A2.0 NL 4520 AMP

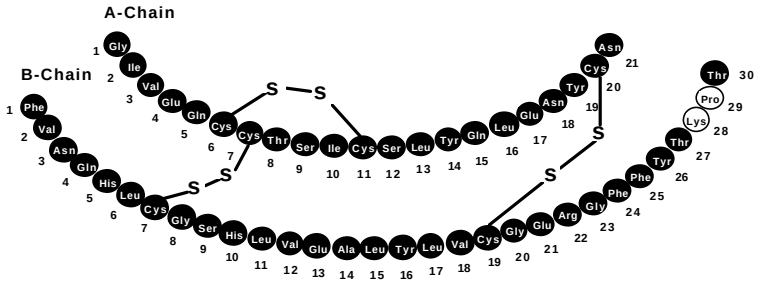
HUMALOG®
INSULIN LISPRO INJECTION
(rDNA ORIGIN)

DESCRIPTION

Humalog® (insulin lispro, 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 by the addition of the gene for insulin lispro.

Humalog has the following primary structure:

Figure 1



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 and cartridges 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 *m*-cresol, 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 7.0-7.8. 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 human regular insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and human regular insulin is comparable when administered to normal volunteers by the intravenous route.

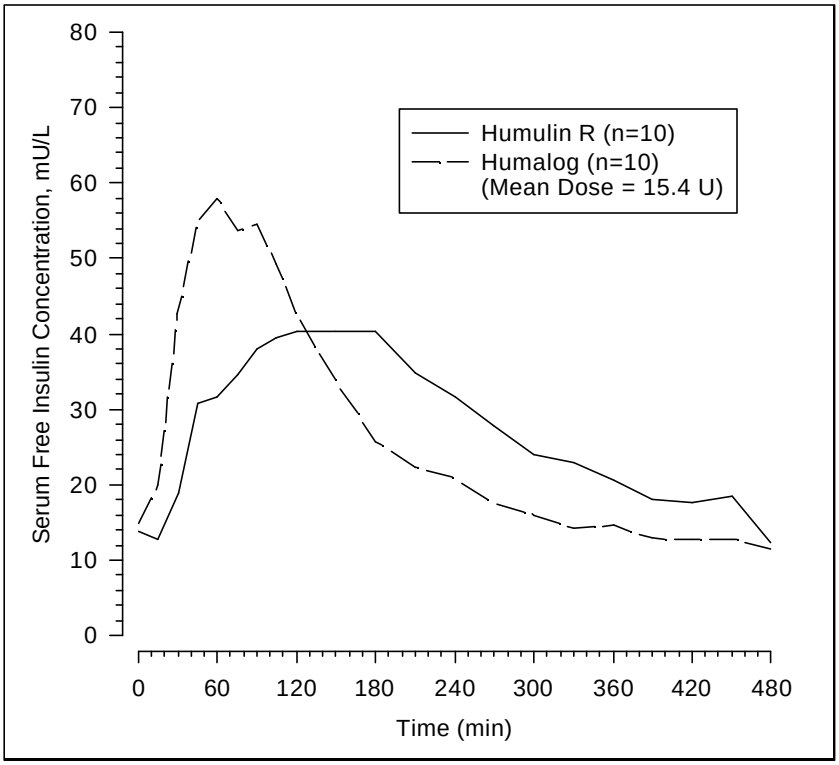
Pharmacokinetics

Absorption and Bioavailability — Humalog is as bioavailable as human regular insulin, with absolute bioavailability ranging between 55%-77% with doses between 0.1-0.2 U/kg, inclusive. Studies in normal volunteers and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog is absorbed faster than human regular insulin (U-100) (Figure 2). In normal volunteers given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum levels

were seen 30-90 minutes after dosing. When normal volunteers received equivalent doses of human regular insulin, peak insulin levels occurred between 50-120 minutes after dosing. Similar results were seen in patients with type 1 diabetes. The pharmacokinetic profiles of Humalog and human regular insulin are comparable to one another when administered to normal volunteers by the intravenous route. Humalog was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular 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 to human regular insulin.

