Important information on discontinuation of original Prefilled Pen containing Humalog®

As of January 1, 2011, Eli Lilly and Company will no longer make the original Prefilled Pen containing Humalog®. However, your same Humalog insulin is currently available in another pen option, Humalog® KwikPen™. This is a different pen device only. The insulin inside remains the same.

Availability of the original Prefilled Pen containing Humalog will depend on the amount your pharmacy has in stock. We anticipate that the pens will start to become unavailable in some areas beginning in summer 2010.

Eli Lilly and Company is honored that you and your doctor have trusted Humalog insulin to help in the management of diabetes. We want to make every effort to continue to keep you up-to-date on all changes and advances in diabetes care.

Original Prefilled Pen containing Humalog® to be discontinued
[insulin lispro injection (rDNA origin)]

Humalog® KwikPen™ available
[insulin lispro injection (rDNA origin)]

Why is Eli Lilly and Company no longer making the original Prefilled Pen containing Humalog?

We introduced Humalog KwikPen in early 2008 and have since decided to stop making the original Prefilled Pen containing Humalog. Humalog remains available in Humalog KwikPen and other delivery options.

How long will the original Prefilled Pen containing Humalog be available?

Availability of the pen will depend on the amount your pharmacy has in stock. We anticipate that the pens will start to become unavailable in some areas beginning in summer 2010. You will need to talk to your pharmacist or your doctor to determine whether or not you will need a new prescription for Humalog KwikPen.

What should I do with the original Prefilled Pens containing Humalog I still have?

If stored properly, you can continue to use the original Prefilled Pen containing Humalog until the expiration date stamped on the carton and pen.

What is Humalog KwikPen?

Just like the original Prefilled Pen containing Humalog, Humalog KwikPen is a prefilled insulin delivery device ("insulin pen") containing 3 mL (300 units) of U-100 Humalog.

How does Humalog KwikPen work?

You can inject from 1 to 60 units of insulin in one injection—you simply dial your dose one unit at a time. If you dial too many units, you can dial backward to correct the dose without wasting any insulin. Visit **www.Humalog.com/PenInfo** to view a demonstration of how a KwikPen works.

Will Humalog KwikPen be covered by my insurance?

For most insurance plans, Humalog KwikPen is available for the same co-pay as the original Prefilled Pen containing Humalog. Since plans may vary, it is important to check with your plan if you have additional questions about your coverage.

How do I store Humalog KwikPen?

Just like the original Prefilled Pen containing Humalog, there is no refrigeration needed after the first use. Please refer to the Patient Information accompanying this document for complete information regarding storage.

What needles can be used with Humalog KwikPen?

You can continue to use the same BD (Becton Dickinson) needles with Humalog KwikPen that you used with the original Prefilled Pen containing Humalog.

What should I do if I have questions about my Humalog options?

If you have questions or concerns about the discontinuation of the original Prefilled Pen containing Humalog or about Humalog KwikPen, please talk to your doctor or pharmacist, visit **www.Humalog.com/PenInfo**, or contact Eli Lilly and Company at **1-800-LillyRx (1-800-545-5979)**.

Indication

Humalog is for use in patients with diabetes to control high blood sugar and should be used with longer-acting insulin, except when used in combination with sulfonylureas in patients with type 2 diabetes.

Select Safety Information:

- Starting or changing insulin therapy should be done cautiously and only under medical supervision
- Low blood sugar is the most common adverse effect associated with insulins, including Humalog
- Humalog is a fast-acting insulin that starts working faster than other insulins that contain regular human insulin. Take Humalog within 15 minutes before eating or right after eating a meal

Please see additional Important Safety Information on back and full Prescribing Information, including Patient Information attached.

Humalog®
insulin lispro injection (rDNA origin)

Lilly

Important Safety Information About Humalog®

Who should use Humalog?

Humalog (insulin lispro injection [rDNA origin]) is for use in patients with diabetes to control high blood sugar and should be used with longer-acting insulin, except when used in combination with sulfonylureas in patients with type 2 diabetes.

What is some important safety information I should know about Humalog?

Starting or changing insulin therapy should be done cautiously and only under medical supervision.

Humalog should not be used during episodes of low blood sugar (hypoglycemia) or if you are allergic to anything in Humalog.

Humalog is an injectable, fast-acting insulin. Humalog starts working faster than other insulins that contain regular human insulin. Take Humalog within 15 minutes before eating or right after eating a meal. Check your blood sugar levels as told by your healthcare professional.

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.

The safety and effectiveness of Humalog in patients less than 3 years of age have not been established. There are no adequate and well-controlled clinical studies of the use of Humalog in pregnant or nursing women.

