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 adult and pediatric patients 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 (2.2):
  - Administer HUMALOG® U-100 or U-200 by subcutaneous injection into the abdominal wall, thigh, upper arm, or buttocks within 15 minutes before a meal or immediately after a meal.
  - Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
- Continuous subcutaneous infusion (Insulin Pump) (2.2):
  - Refer to the insulin infusion pump user manual to see if HUMALOG can be used. Use in accordance with the insulin pump instructions for use.
  - Administer HUMALOG U-100 by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer.
  - Rotate infusion sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
  - DO NOT administer HUMALOG U-200 by continuous subcutaneous infusion.
- Intravenous Infusion (2.2):
  - Administer HUMALOG U-100 by intravenous infusion ONLY after dilution and under medical supervision. DO NOT administer HUMALOG U-200 by intravenous infusion.
- 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 prefilled pens. 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----------

Injection: 100 units/mL (U-100) is available as: (3)
- 10 mL multiple-dose vial
- 3 mL multiple-dose vial
- 3 mL single-patient-use KwikPen® prefilled pen
- 3 mL single-patient-use Tempo Pen™ prefilled pen
- 3 mL single-patient-use Junior KwikPen® prefilled pen
- 3 mL single-patient-use cartridges

Injection: 200 units/mL (U-200) is available as: (3)
- 3 mL single-patient-use KwikPen® prefilled pen

---------- CONTRAINDICATIONS ----------

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

----------WARNINGS AND PRECAUTIONS ----------

- *Never share* a HUMALOG prefilled pen, cartridge, reusable pen compatible with Lilly 3 mL cartridges, or syringe between patients, even if the needle is changed. (5.1)
- *Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased 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.

---------- DRUG INTERACTIONS ----------

- *Drugs that may increase the risk of hypoglycemia:* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7).
- *Drugs that may decrease the blood glucose lowering effect:* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7).
- *Drugs that may increase or decrease the blood glucose lowering effect:* alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7).
- *Drugs that may blunt the signs and symptoms of hypoglycemia:* beta-blockers, clonidine, guanethidine, and reserpine (7).

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

Revised: 07/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HUMALOG is indicated to improve glycemic control in adult and pediatric patients 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.
- Use HUMALOG prefilled pens with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- Do NOT mix HUMALOG U-100 with other insulins when using a continuous subcutaneous infusion pump.
- Do NOT transfer HUMALOG U-200 from the prefilled pen 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 prefilled pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

2.2 Administration Instructions for the Approved Routes 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.
- Rotate the injection site within the same region from one injection to the next (abdominal wall, thigh, upper arm, or buttocks) to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- HUMALOG administered by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
- The HUMALOG U-100 KwikPen, HUMALOG U-100 Tempo Pen and HUMALOG U-200 KwikPen each dial in 1 unit increments and delivers a maximum dose of 60 units per injection.
- The HUMALOG U-100 Junior KwikPen dials in 0.5 unit increments and delivers a maximum dose of 30 units per injection.

Subcutaneous Injection: Diluted HUMALOG U-100

- HUMALOG U-100 may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection ONLY under medical supervision. Dilute one part HUMALOG U-100 to:
  - Nine parts diluent to yield a concentration one-tenth that of HUMALOG U-100 (equivalent to U-10).
  - One part diluent to yield a concentration one-half that of HUMALOG U-100 (equivalent to U-50).
- Diluted HUMALOG for subcutaneous injection may be stored for 28 days when refrigerated at 41°F (5°C) and for 14 days at room temperature up to 80°F (30°C).

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

- Do NOT administer HUMALOG U-200 using a continuous subcutaneous infusion pump.

- Refer to the continuous subcutaneous insulin infusion pump user manual to see if HUMALOG can be used with the insulin pump. Use HUMALOG in accordance with the insulin pump system's instructions for use.
- Administer HUMALOG U-100 by continuous subcutaneous infusion in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*.
- Train patients using continuous subcutaneous insulin infusion therapy to administer insulin by injection and have alternate insulin therapy available in case of insulin pump failure *[see Warnings and Precautions (5.8)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Change HUMALOG U-100 in the pump reservoir at least every 7 days or according to the pump user manual, whichever is shorter.
- Change the infusion set and the infusion set insertion site according to the manufacturer's user manual.
- Do NOT dilute or mix HUMALOG U-100 when administering by continuous subcutaneous infusion.
- Do NOT expose HUMALOG U-100 in the pump reservoir to temperatures greater than 98.6°F (37°C).

