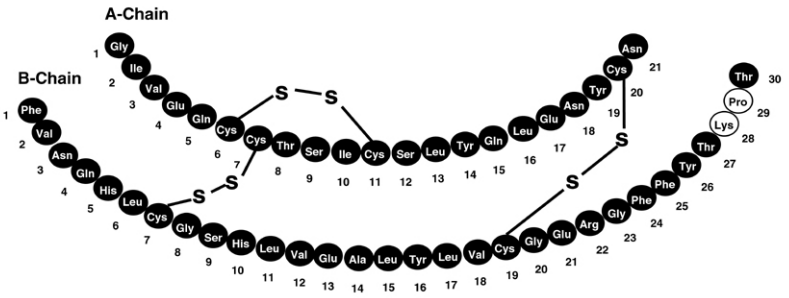
A1.0 PA 9352 FSAMP
A1.0 NL 5741 AMP
A1.0 NL 5751 AMP
A1.0 NL 3693 AMP
A1.0 NL 6832 AMP
A1.0 PA 9164 FSAMP

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

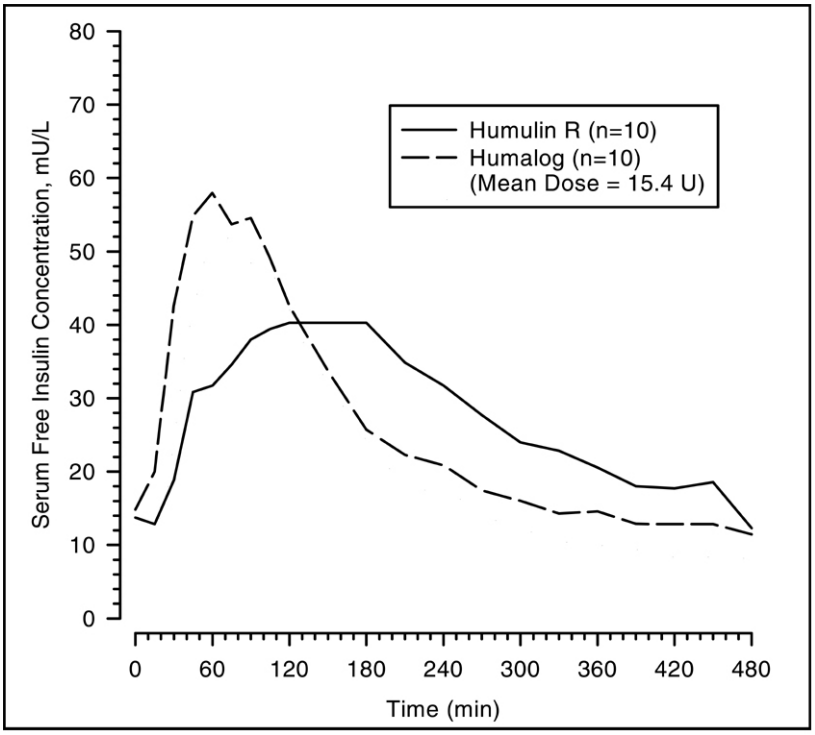
The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids 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.

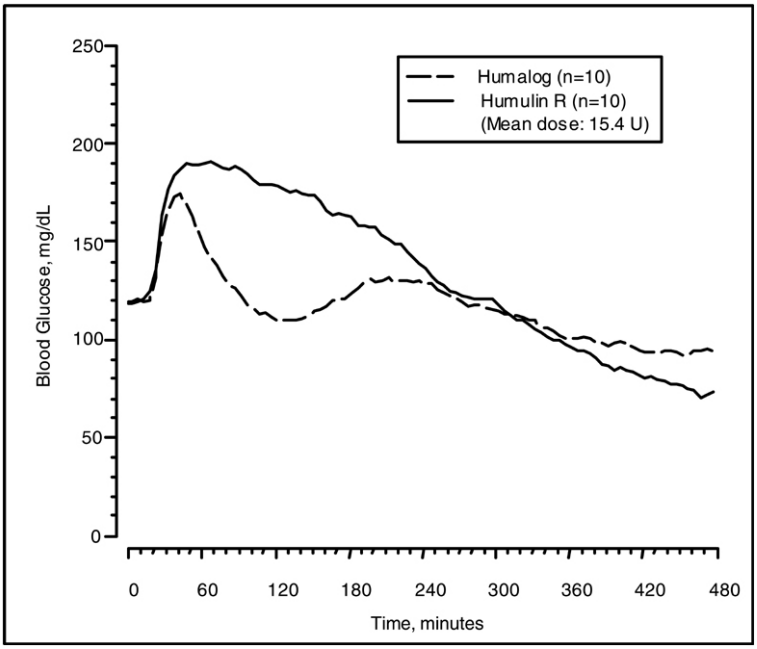
Metabolism — Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of Humalog is identical to that of Regular human insulin.

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 "INFORMATION FOR THE PATIENT" insert 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 “INFORMATION FOR THE PATIENT” insert for information on proper injection technique, timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing and mixing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the “INFORMATION FOR THE PATIENT” insert 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 may be used with the MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog may also be used 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 with 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 Health Care Professional 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 may be used with MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog may also be used 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)] vials are available in the following package size:

100 units per mL (U-100)

10 mL vials NDC 0002-7510-01 (VL-7510)

Humalog [insulin lispro injection, USP (rDNA origin)] cartridges are available in the following package size:

5 x 3 mL cartridges[3] NDC 0002-7516-59 (VL-7516)

Humalog [insulin lispro injection, USP (rDNA origin)] Pen, a disposable insulin delivery device, is available in the following package size:

5 x 3 mL disposable insulin delivery devices NDC 0002-8725-59 (HP-8725)

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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, and Pens 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	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

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
Hospira, Inc., Lake Forest, IL 60045, USA or
Lilly France, F-67640 Fegersheim, France
Cartridges manufactured by
Lilly France, S.A.S. F-67640 Fegersheim, France

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

A1.0 PA 9352 FSAMP
A1.0 NL 5741 AMP
A1.0 NL 5751 AMP
A1.0 NL 3693 AMP
A1.0 NL 6832 AMP
A1.0 PA 9164 FSAMP