Figure 2

Serum Humalog and insulin levels after subcutaneous injection of human regular 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 for Humalog is identical to that of human regular insulin, with a range of 0.26-0.36 L/kg.

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

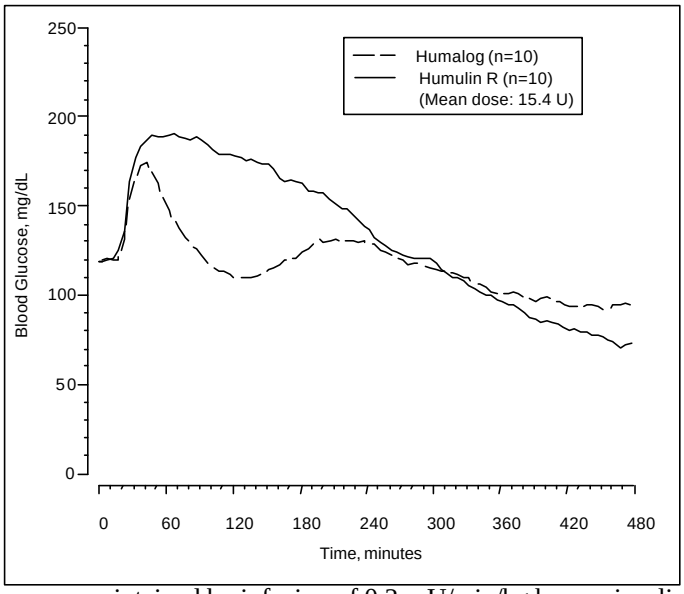
Elimination — When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of human regular insulin (1 vs. 1.5 hours, respectively). When given intravenously, Humalog and human regular insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 and 52 minutes at 0.1 U/kg and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

Pharmacodynamics — Studies in normal volunteers 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 human regular insulin

(Figure 3). 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 designated in Figure 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* PRECAUTIONS, *General*).

Figure 3

Blood glucose levels after subcutaneous injection of human regular 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.

In open-label, crossover studies of 1008 patients with type 1 diabetes and 722 patients with type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with human regular 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.
*Humulin® R (human insulin [rDNA origin] injection).

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

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, subgroup analysis based on age and gender did not indicate any difference in postprandial glucose parameters between Humalog and human regular insulin.

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

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

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics 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 seen 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 human regular 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 adjustments 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 to patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared to human regular insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary in patients with hepatic dysfunction.

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 human regular 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.

CONTRAINDICATIONS

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

WARNINGS

This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime 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.

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 (animal,

human), or method of manufacture (rDNA versus animal-source insulin) 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 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 stresses.

Hypoglycemia — As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose levels 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 a 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.

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 glycosylated hemoglobin 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 circular 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.

Laboratory Tests — As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions — (*see* CLINICAL PHARMACOLOGY) 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 with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and certain antidepressants (monoamine oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors, 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 human regular 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog. Humalog 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 Humalog-induced impairment of fertility.

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 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 no well-controlled 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: human regular 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; human regular 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 type 2 patients. 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 human regular 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. 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 human regular insulin (i.e., one unit of Humalog has the same glucose-lowering capability as one unit of human regular 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. Human regular insulin is best given 30-60 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 is known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular 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 human regular 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 may be diluted with STERILE DILUENT for Humalog®, Humulin® N, Humulin® 50/50, Humulin® 70/30, and NPH Iletin® 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).

Parenteral drug products should be inspected visually prior to administration 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.

HOW SUPPLIED

Humalog (insulin lispro injection, 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)

Also Available

Humalog (insulin lispro injection, rDNA origin) cartridges are available in the following package sizes:

5 X 1.5 mL cartridges*	NDC 0002-7515-59 (VL-7515)
5 X 3 mL cartridges**	NDC 0002-7516-59 (VL-7516)

Humalog (insulin lispro injection, rDNA origin) Pen, 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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* 1.5 mL cartridges are for use in Becton Dickinson and Company's B-D®† Pen and Novo Nordisk A/S's NovoPen®‡, NovolinPen®‡, and NovoPen®‡ 1.5 insulin delivery devices.