Intravenous Administration: HUMALOG U-100 ONLY
- Do NOT administer HUMALOG U-200 intravenously.
- 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)]*.
- Dilute HUMALOG U-100 to concentrations from 0.1 unit/mL to 1.0 unit/mL using 0.9% Sodium Chloride Injection, USP.
- 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.

2.3 Dosage Recommendations
- 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.
- When switching from another insulin to HUMALOG, a different dosage of HUMALOG may be needed *[see Warnings and Precautions (5.2)]*.
- Dosage modifications 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 prefilled pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

2.4 Dosage Modifications for Drug Interactions
Dosage modification may be needed when HUMALOG is used concomitantly with certain drugs *[see Drug Interactions (7)]*.

2.5 Instructions for Mixing with Other Insulins
The table below includes administration instructions regarding mixing HUMALOG U-100 and HUMALOG U-200 with other insulins.

HUMALOG U-100 subcutaneous injection route	• HUMALOG U-100 may be mixed with NPH insulin preparations ONLY. • 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.
HUMALOG U-100 continuous subcutaneous infusion route (Insulin Pump)	Do NOT mix HUMALOG U-100 with any other insulin.
HUMALOG U-200 subcutaneous injection route	Do NOT mix with any other insulin.

3 DOSAGE FORMS AND STRENGTHS
Injection: 100 units/mL (U-100) clear and colorless solution available as:
- 10 mL multiple-dose vial
- 3 mL multiple-dose vial
- 3 mL single-patient-use KwikPen prefilled pen
- 3 mL single-patient-use Tempo Pen prefilled pen

- 3 mL single-patient-use Junior KwikPen prefilled pen
- 3 mL single-patient-use cartridges

Injection: 200 units/mL (U-200) clear and colorless solution available as:
- 3 mL single-patient-use KwikPen prefilled pen

4 CONTRAINDICATIONS

HUMALOG is contraindicated:
- during episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- in patients who are hypersensitive to insulin lispro or to any of the excipients in HUMALOG *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a HUMALOG Prefilled Pen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges[1], or Syringe Between Patients

HUMALOG prefilled pens, 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 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia *[see Adverse Reactions (6)]*.

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant antidiabetic products may be needed.

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 insulins, 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 insulin products 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 insulins, 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 insulin lispro or any of the excipients in HUMALOG *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulins, 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)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*.
- Hypoglycemia Due to Medication Errors *[see Warnings and Precautions (5.4)].*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)].*
- Hypokalemia *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials 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.

Common adverse reactions, excluding hypoglycemia, were defined as events that occurred in ≥5% of patients treated with insulin lispro or regular human insulin. The frequencies of adverse reactions during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Adverse Reactions That Occurred in ≥5% in Patients with Type 1 Diabetes Mellitus

	HUMALOG (%) (n=81)	Regular human insulin (%) (n=86)
Flu syndrome	34.6	32.6
Pharyngitis	33.3	33.7
Rhinitis	24.7	29.1
Headache	29.6	22.1
Pain	19.8	16.3
Cough increased	17.3	17.4
Infection	13.6	20.9
Nausea	6.2	15.1
Accidental injury	8.6	11.6
Surgical procedure	6.2	14.0

Fever	6.2	11.6
Abdominal pain	7.4	8.1
Asthenia	7.4	8.1
Bronchitis	7.4	7.0
Diarrhea	8.6	5.8
Dysmenorrhea	6.2	7.0
Myalgia	7.4	5.8
Urinary tract infection	6.2	4.7

Table 2: Adverse Reactions That Occurred in ≥5% in Patients with Type 2 Diabetes Mellitus

	HUMALOG (%) (n=714)	**Regular human insulin (%) (n=709)**
Headache	11.6	9.3
Pain	10.8	10.0
Infection	10.1	7.6
Pharyngitis	6.6	8.2
Rhinitis	8.1	6.6
Flu syndrome	6.2	8.2
Surgical procedure	7.4	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.

Hypoglycemia
Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including HUMALOG.

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 *[see Dosage and Administration (2.2)]*.

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

Peripheral Edema
Insulins, 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)

In a randomized, 16-week, open-label, parallel design study of pediatric patients with type 1 diabetes, adverse reactions 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 reactions were infusion site erythema and infusion site reaction.

Allergic Reactions
Local Allergy — As with any insulin, 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.

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

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 post-approval use.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7 DRUG INTERACTIONS

The table below includes clinically significant drug interactions with HUMALOG.

