

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMALOG safely and effectively. See full prescribing information for HUMALOG.

**HUMALOG (insulin lispro injection), for subcutaneous or intravenous use**

**Initial U.S. Approval: 1996**

### INDICATIONS AND USAGE

HUMALOG is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1)

### DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for important administration instructions. (2.1, 2.2, 2.3, 2.4)
- Subcutaneous injection: Administer HUMALOG® U-100 or U-200 by subcutaneous injection within 15 minutes before a meal or immediately after a meal. (2.2)
- Continuous subcutaneous infusion (Insulin Pump): Administer HUMALOG U-100 by continuous subcutaneous infusion using an insulin pump. DO NOT administer HUMALOG U-200 by continuous subcutaneous infusion. (2.2)
- Intravenous Infusion: Administer HUMALOG U-100 by intravenous infusion ONLY after dilution and under medical supervision. DO NOT administer HUMALOG U-200 by intravenous infusion. (2.2)
- The dosage of HUMALOG must be individualized based on the route of administration and the individual's metabolic needs, blood glucose monitoring results and glycemic control goal. (2.3)
- Do not perform dose conversion when using the HUMALOG U-100 or U-200 KwikPens. The dose window shows the number of insulin units to be delivered and no conversion is needed. (2.1, 2.3)
- Do not mix HUMALOG U-200 with any other insulin. (2.4)

### DOSAGE FORMS AND STRENGTHS

HUMALOG 100 units/mL (U-100) is available as: (3)

- 10 mL vials
- 3 mL vials
- 3 mL Humalog KwikPen® (prefilled)
- 3 mL Humalog® Junior KwikPen® (prefilled)
- 3 mL cartridges

HUMALOG 200 units/mL (U-200) is available as: (3)

- 3 mL Humalog KwikPen® (prefilled)

### CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to HUMALOG or any of its excipients. (4)

### WARNINGS AND PRECAUTIONS

- *Never share* a HUMALOG KwikPen, cartridge, reusable pen compatible with Lilly 3 mL cartridges, or syringe between patients, even if the needle is changed. (5.1)
- *Hyper- or Hypoglycemia with Changes in Insulin Regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)
- *Hypoglycemia:* May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3, 7, 8.6, 8.7)
- *Hypoglycemia Due to Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. Do not transfer HUMALOG U-200 from the HUMALOG KwikPen to a syringe as overdosage and severe hypoglycemia can result. (5.4)
- *Hypersensitivity Reactions:* May be life-threatening. Discontinue HUMALOG, monitor and treat if indicated. (5.5)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
- *Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)
- *Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:* Monitor glucose and administer HUMALOG U-100 by subcutaneous injection if pump malfunction occurs. (5.8)

### ADVERSE REACTIONS

Adverse reactions associated with HUMALOG include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- *Drugs that Affect Glucose Metabolism:* Adjustment of insulin dosage may be needed. (7.1, 7.2, 7.3)
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent. (5.3, 7.4)

### USE IN SPECIFIC POPULATIONS

*Pediatrics:* Not studied in children with type 2 diabetes or in children with type 1 diabetes <3 years of age. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

**Revised: 06/2017**

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

HUMALOG is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

**2 DOSAGE AND ADMINISTRATION****2.1 Important Administration Instructions**

- Always check insulin labels before administration *[see Warnings and Precautions (5.4)]*.
- Inspect HUMALOG visually before use. It should appear clear and colorless. Do not use HUMALOG if particulate matter or coloration is seen.
- Do NOT mix HUMALOG U-100 with other insulins when administering using a continuous subcutaneous infusion pump.
- Do NOT transfer HUMALOG U-200 from the KwikPen to a syringe for administration *[see Warnings and Precautions (5.4)]*.
- Do NOT perform dose conversion when using any HUMALOG U-100 or U-200 KwikPens. **The dose window shows the number of insulin units to be delivered and no conversion is needed.**
  - Humalog U-100 and U-200 KwikPens are designed to dial doses in increments of 1 unit.
  - Humalog Junior KwikPen is designed to dial doses in 0.5 (1/2) unit increments.
- Do NOT mix HUMALOG U-200 with any other insulins.
- Do NOT administer HUMALOG U-200 using a continuous subcutaneous infusion pump (i.e., insulin pump).
- Do NOT administer HUMALOG U-200 intravenously.