** 3 mL cartridge is for use in Owen Mumford, Ltd.'s Autopen®§ 3 mL insulin delivery device.

† B-D® is a registered trademark of Becton Dickinson and Company.

‡ NovolinPen® and NovoPen® are registered trademarks of Novo Nordisk A/S.

§ Autopen® is a registered trademark of Owen Mumford, Ltd.

Storage — 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	Not in-use (unopened) Refrigerated	In-use (opened) Room temperature, below 30°C
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature
1.5 mL and 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.**

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INFORMATION FOR THE PATIENT
VIAL

HUMALOG®
INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 Units per mL (U-100)

WARNINGS

THIS LILLY HUMAN INSULIN ANALOG IS DIFFERENT FROM OTHER INSULINS BECAUSE IT HAS A RAPID ONSET AND SHORTER DURATION OF ACTION. THE RAPID ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF HUMALOG® (INSULIN LISPRO INJECTION, rDNA ORIGIN) WITHIN 15 MINUTES BEFORE OR IMMEDIATELY AFTER EATING. THE SHORT DURATION OF ACTION OF HUMALOG MEANS THAT IF YOU HAVE TYPE 1 DIABETES, YOU ALSO NEED TO USE A LONGER-ACTING INSULIN TO GIVE THE BEST GLUCOSE CONTROL. IF YOU HAVE TYPE 2 DIABETES, HUMALOG MAY BE USED WITHOUT A LONGER-ACTING INSULIN WHEN USED IN COMBINATION THERAPY WITH SULFONYLUREA AGENTS.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, LENTE), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG OR THE LONGER-ACTING INSULIN, OR BOTH.

PATIENTS TAKING HUMALOG MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or your urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. The American Diabetes Association recommends that if your pre-meal glucose levels are consistently above 140 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 8%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-normal glucose levels you should also let your doctor know. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed.

Always keep an extra supply of Humalog as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

HUMALOG

Description

Humalog is made by a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for this human insulin analog. Humalog consists of zinc-insulin lispro crystals dissolved in a clear fluid. Humalog is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog is 100 units/mL (U-100). Humalog starts lowering blood glucose more quickly and has a shorter duration of action compared to regular human insulin. This means that your dose of Humalog should be given within 15 minutes before or immediately after a meal (regular insulin works best when given 30-60 minutes before a meal). The short duration of action of Humalog means that if you have type 1 diabetes, you need to use a longer-acting insulin to give the best glucose control. If you have type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents. The time course of Humalog action, like that of other insulins, may vary in different individuals or at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity.

Identification

Insulin lispro injection (rDNA origin), by Eli Lilly and Company, has the trademark Humalog. Your doctor has prescribed the type of insulin that he/she believes is best for you.

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

Always check the carton and bottle labels of the Humalog you receive from your pharmacy to make sure it is the same as that your doctor has prescribed.

Always examine the appearance of your bottle of Humalog solution before withdrawing each dose. Humalog is a clear and colorless liquid with a water-like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly colored, or if solid particles are visible. Always check the appearance of your bottle of Humalog before using, and if you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

Storage

Humalog should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of Humalog that you are currently using can be kept unrefrigerated, **up to 28 days**, as long as it is kept as cool as possible (below 86°F [30°C]) and away from direct heat and light. Do not use Humalog if it has been frozen. Do not use a bottle of Humalog after the expiration date stamped on the label. Humalog may be diluted with the appropriate sterile diluent only under the direction of a physician. After withdrawal of the initial dose, diluted Humalog may remain in use for 28 days when refrigerated and for 14 days when stored at room temperature.

