Do not share your Pen or needles.
- Keep these directions for future reference.

Frequently Asked Questions about Preparing the KwikPen

- **What should my insulin look like?** Some insulins are cloudy while others are clear. Be sure to refer to your *Patient Information Sheet* for the appearance of your specific insulin.
- **Why should I use a new needle for each injection?** This will help ensure sterility. If needles are reused, you may get the wrong amount of insulin, a clogged needle or a jammed Pen.
- **What should I do if I am not sure how much insulin remains in my cartridge?** Hold the Pen with the needle end pointing down. The scale on the clear Cartridge Holder shows an estimate of the number of units remaining. **These numbers should NOT be used for measuring an insulin dose.**

Priming the KwikPen

Important Notes

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

Frequently Asked Questions about Priming

- **Why should I prime my KwikPen before each dose?**
  1. Ensures that the Pen is ready to dose.
  2. Confirms that a stream of insulin comes out of the tip of the needle when you push the Dose Knob in.
  3. Removes air that may collect in the needle or insulin cartridge during normal use.
- **What should I do if I cannot completely push in the Dose Knob when priming the KwikPen?**
  1. Attach a new needle.
  2. Prime the Pen.
- **What should I do if I see an air bubble in the cartridge?** You need to prime the Pen. Remember, do not store the Pen with the needle attached as this may cause air bubbles to collect in the insulin cartridge. A small air bubble will not affect your dose and you can continue to take your dose as usual.

Injecting Your Dose

Important Notes

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

Injecting Your Dose (continued)

Frequently Asked Questions about Injecting Your Dose

- **Why is it difficult to push the Dose Knob when I try to inject?**
  1. Your needle may be clogged. Try attaching a new needle. When you do this you may see insulin come out of the needle. Then prime the Pen.
  2. Pressing the Dose Knob quickly may make the Dose Knob harder to push. Pressing the Dose Knob more slowly may make it easier.
  3. Using a larger diameter needle will make it easier to push the Dose Knob during your injection. See your healthcare professional to determine which needle size is best for you.
  4. If the Dose Knob continues to be difficult to push after following the steps above, try the steps below under "What should I do if my **KwikPen** is jammed?".
- **What should I do if my KwikPen is jammed?** Your Pen may be jammed if it is difficult to inject a dose or dial a dose. To clear the jam:
  1. Attach a new needle. When you do this you may see insulin come out of the needle.
  2. Prime the Pen.
  3. Dial your dose and inject.
  4. If the Dose Knob is still difficult to push, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979).
- **Why is insulin leaking from the needle after I finished injecting my dose?** You may have removed the needle from your skin too quickly.
  1. Make sure you see a 0 in the Dose Window to confirm you received the complete dose.
  2. For the next dose, **push and hold** the Dose Knob in and **count to 5 slowly** before removing the needle.
- **What should I do if my dose is dialed and the Dose Knob is accidentally pushed in without a needle attached?**
  1. Dial back to zero.
  2. Attach a new needle. When you do this you may see insulin come out of the needle.
  3. Prime the Pen.
  4. Dial your dose and inject.
- **What should I do if I dial a wrong dose (too high or too low)?** Turn the Dose Knob backward or forward to correct the dose before injecting.
- **What should I do if I see insulin leaking from the KwikPen needle while dialing the dose or correcting the dose?** Do not inject the dose because you may not get your complete dose.
  Dial the Pen down to zero and prime the Pen again (see "Priming the **KwikPen**" steps 2 A-D). Dial your dose and inject.
- **What should I do if my full dose cannot be dialed?** The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the cartridge you will not be able to dial past 25. Do not attempt to dial past this point. You may either:
  1. Inject the partial dose and then inject the remaining dose using a new Pen.
     or
  2. Inject the full dose with a new Pen.
- **Why can I not dial the dose to use the small amount of insulin that remains in my cartridge?** The Pen is designed to deliver at least 300 units of insulin. The Pen design prevents the cartridge from being completely emptied because the small amount of insulin that remains in the cartridge cannot be delivered.

Storage and Disposal

Important Notes

- Refer to the *Patient Information Sheet* for complete insulin storage instructions.
- Pens that have not been used should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen.
- Do not store the Pen with the needle attached. If the needle is remains attached, insulin may leak from the Pen, insulin may dry inside the needle causing the needle to clog, or air bubbles may form inside the cartridge.
- The Pen you are currently using should be kept at room temperature and away from heat and light.
- Keep the Pen out of the reach of children.
- Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.
- Dispose of used Pens as instructed by your healthcare professional and without the needle attached.