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of HUMALOG	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of HUMALOG	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when HUMALOG is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies with insulin lispro used during pregnancy have not reported an association between insulin lispro and the induction of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

Pregnant rats and rabbits were exposed to insulin lispro in animal reproduction studies during organogenesis. No adverse effects on embryo/fetal viability or morphology were observed in offspring of rats exposed to insulin lispro at a dose approximately 3 times the human subcutaneous dose of 1 unit insulin lispro/kg/day. No adverse effects on embryo/fetal development were observed in offspring of rabbits exposed to insulin lispro at doses up to approximately 0.2 times the human subcutaneous dose of 1 unit/kg/day *(see Data)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from retrospective studies and meta-analyses do not report an association with insulin lispro and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin lispro is used during pregnancy. However, these studies cannot definitely establish or exclude the absence of any risk because of methodological limitations including small sample size, selection bias, confounding by unmeasured factors, and some lacking comparator groups.

Animal Data

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 1, 5, and 20 units/kg/day (0.2, 0.8, and 3 times the human subcutaneous dose of 1 unit insulin lispro/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 0.2 times the human subcutaneous dose of 1 unit insulin lispro/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.

8.2 Lactation

Risk Summary

Available data from published literature suggests that exogenous human insulin products, including insulin lispro, are transferred into human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including insulin lispro, on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from HUMALOG or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of HUMALOG to improve glycemic control have been established in pediatric patients with diabetes mellitus. Use of HUMALOG for this indication is supported by evidence from adequate and well-controlled studies in 831 pediatric patients with type 1 diabetes mellitus aged 3 years and older and from studies in adults with diabetes mellitus *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].*

8.5 Geriatric Use

Of the total number of patients (n=2,834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these patients had type 2 diabetes. HbA_{1c} values and hypoglycemia rates did not differ by

age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

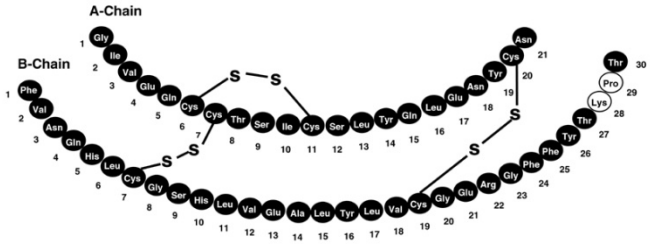
8.6 Renal Impairment
Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring *[see Clinical Pharmacology (12.3)]*.

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 a glucagon product for emergency use 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
Insulin lispro is a rapid-acting human insulin analog 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 $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5.808 kDa, both identical to that of human insulin.

Insulin lispro has the following primary structure:



HUMALOG (insulin lispro) injection is a sterile, clear, and colorless solution for subcutaneous or intravenous use.

Each mL of HUMALOG U-100 contains 100 units of insulin lispro, and the inactive ingredients: dibasic sodium phosphate (1.0 mg), glycerin (16 mg), metacresol (3.15 mg), trace amounts of phenol, zinc oxide (content adjusted to provide 0.0197 mg zinc ion), and Water for Injection, USP.

Each mL of HUMALOG U-200 contains 200 units of insulin lispro, and the inactive ingredients: glycerin (16 mg), metacresol (3.15 mg), trace amounts of phenol, tromethamine (5 mg), zinc oxide (content adjusted to provide 0.046 mg zinc ion), and Water for Injection, USP.

HUMALOG has a pH of 7.0 to 7.8.

Hydrochloric acid 10% and/or sodium hydroxide 10% is added to adjust the pH.

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)]*.

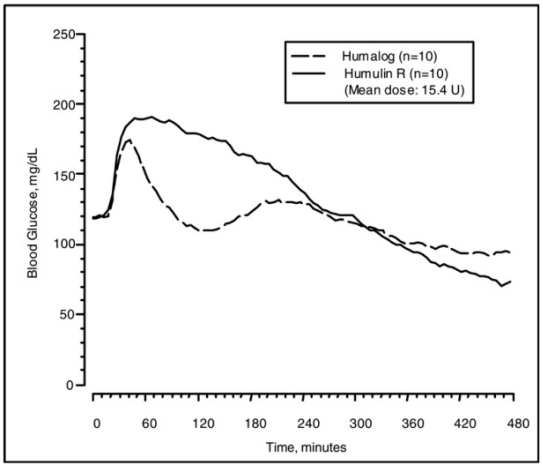


Figure 1: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].