INJECTION PROCEDURES

NEVER SHARE NEEDLES AND SYRINGES

Correct Syringe Type

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL=1 cc). With Humalog, it is important to use a syringe that is marked for U-100 insulin preparations. For this reason, you should always use a syringe marked for the strength of Humalog you are injecting. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable plastic syringes and needles should be used only once and then discarded in a responsible manner.

Reusable glass syringes and needles must be sterilized before each injection. **Follow the package directions supplied with your syringe.** Described below are 2 methods of sterilizing.

Boiling

1. Put syringe, plunger, and needle in strainer, place in saucepan, and cover with water. Boil for 5 minutes.
2. Remove articles from water. When they have cooled, insert plunger into barrel, and fasten needle to syringe with a slight twist.
3. Push plunger in and out several times until water is completely removed.

Isopropyl Alcohol

If the syringe, plunger, and needle cannot be boiled, as when you are traveling, they may be sterilized by immersion for at least 5 minutes in Isopropyl Alcohol, 91%. Do not use bathing, rubbing, or medicated alcohol for this sterilization. If the syringe is sterilized with alcohol, it must be absolutely dry before use.

Preparing the Dose

1. Wash your hands.
2. Inspect the appearance of Humalog solution in the bottle. It should look clear and colorless. Do not use Humalog if it appears cloudy, thickened, or slightly colored, or if solid particles are visible.
3. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
4. Wipe the top of the bottle with an alcohol swab.
5. If you are mixing insulins, refer to the instructions for mixing that follow.
6. Draw air into the syringe equal to your Humalog dose. Put the needle through rubber top of the Humalog bottle and inject the air into the bottle.
7. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
8. Making sure the tip of the needle is in the Humalog, withdraw the correct dose into the syringe.
9. Before removing the needle from the bottle, check your syringe for air bubbles, which reduce the amount of Humalog. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
10. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.

Mixing Humalog with Longer-acting Human Insulins

1. Humalog should be mixed with longer-acting human insulins only on the advice of your doctor.
2. Draw air into your syringe equal to the amount of longer-acting insulin you are taking. Insert the needle into the longer-acting insulin bottle and inject the air. Withdraw the needle.
3. Now inject air into your Humalog bottle in the same manner, but **do not** withdraw the needle.
4. Turn the bottle and syringe upside down.
5. Making sure the tip of the needle is in the Humalog, withdraw the correct dose of Humalog into the syringe.
6. Before removing the needle from the bottle of Humalog, check your syringe for air bubbles, which reduce the amount of Humalog in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
7. Remove the needle from the bottle of Humalog and insert it into the bottle of the longer-acting insulin. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand and shake gently. Making sure the tip of the needle is in the insulin, withdraw your dose of longer-acting insulin.
8. Remove the needle and lay the syringe down so that the needle does not touch anything.

When you are mixing two types of insulin, always draw Humalog into the syringe first. Always mix the insulin preparations in this same sequence in order to maintain purity of the Humalog vial. You should inject your insulins immediately after mixing.

Syringes from different manufacturers may vary in the amount of space between the bottom line and the needle. Because of this, do not change:

- the sequence of mixing, or
- the model and brand of syringe or needle that the doctor has prescribed.

Injection

Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply gentle pressure over the injection site for several seconds. To avoid tissue damage, give the next injection at a site at least 1/2" from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you. Your usual Humalog dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your Humalog dose are:

Illness

Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine glucose and ketones frequently and call your doctor as instructed.

Pregnancy

Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor. Humalog has not been tested in pregnant or nursing women.

Geriatric Use

Elderly patients using Humalog had HbA_{1c} values and hypoglycemia rates similar to those observed in younger patients. The onset of action of Humalog may be different in elderly patients.

Medication

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs with blood-glucose-lowering activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and certain antidepressants. Your health care professional is aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin products during and for some time after the physical activity. Exercise may also speed up the effect of a Humalog dose, especially if the exercise involves the area of injection site. Discuss with your doctor how you should adjust your regimen to accommodate exercise.

Travel

Persons traveling across more than 2 time zones should consult their doctor concerning adjustments in their insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. **Missing or delaying meals**
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnorma1 behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

Therefore, it is important that assistance be obtained immediately.