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

Pen 1 – First used on _____ (DATE) Throw out on _____ (DATE)

Pen 2 – First used on _____ (DATE) Throw out on _____ (DATE)

Pen 3 – First used on _____ (DATE) Throw out on _____ (DATE)

Pen 4 – First used on _____ (DATE) Throw out on _____ (DATE)

Pen 5 – First used on _____ (DATE) Throw out on _____ (DATE)

Example:

Pen 1 – First used on _____ (DATE) + Number of days you should use **KwikPen** (from *Patient Information Sheet*) =

Throw out on _____ (DATE)

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

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

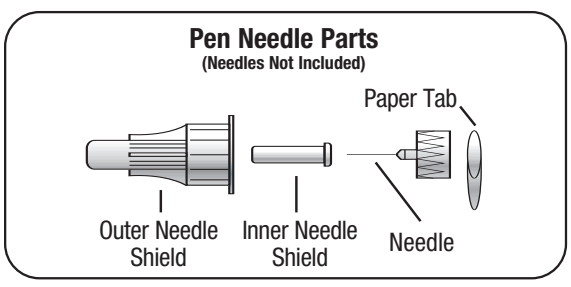
Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46285, USA

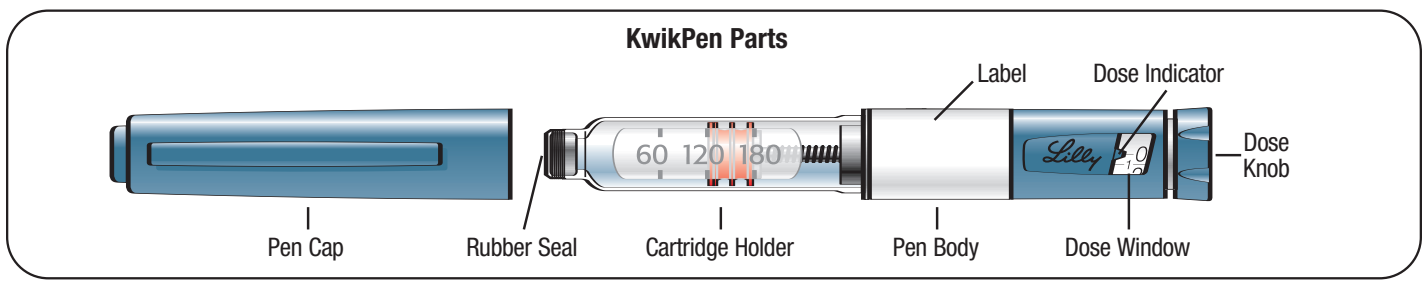
The **KwikPen** meets the current dose accuracy and functional requirements of ISO 11608-1:2000

Getting Ready

Make sure you have the following items: ❑ **KwikPen** ❑ **New Pen Needle** ❑ **Alcohol Swab**

Pen Parts KwikPen, and Needle* Assembly *sold separately

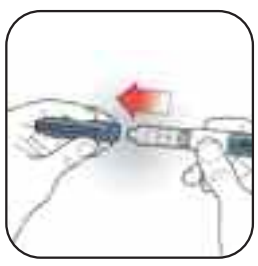




Follow these instructions for each injection

1. Preparing the KwikPen

A.



Pull Pen Cap to remove.

Be sure to check your insulin for:
- Type
- Expiration date
- Appearance

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

B.

For Cloudy Insulin only:

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

Note: Some insulins are meant to be cloudy (e.g., the insulin mixtures) while others are meant to be clear. Be sure to refer to the *Patient Information Sheet* for the appearance of your specific insulin.

C.

Remove Paper Tab from Outer Needle Shield.

D.

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

Screw needle on until secure.

2. Priming the KwikPen

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

A.

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

Pull off Inner Needle Shield and throw away.

B.

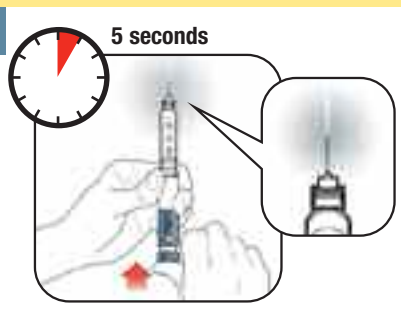
Dial 2 Units by turning the Dose Knob.

C.

Point Pen up.

Tap Cartridge Holder to collect air at top.

D.



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

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

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

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

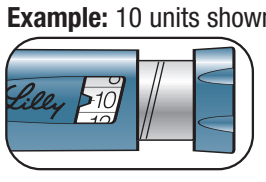
Note: If you do not see a stream of insulin from the tip of the needle and the Dose Knob becomes hard to push, then change the needle and prime the Pen.

3. Injecting Your Dose

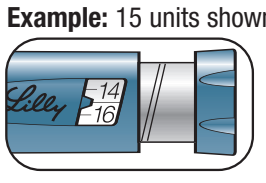
A.

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

Example: 10 units shown.



Example: 15 units shown.

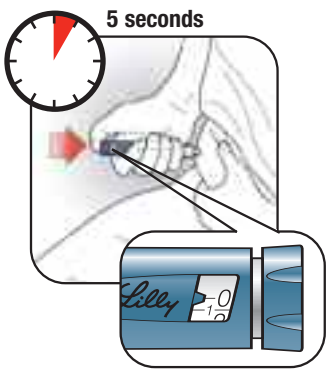


The **even** numbers are printed on the dial. The **odd** numbers, after the number one, are shown as full lines.

B.

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

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



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

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

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

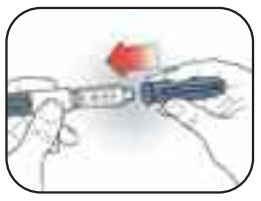
C.

Carefully replace the Outer Needle Shield.

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

D.

Unscrew the capped needle and dispose of as directed by your health-care professional.



Replace Pen Cap.