**2.2 Route of Administration**Subcutaneous Injection: HUMALOG U-100 or U-200

- Administer the dose of HUMALOG U-100 or HUMALOG U-200 within fifteen minutes before a meal or immediately after a meal by injection into the subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks. To reduce the risk of lipodystrophy, rotate the injection site within the same region from one injection to the next *[see Adverse Reactions (6)]*.
- HUMALOG administered by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

Continuous Subcutaneous Infusion (Insulin Pump): HUMALOG U-100 ONLY

- Do NOT administer HUMALOG U-200 using a continuous subcutaneous infusion pump.
- Administer HUMALOG U-100 by continuous subcutaneous infusion into the subcutaneous tissue of the abdominal wall. Rotate infusion sites within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- Follow healthcare professional recommendations when setting basal and meal time infusion rate.
- Do NOT dilute or mix HUMALOG U-100 when administering by continuous subcutaneous infusion.
- Change HUMALOG U-100 in the pump reservoir at least every 7 days.
- Change the infusion sets and the infusion set insertion site at least every 3 days.
- Do NOT expose HUMALOG U-100 in the pump reservoir to temperatures greater than 98.6°F (37°C).
- Use HUMALOG U-100 in pump systems suitable for insulin infusion *[see Patient Counseling Information (17.7)]*.

Intravenous Administration: HUMALOG U-100 ONLY

- Do NOT administer HUMALOG U-200 intravenously.

- Dilute HUMALOG U-100 to concentrations from 0.1 unit/mL to 1.0 unit/mL using 0.9% sodium chloride.
- Administer HUMALOG U-100 intravenously **ONLY** under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [see *Warnings and Precautions* (5.3, 5.6) and *How Supplied/Storage and Handling* (16.4)].

## 2.3 Dosage Information

- Individualize and adjust the dosage of HUMALOG based on route of administration, the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness [see *Warnings and Precautions* (5.2, 5.3) and *Use in Specific Populations* (8.6, 8.7)].
- Do NOT perform dose conversion when using any HUMALOG U-100 or U-200 KwikPens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

## 2.4 Dosage Adjustment Due to Drug Interactions

- Dosage adjustment may be needed when HUMALOG is coadministered with certain drugs [see *Drug Interactions* (7)].
- Dosage adjustment may be needed when switching from another insulin to HUMALOG [see *Warnings and Precautions* (5.2)].
- Instructions for Mixing with Other Insulins

<b>HUMALOG U-100 subcutaneous injection route</b>	<ul style="list-style-type: none"> <li>• HUMALOG U-100 may be mixed with NPH insulin preparations <b>ONLY</b>.</li> <li>• If HUMALOG U-100 is mixed with NPH insulin, HUMALOG U-100 should be drawn into the syringe first. Injection should occur immediately after mixing.</li> </ul>
<b>HUMALOG U-100 continuous subcutaneous infusion route (Insulin Pump)</b>	<ul style="list-style-type: none"> <li>• <b>Do NOT mix</b> HUMALOG U-100 with any other insulin.</li> </ul>
<b>HUMALOG U-200 subcutaneous injection route</b>	<ul style="list-style-type: none"> <li>• <b>Do NOT mix</b> with any other insulin.</li> </ul>

## 3 DOSAGE FORMS AND STRENGTHS

HUMALOG 100 units per mL (U-100) is available as:

- 10 mL vials
- 3 mL vials
- 3 mL Humalog KwikPen (prefilled)
- 3 mL Humalog Junior KwikPen (prefilled)
- 3 mL cartridges

HUMALOG 200 units per mL (U-200) is available as:

- 3 mL Humalog KwikPen (prefilled)

## 4 CONTRAINDICATIONS

HUMALOG is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to HUMALOG or to any of its excipients.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Never Share a HUMALOG KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges<sup>1</sup>, or Syringe Between Patients

HUMALOG KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using HUMALOG vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

### 5.2 Hyper- or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see *Warnings and Precautions* (5.3)] or hyperglycemia. These changes should be made cautiously and under close medical supervision and the frequency of blood glucose monitoring should be increased.

### 5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including HUMALOG. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see *Drug Interactions* (7)], or in patients who experience recurrent hypoglycemia.

#### Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of HUMALOG may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see *Clinical Pharmacology* (12.2)]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions* (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations* (8.6, 8.7)].

#### Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

### **5.4 Hypoglycemia Due to Medication Errors**

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between HUMALOG and other insulins, instruct patients to always check the insulin label before each injection.

Do not transfer HUMALOG U-200 from the HUMALOG KwikPen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.3)].

### **5.5 Hypersensitivity Reactions**

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG. If hypersensitivity reactions occur, discontinue HUMALOG; treat per standard of care and monitor until symptoms and signs resolve [see *Adverse Reactions* (6.1)]. HUMALOG is contraindicated in patients who have had hypersensitivity reactions to HUMALOG or any of its excipients [see *Contraindications* (4)].

### **5.6 Hypokalemia**

All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

### **5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists**

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including HUMALOG, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

### **5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction**

Malfunction of the insulin pump or insulin infusion set or insulin degradation can rapidly lead to hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure [see *How Supplied/Storage and Handling* (16.2) and *Patient Counseling Information* (17.7)].