[a] 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 (±SE) required to attain near normoglycemia was 129 ± 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[a]
0	224 ± 16
30	205 ± 21
60	195 ± 20
120	165 ± 26
180	140 ± 26
240	123 ± 20
300	120 ± 27
360	122 ± 25

[a] Results shown as mean ± 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).

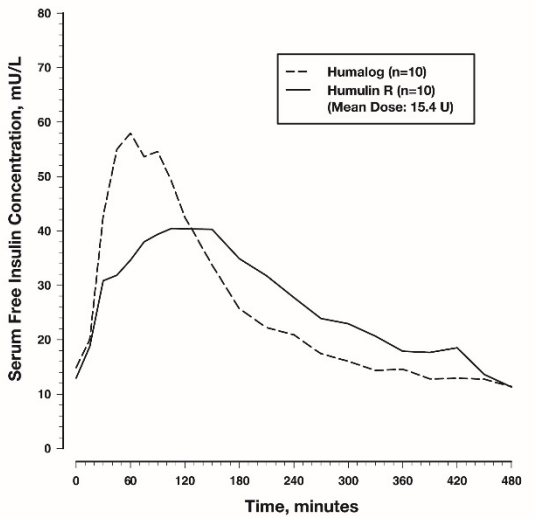


Figure 2: Serum HUMALOG and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].

[a] 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 *[see Use in Specific Populations (8.6)].*

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 *[see Use in Specific Populations (8.7)].*

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 (0.2, 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 pediatric 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 Pediatric Patients Aged 12 years and Older

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 [insulin human injection (100 units/mL)] (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 Pediatric Patients Aged 12 years and Older

Treatment Duration Treatment in Combination with:	12 months Humulin U	
	HUMALOG	Humulin R
N	81	86
Baseline HbA_{1c} (%)[a]	8.2 ± 1.4	8.3 ± 1.7
Change from baseline HbA_{1c} (%)[a]	-0.1 ± 0.9	0.1 ± 1.1
Treatment Difference in HbA_{1c} 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, %)[b]	14 (17%)	18 (21%)

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

14.2 Type 1 Diabetes – Pediatric Patients

An 8-month, crossover study of pediatric patients 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_{1c} (*see* Table 6), and both treatment groups had a comparable incidence of hypoglycemia. In a 9-month, crossover study of pediatric patients (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_{1c}, and incidence of hypoglycemia, regardless of treatment group.

Table 6: Pediatric Subcutaneous Administration of HUMALOG in Type 1 Diabetes

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

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia that required glucagon or glucose injection or resulted in coma.

14.3 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_{1c} values decreased from 7.8% to 7.2% in the HUMALOG-treated patients and from 7.8% to 7.5% in the regular human insulin-treated patients. Another study involved 60 patients (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_{1c} 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.

14.4 Type 1 Diabetes – Pediatric Continuous Subcutaneous Insulin Infusion

A randomized, 16-week, open-label, parallel design, study of pediatric patients 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_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment (*see* Table 7). Infusion site reactions were similar between groups.

Table 7: Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

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

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

14.5 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^2. 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_{1c} 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 8).

Table 8: Type 2 Diabetes Mellitus — Adults

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

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMALOG (insulin lispro) injection is a clear and colorless solution available as:

HUMALOG	Total Volume	Concentration	NDC Number	Package Size
U-100 multiple-dose vial	10 mL	100 units/mL	0002-7510-01	1 vial
U-100 multiple-dose vial	3 mL	100 units/mL	0002-7510-17	1 vial
U-100 single-patient-use cartridge[1]	3 mL	100 units/mL	0002-7516-59	5 cartridges
U-100 single-patient-use KwikPen	3 mL	100 units/mL	0002-8799-59	5 pens
U-100 single-patient-use Tempo Pen[a]	3 mL	100 units/mL	0002-8213-05	5 pens
U-100 single-patient-use Junior KwikPen	3 mL	100 units/mL	0002-7714-59	5 pens
U-200 single-patient-use KwikPen	3 mL	200 units/mL	0002-7712-27	2 pens

[a] Tempo Pen contains a component that allows for data connectivity when used with a compatible transmitter.

The U-100 KwikPen, U-100 Tempo Pen, and U-200 KwikPen dial in 1-unit increments. The U-100 Junior KwikPen dials in 0.5-unit increments.

Each prefilled pen, cartridge, and reusable pen compatible with Lilly 3 mL cartridges is for single-patient-use only. HUMALOG prefilled pens, 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

Dispense in the original sealed carton with the enclosed Instructions for Use.