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, changing insulin preparations, or intensified control (3 or more injections per day) of diabetes. A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia and Diabetic Acidosis

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by any of the following:

1. Omitting your insulin or taking less than the doctor has prescribed
2. Eating significantly more than your meal plan suggests
3. Developing a fever, infection, or other significant stressful situation

In patients with insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With acidosis, urine tests show large amounts of glucose and acetone. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or diabetic acidosis can lead to nausea, vomiting, dehydration, loss of consciousness, or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy

Local Allergy — Patients occasionally experience redness, swelling, and itching at the site of injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

Systemic Allergy — Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction, notify a doctor immediately.

ADDITIONAL INFORMATION

Additional information about diabetes may be obtained from your diabetes educator.

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314, 1-800-DIABETES (1-800-342-2383). Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). Additional information about Humalog can be obtained by calling 1-888-88-LILLY (1-888-885-4559).

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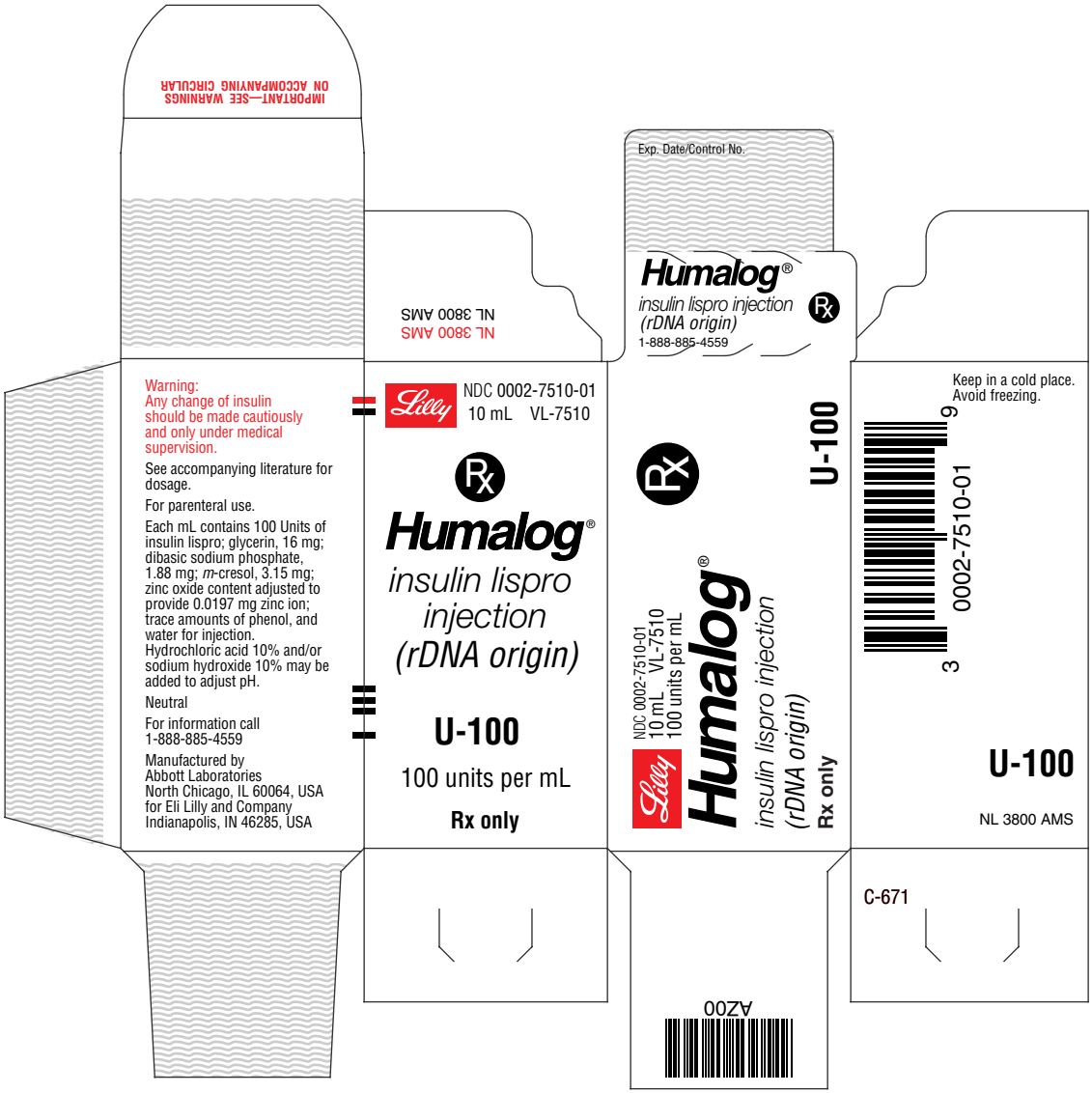