## **6 ADVERSE REACTIONS**

#### Observed with HUMALOG U-100

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions* (5.3)].
- Hypokalemia [see *Warnings and Precautions* (5.6)].

### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus**  
(adverse events with frequency  $\geq 5\%$ )

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)
Flu syndrome	28 (34.6)	28 (32.6)
Pharyngitis	27 (33.3)	29 (33.7)
Rhinitis	20 (24.7)	25 (29.1)
Headache	24 (29.6)	19 (22.1)
Pain	16 (19.8)	14 (16.3)
Cough increased	14 (17.3)	15 (17.4)
Infection	11 (13.6)	18 (20.9)
Nausea	5 (6.2)	13 (15.1)
Accidental injury	7 (8.6)	10 (11.6)
Surgical procedure	5 (6.2)	12 (14.0)
Fever	5 (6.2)	10 (11.6)
Abdominal pain	6 (7.4)	7 (8.1)
Asthenia	6 (7.4)	7 (8.1)
Bronchitis	6 (7.4)	6 (7.0)
Diarrhea	7 (8.6)	5 (5.8)
Dysmenorrhea	5 (6.2)	6 (7.0)
Myalgia	6 (7.4)	5 (5.8)
Urinary tract infection	5 (6.2)	4 (4.7)

**Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus**  
(adverse events with frequency  $\geq 5\%$ )

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)
Headache	63 (11.6)	66 (9.3)
Pain	77 (10.8)	71 (10.0)
Infection	72 (10.1)	54 (7.6)
Pharyngitis	47 (6.6)	58 (8.2)
Rhinitis	58 (8.1)	47 (6.6)
Flu syndrome	44 (6.2)	58 (8.2)
Surgical procedure	53 (7.4)	48 (6.8)

#### Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

#### Lipodystrophy

Long-term use of insulin, including HUMALOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy [see *Dosage and Administration* (2.2)].

#### Weight gain

Weight gain can occur with insulin therapy, including HUMALOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

#### Peripheral Edema

Insulin, including HUMALOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

#### Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII) — HUMALOG U-100

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for HUMALOG U-100 and regular human insulin treated patients (see Table 3).

**Table 3: Catheter Occlusions and Infusion Site Reactions**

	HUMALOG U-100 (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10

Infusion site reactions	2.6% (1/38)	2.6% (1/39)
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In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

#### Allergic Reactions

**Local Allergy** — As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. 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** — Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG [see *Contraindications* (4)].

#### Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

## **6.2 Postmarketing Experience**

### HUMALOG U-100

The following additional adverse reactions have been identified during post-approval use of HUMALOG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use [see *Patient Counseling Information* (17.4)].

## **7 DRUG INTERACTIONS**

### **7.1 Drugs That May Increase the Risk of Hypoglycemia**

The risk of hypoglycemia associated with HUMALOG use may be increased when co-administered with antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide). Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.

### **7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of HUMALOG**

The glucose lowering effect of HUMALOG may be decreased when co-administered with corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.

### **7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of HUMALOG**

The glucose lowering effect of HUMALOG may be increased or decreased with co-administered with beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.

### **7.4 Drugs That May Blunt Signs and Symptoms of Hypoglycemia**

The signs and symptoms of hypoglycemia [see *Warnings and Precautions* (5.3)] may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with HUMALOG.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

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.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

### 8.3 Nursing Mothers

It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

### 8.4 Pediatric Use

HUMALOG is approved for use in children for subcutaneous daily injections [see *Clinical Studies (14)*]. Only the U-100 formulation of HUMALOG is approved for use in children by continuous subcutaneous infusion in insulin pumps. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

### 8.5 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 had type 2 diabetes. HbA<sub>1c</sub> 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.

### 8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring [see *Clinical Pharmacology (12.3)*].

### 8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring [see *Clinical Pharmacology (12.3)*].

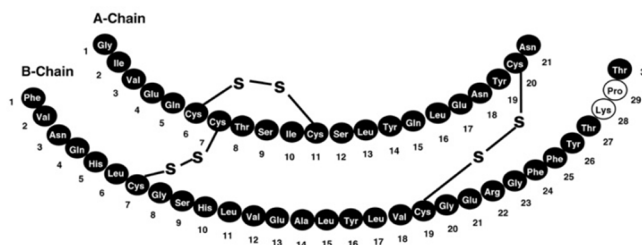
## 10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. 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. Hypokalemia must be corrected appropriately.