Low Blood Sugar

Low blood sugar is the most common adverse effect associated with insulins, including Humalog. Low blood sugar can happen suddenly, and symptoms may be different for each person and may change from time to time. Know your symptoms of low blood sugar. Severe low blood sugar can cause seizures and be life threatening. Follow your healthcare professional's instructions for treating low blood sugar. Talk to your healthcare professional if low blood sugar is a problem for you.

Other Side Effects

Other potential side effects associated with the use of insulins include: low blood potassium, weight gain, changes in fat tissue at the injection site, and allergic reactions. Allergic reactions can happen at the site of injection and over the whole body. Whole-body allergic reactions are less common, but may be life threatening.

For other important information, see accompanying full Prescribing Information, including Patient Information attached.

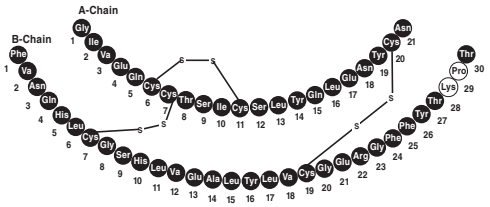
Humalog® KwikPen™

insulin lispro injection (rDNA origin)

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, Humalog® KwikPen™ 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.

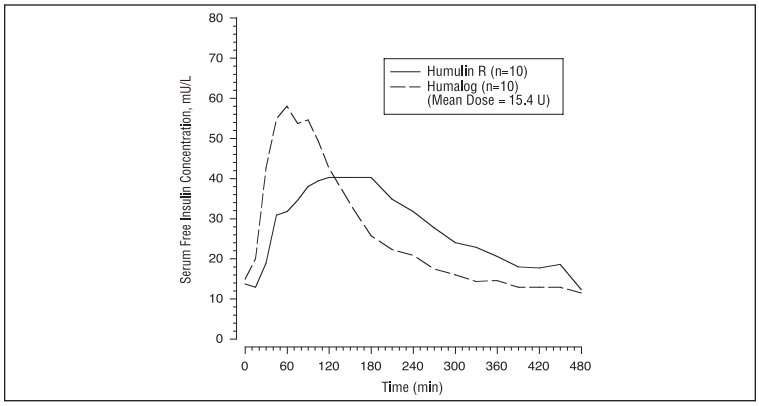
Each milliliter of Humalog injection contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric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

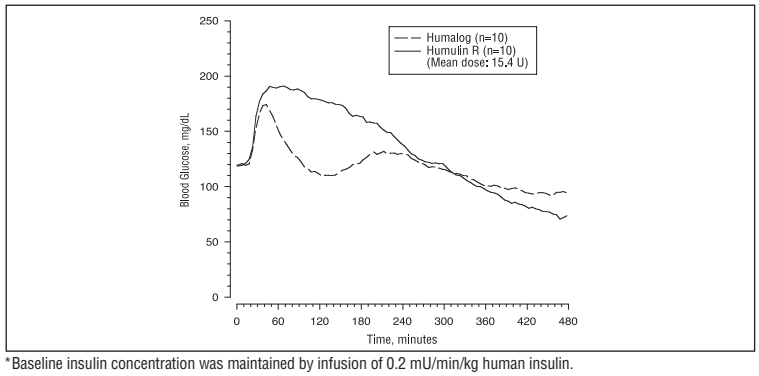
Distribution—The volume of distribution following injection of Humalog is identical to that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

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 to a stream of insulin, 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)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges[3]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59 (HP-8725)
5 x 3 mL prefilled insulin delivery devices (Humalog KwikPen)	NDC 0002-8799-59 (HP-8799)

[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®, Humalog®, Humalog® KwikPen™, 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 Humalog KwikPen 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 and 3 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 Humalog KwikPen (prefilled)	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 revised September 2, 2009

PV 5532 AMP PRINTED IN USA

Lilly

Humalog KwikPen 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

10 mL 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

3 mL Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA

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

www.humalog.com

HUMALOG® INSULIN LISPRO INJECTION (rDNA ORIGIN) PV 5532 AMP

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
- 3 mL vials (bottles) for use with a syringe or external insulin pump
- 3 mL 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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[2] Disetronic®, H-TRONplus®, D-TRON®, D-TRONplus and Rapid® are registered trademarks of Roche Diagnostics GMBH.

Patient Information revised September 2, 2009

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Lilly

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Lilly France, F-67640 Fegersheim, France
10 mL 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
3 mL Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Cartridges manufactured by
Lilly France, F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA
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Humalog® (HU-ma-log) insulin lispro injection, USP (rDNA origin) PV 5561 AMP