Protect from direct heat and light. Do not freeze and do not use if it has been frozen.

See table below for storage information:

	Not In-Use (Unopened) Room Temperature (Up to 86°F [30°C])	Not In-Use (Unopened) Refrigerated (36° to 46°F [2° to 8°C])	In-Use (Opened) (see temperature below)
HUMALOG U-100*			
10 mL multiple-dose vial	28 days	Until expiration date	28 days Refrigerated or room temperature.
3 mL multiple-dose vial	28 days	Until expiration date	28 days Refrigerated or room temperature.
3 mL single-patient-use cartridge	28 days	Until expiration date	28 days Room temperature only (Do not refrigerate)
3 mL single-patient-use Humalog KwikPen	28 days	Until expiration date	28 days Room temperature only (Do not refrigerate)
3 mL single-patient-use Humalog Tempo Pen	28 days	Until expiration date	28 days Room temperature only (Do not refrigerate)
3 mL single-patient-use Humalog Junior KwikPen	28 days	Until expiration date	28 days Room temperature only (Do not refrigerate)
HUMALOG U-200*			
3 mL single-patient use Humalog KwikPen	28 days	Until expiration date	28 days Room temperature only (Do not refrigerate)

* When stored at room temperature, HUMALOG U-100 and U-200 can only be used for a total of 28 days, including both not in-use (unopened) and in-use (opened) storage time.

Use in an External Insulin Pump — Change the HUMALOG U-100 in the reservoir at least every 7 days, or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 98.6°F (37°C).

Storage of Diluted HUMALOG U-100 for Subcutaneous Injection — Diluted HUMALOG for subcutaneous injection may be stored for 28 days when refrigerated at 41°F (5°C) and for 14 days at room temperature up to 86°F (30°C) *[see Dosage and Administration (2.2*)]. Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Storage of Intravenous Infusion Preparations with HUMALOG U-100
Intravenous infusion bags prepared with HUMALOG U-100 may be stored for 48 hours when refrigerated at 36° to 46°F (2° to 8°C). The prepared intravenous infusions bags may then 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).

Never Share a HUMALOG Prefilled Pen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges, or Syringe Between Patients
Advise patients that they must never share a HUMALOG prefilled pen, 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 *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or 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)]*.

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

Hypoglycemia due to Medication Errors
Instruct patients to always check the insulin container label before each injection to avoid mix-ups between insulin products *[see Warnings and Precautions (5.4)]*.

Inform patients that HUMALOG U-200 contains 2 times as much insulin per mL as HUMALOG U-100. The HUMALOG U-200 KwikPen dose window shows the number of units of HUMALOG U-200 to be injected so no dose conversion is required *[see Dosage and Administration (2.1)].*

Instruct patients to NOT transfer HUMALOG U-200 from the HUMALOG U-200 KwikPen to a syringe. The markings on the syringe will not measure the dose correctly and this can result in overdosage and severe hypoglycemia. *[see Warnings and Precautions (5.4)].*

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)]*.

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

Instructions For Patients Using Continuous Subcutaneous Insulin Pumps
- Do not use HUMALOG U-200 in a subcutaneous insulin pump.
- Train patients in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.
- Instruct patients to follow healthcare provider recommendations when setting pump basal rates and bolus settings.
- Refer to the continuous subcutaneous infusion pump user manual to see if HUMALOG can be used with the pump. See recommended reservoir and infusion sets in the insulin pump user manual.
- Instruct patients to replace insulin in the reservoir at least every 7 days, or according to the pump user manual, whichever is shorter; infusion sets and infusion set insertion sites should be changed in accordance with the manufacturers' user manual. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin preservative.
- Instruct patients to discard insulin exposed to temperatures higher than 98.6°F (37°C). 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.
- Instruct patients to inform healthcare provider and select a new site for infusion if infusion site becomes erythematous, pruritic, or thickened.
- Instruct patients on the risk of rapid hyperglycemia and ketosis due to pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Instruct patients on the risk of hypoglycemia from pump malfunction. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their healthcare provider *[see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)]*.

Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891

[1] 3 mL cartridge is for use in compatible insulin delivery devices, including HumaPen® Luxura® HD
Humalog®, Humalog KwikPen®, Humalog Tempo Pen™, Humalog® Junior KwikPen®, HumaPen®, HumaPen® Luxura® and HumaPen® Luxura® HD are trademarks of Eli Lilly and Company.