## 11 DESCRIPTION

HUMALOG<sup>®</sup> (insulin lispro injection) is a rapid-acting human insulin analog used to lower blood glucose. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analog and has the empirical formula C<sub>257</sub>H<sub>383</sub>N<sub>65</sub>O<sub>77</sub>S<sub>6</sub> and a molecular weight of 5808, both identical to that of human insulin.

HUMALOG has the following primary structure:



HUMALOG is a sterile, aqueous, clear, and colorless solution. Each milliliter of HUMALOG U-100 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. The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%. Each milliliter of HUMALOG U-200 contains insulin lispro 200 units, 16 mg glycerin, 5 mg tromethamine, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.046 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%.

## 12 CLINICAL PHARMACOLOGY

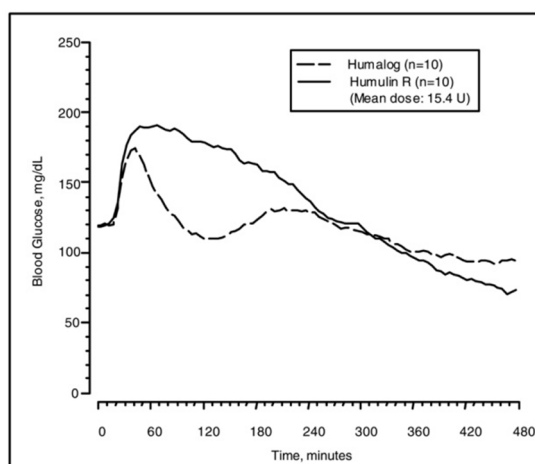
### 12.1 Mechanism of Action

Regulation of glucose metabolism is the primary activity of insulins and insulin analogs, including insulin lispro. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

### 12.2 Pharmacodynamics

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. Studies in normal volunteers and patients with diabetes demonstrated that HUMALOG has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

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 1 should be considered only as general guidelines. 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 [see *Warnings and Precautions* (5.2)].



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

<sup>a</sup> Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

**Intravenous Administration of HUMALOG U-100** — The glucose lowering effect of intravenously administered HUMALOG was tested in 21 patients with type 1 diabetes. For the study, the patients' usual doses of insulin were held and blood glucose concentrations were allowed to reach a stable range of 200 to 260 mg/dL during a one to three hours run-in phase. The run-in phase was followed by a 6-hour assessment phase. During the assessment phase, patients received intravenous HUMALOG at an initial infusion rate of 0.5 units/hour. The infusion rate of HUMALOG could be adjusted at regular timed intervals to achieve and maintain blood glucose concentrations between 100 to 160 mg/dL.

The mean blood glucose levels during the assessment phase for patients on HUMALOG therapy are summarized below in Table 4. All patients achieved the targeted glucose range at some point during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 17 of 20 patients treated with HUMALOG. The average time ( $\pm$ SE) required to attain near normoglycemia was  $129 \pm 14$  minutes for HUMALOG.

**Table 4: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of HUMALOG U-100**

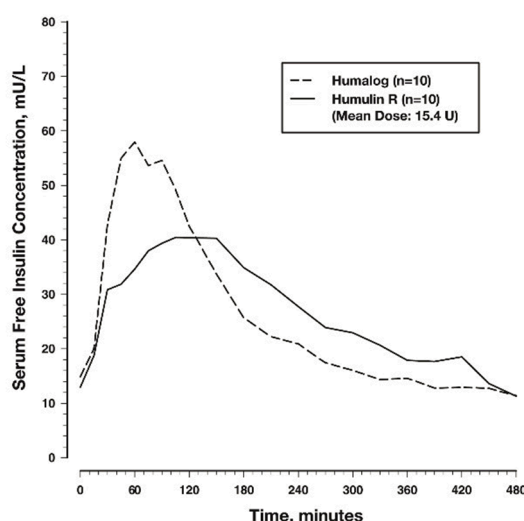
Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous <sup>a</sup>
0	224 $\pm$ 16
30	205 $\pm$ 21
60	195 $\pm$ 20
120	165 $\pm$ 26
180	140 $\pm$ 26
240	123 $\pm$ 20
300	120 $\pm$ 27
360	122 $\pm$ 25

<sup>a</sup> Results shown as mean  $\pm$  SD

The pharmacodynamics of a single 20 unit dose of HUMALOG U-200 administered subcutaneously were compared to the pharmacodynamics of a single 20 unit dose of HUMALOG U-100 administered subcutaneously in a euglycemic clamp study enrolling healthy subjects. In this study, the overall, maximum, and time to maximum glucose lowering effect were similar between HUMALOG U-200 and HUMALOG U-100. The mean area under the glucose infusion rate curves (measure of overall pharmacodynamic effect) were 125 g and 126 g for HUMALOG U-200 and HUMALOG U-100, respectively. The maximum glucose infusion rate was 534 mg/min and 559 mg/min and the corresponding median time (min, max) to maximum effect were 2.8 h (0.5 h – 6.3 h) and 2.4 h (0.5 h – 4.7 h) for HUMALOG U-200 and HUMALOG U-100, respectively.