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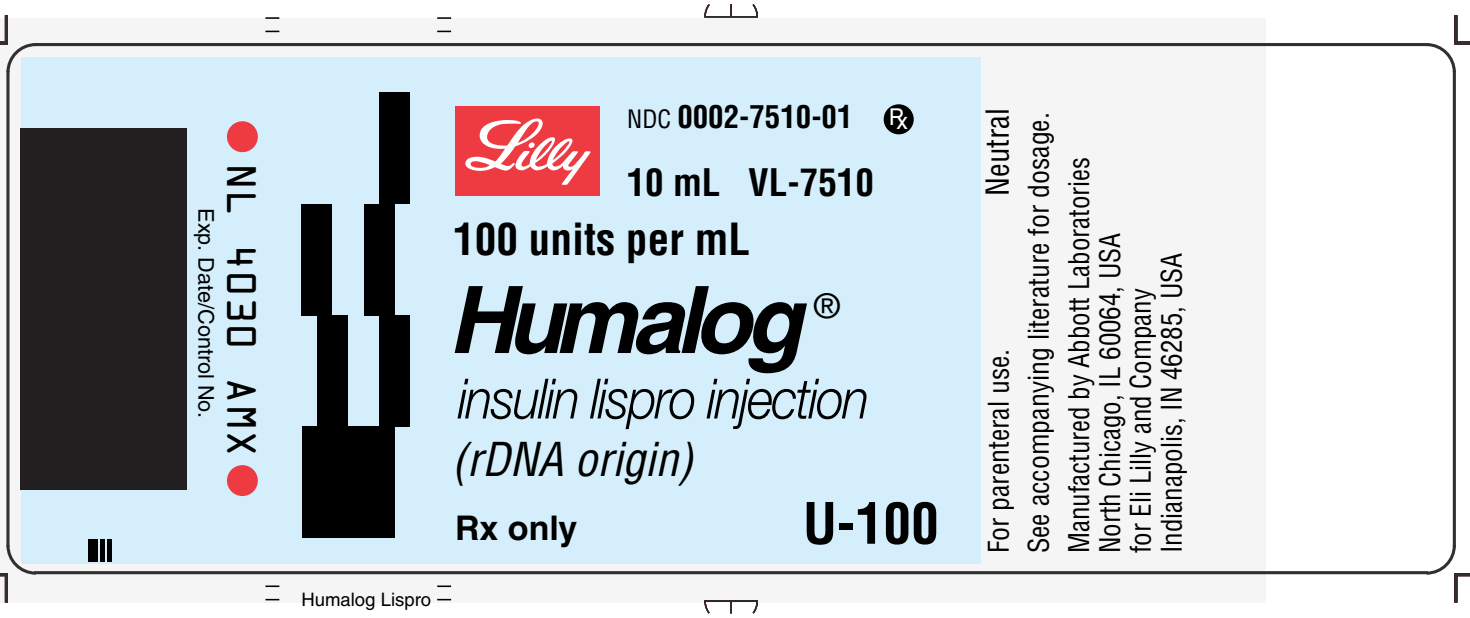
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