### 12.3 Pharmacokinetics

**Absorption and Bioavailability** — Studies in healthy volunteers and patients with diabetes demonstrated that HUMALOG is absorbed more quickly than regular human insulin. In healthy volunteers given subcutaneous doses of HUMALOG ranging from 0.1 to 0.4 unit/kg, peak serum levels were seen 30 to 90 minutes after dosing. When healthy volunteers received equivalent doses of regular human insulin, peak insulin levels occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes (see Figure 2).



**Figure 2: Serum HUMALOG and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes<sup>a</sup>.**

<sup>a</sup> Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

HUMALOG U-100 was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 unit/kg at abdominal, deltoid, or femoral subcutaneous sites. After HUMALOG was administered in the abdomen, serum drug levels were higher and the duration of action was slightly shorter than after deltoid or thigh administration. Bioavailability of HUMALOG is similar to that of regular human insulin. The absolute bioavailability after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

The results of a study in healthy subjects demonstrated that HUMALOG U-200 is bioequivalent to HUMALOG U-100 following administration of a single 20 unit dose.

The mean observed area under the serum insulin concentration-time curve from time zero to infinity was 2360 pmol hr/L and 2390 pmol hr/L for HUMALOG U-200 and HUMALOG U-100, respectively. The corresponding mean peak serum insulin concentration was 795 pmol/L and 909 pmol/L for HUMALOG U-200 and HUMALOG U-100, respectively. The median time to maximum concentration was 1.0 hour for both formulations.

**Distribution** — When administered intravenously as bolus injections of 0.1 and 0.2 U/kg dose in two separate groups of healthy subjects, the mean volume of distribution of HUMALOG appeared to decrease with increase in dose (1.55 and 0.72 L/kg, respectively) in contrast to that of regular human insulin for which, the volume of distribution was comparable across the two dose groups (1.37 and 1.12 L/kg for 0.1 and 0.2 U/kg dose, respectively).

**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** — After subcutaneous administration of HUMALOG, the  $t_{1/2}$  is shorter than that of regular human insulin (1 versus 1.5 hours, respectively). When administered intravenously, HUMALOG and regular human insulin demonstrated similar dose-dependent clearance, with a mean clearance of 21.0 mL/min/kg and 21.4 mL/min/kg, respectively (0.1 unit/kg dose), and 9.6 mL/min/kg and 9.4 mL/min/kg, respectively (0.2 unit/kg dose). Accordingly, HUMALOG demonstrated a mean  $t_{1/2}$  of 0.85 hours (51 minutes) and 0.92 hours (55 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses, and regular human insulin mean  $t_{1/2}$  was 0.79 hours (47 minutes) and 1.28 hours (77 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses.

#### **Specific Populations**

The effects of age, gender, race, obesity, pregnancy, or smoking on the pharmacokinetics of HUMALOG have not been studied.

**Renal Impairment** — Type 2 diabetic patients with varying degree of renal impairment showed no difference in pharmacokinetics of regular insulin and HUMALOG. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including HUMALOG, may be necessary in patients with renal dysfunction.

**Hepatic Impairment** — Type 2 diabetic patients with impaired hepatic function showed no effect on the pharmacokinetics of HUMALOG as compared to patients with no hepatic dysfunction. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including HUMALOG, may be necessary in patients with hepatic dysfunction.

### **13 NONCLINICAL TOXICOLOGY**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Standard 2-year carcinogenicity studies in animals have not been performed. In Fischer 344 rats, a 12-month repeat-dose toxicity study was conducted with insulin lispro at subcutaneous doses of 20 and 200 units/kg/day (approximately 3 and 32 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area). Insulin lispro did not produce important target organ toxicity including mammary tumors at any dose.

Insulin lispro was not mutagenic in the following genetic toxicity assays: bacterial mutation, unscheduled DNA synthesis, mouse lymphoma, chromosomal aberration and micronucleus assays.

Male fertility was not compromised when male rats given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area) for 6 months were mated with untreated female rats. In a combined fertility, perinatal, and postnatal study in male and female rats given 1, 5, and 20 units/kg/day subcutaneously (0.16, 0.8, and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area), mating and fertility were not adversely affected in either gender at any dose.

#### **13.2 Animal Toxicology and/or Pharmacology**

In standard biological assays in fasted rabbits, 0.2 unit/kg of insulin lispro injected subcutaneously had the same glucose-lowering effect and had a more rapid onset of action as 0.2 unit/kg of regular human insulin.

### **14 CLINICAL STUDIES**

The safety and efficacy of HUMALOG U-100 were studied in children, adolescent, and adult patients with type 1 diabetes (n=789) and adult patients with type 2 diabetes (n=722).

#### **14.1 Type 1 Diabetes – Adults and Adolescents**

A 12-month, randomized, parallel, open-label, active-controlled study was conducted in patients with type 1 diabetes to assess the safety and efficacy of HUMALOG (n=81) compared with Humulin® R [REGULAR insulin human injection, USP (rDNA origin)] (n=86). HUMALOG was administered by subcutaneous injection immediately prior to meals and Humulin R was administered 30 to 45 minutes before meals. Humulin® U [ULTRALENTE® human insulin (rDNA origin) extended zinc suspension] was administered once or twice daily as the basal insulin. There was a 2- to 4-week run-in period with Humulin R and Humulin U before randomization. Most patients were Caucasian (97%). Forty-seven percent of the patients were male. The mean age was 31 years (range 12 to 70 years). Glycemic control, the total daily

doses of HUMALOG and Humulin R, and the incidence of severe hypoglycemia (as determined by the number of events that were not self-treated) were similar in the two treatment groups. There were no episodes of diabetic ketoacidosis in either treatment group.

**Table 5: Type 1 Diabetes Mellitus – Adults and Adolescents**

Treatment Duration Treatment in Combination with:	12 months Humulin U	
	HUMALOG	Humulin R
N	81	86
Baseline HbA <sub>1c</sub> (%) <sup>a</sup>	8.2 ± 1.4	8.3 ± 1.7
Change from baseline HbA <sub>1c</sub> (%) <sup>a</sup>	-0.1 ± 0.9	0.1 ± 1.1
Treatment Difference in HbA <sub>1c</sub> Mean (95% confidence interval)	0.4 (0.0, 0.8)	
Baseline short-acting insulin dose (units/kg/day)	0.3 ± 0.1	0.3 ± 0.1
End-of-Study short-acting insulin dose (units/kg/day)	0.3 ± 0.1	0.3 ± 0.1
Change from baseline short-acting insulin dose (units/kg/day)	0.0 ± 0.1	0.0 ± 0.1
Baseline Body weight (kg)	72 ± 12.7	71 ± 11.3
Weight change from baseline (kg)	1.4 ± 3.6	1.0 ± 2.6
Patients with severe hypoglycemia (n, %) <sup>b</sup>	14 (17%)	18 (21%)

<sup>a</sup> Values are Mean ± SD

<sup>b</sup> Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

## 14.2 Type 2 Diabetes – Adults

A 6-month randomized, crossover, open-label, active-controlled study was conducted in insulin-treated patients with type 2 diabetes (n=722) to assess the safety and efficacy of HUMALOG for 3 months followed by Humulin R for 3 months or the reverse sequence. HUMALOG was administered by subcutaneous injection immediately before meals and Humulin R was administered 30 to 45 minutes before meals. Humulin® N [NPH human insulin (rDNA origin) isophane suspension] or Humulin U was administered once or twice daily as the basal insulin. All patients participated in a 2- to 4-week run-in period with Humulin R and Humulin N or Humulin U. Most of the patients were Caucasian (88%), and the numbers of men and women in each group were approximately equal. The mean age was 58.6 years (range 23.8 to 85 years). The average body mass index (BMI) was 28.2 kg/m<sup>2</sup>. During the study, the majority of patients used Humulin N (84%) compared with Humulin U (16%) as their basal insulin. The reductions from baseline in HbA<sub>1c</sub> and the incidence of severe hypoglycemia (as determined by the number of events that were not self-treated) were similar between the two treatments from the combined groups (see Table 6).

**Table 6: Type 2 Diabetes Mellitus — Adults**

	Baseline	End point	
		HUMALOG + Basal	Humulin R + Basal
HbA <sub>1c</sub> (%) <sup>a</sup>	8.9 ± 1.7	8.2 ± 1.3	8.2 ± 1.4
Change from baseline HbA <sub>1c</sub> (%) <sup>a</sup>	—	-0.7 ± 1.4	-0.7 ± 1.3
Short-acting insulin dose (units/kg/day) <sup>a</sup>	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2
Change from baseline short-acting insulin dose (units/kg/day) <sup>a</sup>	—	0.0 ± 0.1	0.0 ± 0.1
Body weight (kg) <sup>a</sup>	80 ± 15	81 ± 15	81 ± 15
Weight change from baseline	—	0.8 ± 2.7	0.9 ± 2.6
Patients with severe hypoglycemia (n, %) <sup>b</sup>	—	15 (2%)	16 (2%)

<sup>a</sup> Values are Mean ± SD

<sup>b</sup> Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

## 14.3 Type 1 Diabetes – Pediatric and Adolescents

An 8-month, crossover study of adolescents with type 1 diabetes (n=463), aged 9 to 19 years, compared two subcutaneous multiple-dose treatment regimens: HUMALOG or Humulin R, both administered with Humulin N (NPH human insulin) as the basal insulin. HUMALOG achieved glycemic control comparable to Humulin R, as measured by HbA<sub>1c</sub> (see Table 7), and both treatment groups had a comparable incidence of hypoglycemia. In a 9-month, crossover study of prepubescent children (n=60) with type 1 diabetes, aged 3 to 11 years, HUMALOG administered immediately before meals, HUMALOG administered immediately after meals and Humulin R administered 30 minutes before meals resulted in similar glycemic control, as measured by HbA<sub>1c</sub>, and incidence of hypoglycemia, regardless of treatment group.

**Table 7: Pediatric Subcutaneous Administration of HUMALOG in Type 1 Diabetes**

	Baseline	End point	
		HUMALOG + NPH	Humulin R + NPH
HbA <sub>1c</sub> (%) <sup>a</sup>	8.6 ± 1.5	8.7 ± 1.5	8.7 ± 1.6
Change from baseline HbA <sub>1c</sub> (%) <sup>a</sup>	—	0.1 ± 1.1	0.1 ± 1.3
Short-acting insulin dose (units/kg/day) <sup>a</sup>	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
Change from baseline short-acting insulin dose (units/kg/day) <sup>a</sup>	—	0.01 ± 0.1	-0.01 ± 0.1
Body weight (kg) <sup>a</sup>	59.1 ± 13.1	61.1 ± 12.7	61.4 ± 12.9
Weight change from baseline (kg) <sup>a</sup>	—	2.0 ± 3.1	2.3 ± 3.0
Patients with severe hypoglycemia (n, %) <sup>b</sup>	—	5 (1.1%)	5 (1.1%)
Diabetic ketoacidosis (n, %)	—	11 (2.4%)	9 (1.9%)

<sup>a</sup> Values are Mean ± SD

<sup>b</sup> Severe hypoglycemia refers to hypoglycemia that required glucagon or glucose injection or resulted in coma.

#### 14.4 Type 1 Diabetes – Adults Continuous Subcutaneous Insulin Infusion

To evaluate the administration of HUMALOG U-100 via external insulin pumps, two open-label, crossover design studies were performed in patients with type 1 diabetes. One study involved 39 patients, ages 19 to 58 years, treated for 24 weeks with HUMALOG or regular human insulin. After 12 weeks of treatment, the mean HbA<sub>1c</sub> 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 (mean age 39, range 15 to 58 years) treated for 24 weeks with either HUMALOG or buffered regular human insulin. After 12 weeks of treatment, the mean HbA<sub>1c</sub> values decreased from 7.7% to 7.4% in the HUMALOG-treated patients and remained unchanged from 7.7% in the buffered regular human insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in both studies.

#### 14.5 Type 1 Diabetes – Pediatric Continuous Subcutaneous Insulin Infusion

A randomized, 16-week, open-label, parallel design, study of children and adolescents with type 1 diabetes (n=298) aged 4 to 18 years compared two subcutaneous infusion regimens administered via an external insulin pump: insulin aspart (n=198) or HUMALOG U-100 (n=100). These two treatments resulted in comparable changes from baseline in HbA<sub>1c</sub> and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 8). Infusion site reactions were similar between groups.

**Table 8: Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)**

	HUMALOG	Aspart
N	100	198
Baseline HbA <sub>1c</sub> (%) <sup>a</sup>	8.2 ± 0.8	8.0 ± 0.9
Change from Baseline HbA <sub>1c</sub> (%)	-0.1 ± 0.7	-0.1 ± 0.8
Treatment Difference in HbA <sub>1c</sub> , Mean (95% confidence interval)	0.1 (-0.3, 0.1)	
Baseline insulin dose (units/kg/24 hours) <sup>a</sup>	0.9 ± 0.3	0.9 ± 0.3
End-of-Study insulin dose (units/kg/24 hours) <sup>a</sup>	0.9 ± 0.2	0.9 ± 0.2
Patients with severe hypoglycemia (n, %) <sup>b</sup>	8 (8%)	19 (10%)
Diabetic ketoacidosis (n, %)	0 (0)	1 (0.5%)
Baseline body weight (kg) <sup>a</sup>	55.5 ± 19.0	54.1 ± 19.7
Weight Change from baseline (kg) <sup>a</sup>	1.6 ± 2.1	1.8 ± 2.1

<sup>a</sup> Values are Mean ± SD

<sup>b</sup> Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

HUMALOG is available as:

HUMALOG	Total Volume	Concentration	Total Units Available in Presentation	NDC Number	Max Dose per Injection	Dose Increment	Package Size
U-100 vial	10 mL	100 units/mL	1000 units	0002-7510-01	n/a	n/a	1 vial
U-100 vial	3 mL	100 units/mL	300 units	0002-7510-17	n/a	n/a	1 vial
U-100 cartridge <sup>1</sup>	3 mL	100 units/mL	300 units	0002-7516-59	n/a	n/a	5 cartridges
U-100 KwikPen	3 mL	100 units/mL	300 units	0002-8799-59	60 units	1 unit	5 pens
U-100 Junior KwikPen	3 mL	100 units/mL	300 units	0002-7714-59	30 units	0.5 units	5 pens

U-200 KwikPen	3 mL	200 units/mL	600 units	0002-7712-27	60 units	1 unit	5 pens
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Each prefilled KwikPen, cartridge, and reusable pen compatible with Lilly 3 mL cartridges is for use by a single patient. HUMALOG KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using HUMALOG vials must never share needles or syringes with another person.

## 16.2 Storage and Handling

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, and HUMALOG KwikPen should be stored at room temperature, below 86°F (30°C) and 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 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
<b>HUMALOG U-100</b>			
10 mL vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>
3 mL Humalog Junior KwikPen (prefilled)	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>
<b>HUMALOG U-200</b>			
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, <b>Do not refrigerate.</b>

Use in an External Insulin Pump — Change the HUMALOG U-100 in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG U-100 for Subcutaneous Injection — Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

## 16.3 Preparation and Handling

Diluted HUMALOG U-100 for Subcutaneous Injection — HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

## 16.4 Admixture for Intravenous Administration

Infusion bags prepared with HUMALOG U-100 are stable when stored in a refrigerator (2° to 8°C [36° to 46°F]) for 48 hours and then may be used at room temperature for up to an additional 48 hours [see *Dosage and Administration* (2.2)].

## 17 PATIENT COUNSELING INFORMATION

*Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).*

### 17.1 Never Share a HUMALOG KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges, or Syringe Between Patients

Advise patients that they must never share a HUMALOG KwikPen, cartridge, or reusable pen compatible with Lilly 3 mL cartridges with another person, even if the needle is changed. Advise patients using HUMALOG vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

### 17.2 Hypoglycemia

Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of HUMALOG therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or

skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia.

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery [see *Warnings and Precautions* (5.3)].

### 17.3 Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with HUMALOG. Inform patients on the symptoms of hypersensitivity reactions [see *Warnings and Precautions* (5.5)].

### 17.4 Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Inform patients that HUMALOG U-200 contains 2 times as much insulin in 1 mL as HUMALOG U-100.

Inform patients that the HUMALOG U-200 KwikPen dose window shows the number of units of HUMALOG U-200 to be injected and that no dose conversion is required.

Instruct patients to NOT transfer HUMALOG U-200 from the HUMALOG KwikPen to a syringe. The markings on the syringe will not measure the dose correctly and this can result in overdosage and severe hypoglycemia.

### 17.5 Administration Instruction for HUMALOG U-200

Instruct patients to NOT mix HUMALOG U-200 with any other insulin.

### 17.6 Women of Reproductive Potential

Advise females of reproductive potential with diabetes to inform their doctor if they are pregnant or are contemplating pregnancy [see *Use in Specific Populations* (8.1)].

### 17.7 Instructions For Patients Using Continuous Subcutaneous Insulin Pumps

Patients using external pump infusion therapy should be trained appropriately.

The following insulin pumps have been tested in HUMALOG clinical trials conducted by Eli Lilly and Company.

- Disetronic® H-Tron® plus V100, D-Tron® and D-Tronplus® with Disetronic Rapid infusion sets<sup>2</sup>
- MiniMed® Models 506, 507 and 508 and Polyfin® infusion sets<sup>3</sup>

HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps. Before using HUMALOG in a pump system, read the pump label to make sure the pump is indicated for continuous delivery of fast-acting insulin. HUMALOG is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual. Do not use HUMALOG U-200 in an external insulin pump.

**To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), insulin in the reservoir should be replaced at least every 7 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.**

**Insulin exposed to temperatures higher than 98.6°F (37°C) should be discarded.** The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to the healthcare professional, and a new site selected because continued infusion may increase the skin reaction or alter the absorption of HUMALOG.

Pump or infusion set malfunctions or insulin degradation can lead to rapid hyperglycemia and ketosis. This is especially pertinent for rapid acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their healthcare professionals [see *Dosage and Administration* (2.2) and *How Supplied/Storage and Handling* (16.2)].

<sup>1</sup> 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Luxura® HD insulin delivery device, and Disetronic D-TRON® and D-TRON® Plus pumps.

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