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 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.

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

<u>Subcutaneous Injection: HUMALOG U-100 or U-200</u>

- 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.

<u>Continuous Subcutaneous Infusion (Insulin Pump): HUMALOG U-100 ONLY</u>

- 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)]*.

<u>Intravenous Administration: HUMALOG U-100 ONLY</u>

- 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

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

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

- 10 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[1], 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 ≥5%)

Events, n (%)	Lispro	Regular human insulin

	(n=81)	(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 ≥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)

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_{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)]*.

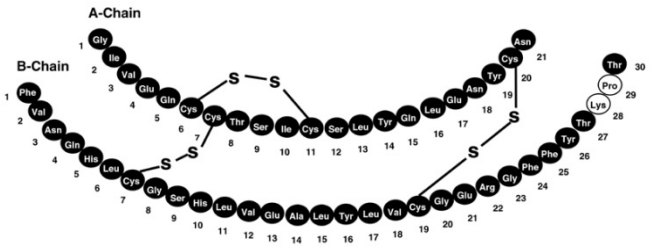
10 OVERDOSAGE

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 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® (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 $C_{257}H_{383}N_{65}O_{77}S_6$ 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)]*.

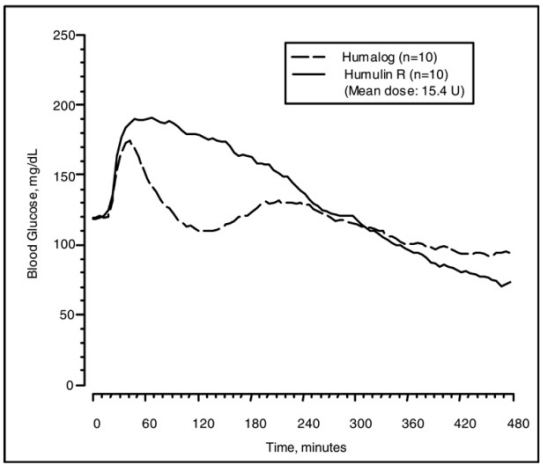


Figure 1: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].

[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).

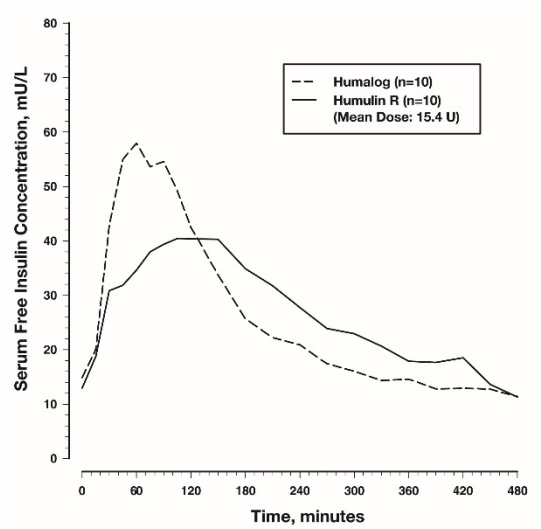


Figure 2: Serum HUMALOG and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].

[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. 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_{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 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 6).

Table 6: 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.

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_{1c} (*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_{1c}, and incidence of hypoglycemia, regardless of treatment group.

Table 7: 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.

14.4 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_{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.

14.5 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_{1c} 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_{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.

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 cartridge[1]	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

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])

HUMALOG U-100			
10 mL vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog Junior KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**
HUMALOG U-200			
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**

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[2]
- MiniMed® Models 506, 507 and 508 and Polyfin® infusion sets[3]

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)]*.

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[1] 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.
Humalog®, Humalog KwikPen®, Humalog® Junior KwikPen®, HumaPen®, HumaPen® Luxura® and HumaPen® Luxura® HD are trademarks of Eli Lilly and Company.

[2] Disetronic®, H-Tron®, D-Tron®, and D-Tronplus® are registered trademarks of Roche Diagnostics GmbH.

[3] MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

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Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

www.humalog.com

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Patient Information
HUMALOG KwikPen®
insulin lispro injection
U-200 (200 units per mL)

Do not share your HUMALOG KwikPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is HUMALOG?

- HUMALOG is a rapid-acting man-made insulin used to control high blood sugar in adults and children with diabetes mellitus.
- This HUMALOG KwikPen ("Pen") contains **2** times as much insulin (200U/mL) in 1 mL as standard insulin (100U/mL).
- It is not known if HUMALOG is safe and effective in children less than 3 years of age.
- It is not known if HUMALOG is safe and effective in children with type 2 diabetes.

Who should not take HUMALOG?

Do not take HUMALOG if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to insulin lispro or any of the ingredients in HUMALOG. See the end of this Patient Information leaflet for a complete list of ingredients in HUMALOG.

What should I tell my healthcare provider before using HUMALOG?

Before using HUMALOG, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- take other medicines, especially ones called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with HUMALOG.
- are pregnant, planning to become pregnant, or breastfeeding. It is not known if HUMALOG may harm your unborn or breastfeeding baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Before you start using HUMALOG, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use HUMALOG KwikPen?

- Read the detailed **Instructions for Use** that come with your HUMALOG KwikPen.
- Use HUMALOG KwikPen exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much HUMALOG to use and when to use it.
- Know the amount of HUMALOG you use. **Do not** change the amount of HUMALOG you use unless your healthcare provider tells you to.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.
- HUMALOG comes in a KwikPen which is a disposable prefilled pen that you must use to give your HUMALOG. The dose window on your pen shows your dose of HUMALOG. **Do not** make any dose changes unless your healthcare provider tells you to.
- **Do not** use a syringe to remove HUMALOG from your KwikPen disposable prefilled pen.
- **Do not** re-use needles. Always use a new needle for each injection. Re-use of needles increases your risk of having blocked needles, which may cause you to get the wrong dose of HUMALOG. Using a new needle for each injection also lowers your risk of getting an infection. If your needle is blocked, follow the instructions in the **"General information about the safe and effective use of your Pen"** section of the Instructions for Use.
- HUMALOG is a rapid-acting insulin. Take HUMALOG **within 15** minutes before eating or right after eating a meal.
- Inject HUMALOG under your skin (subcutaneously). **Do not** use HUMALOG KwikPen ("Pen") in an insulin pump or inject HUMALOG KwikPen into your vein (intravenously).
- Change (rotate) your injection site with each dose.
- **Do not** mix the HUMALOG in the HUMALOG KwikPen with any other type of insulin or liquid medicine.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

Keep HUMALOG KwikPen and all medicines out of reach of children.

Your dose of HUMALOG may need to change because of a:

- change in physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What should I avoid while using HUMALOG KwikPen?

While using HUMALOG KwikPen do not:

- drive or operate heavy machinery, until you know how HUMALOG KwikPen affects you
- drink alcohol or use over-the-counter medicines that contain alcohol

What are the possible side effects of HUMALOG?

HUMALOG may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms of low blood sugar may include:
  - dizziness or lightheadedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood changes, hunger.
- **severe allergic reaction (whole body reaction). Get medical help right away, if you have any of these signs or symptoms of a severe allergic reaction:**
  - a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with HUMALOG may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with HUMALOG. Your healthcare provider should monitor you closely while you are taking TZDs with HUMALOG. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
  - shortness of breath, swelling of your ankles or feet, sudden weight gain

Treatment with TZDs and HUMALOG may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

The most common side effects of HUMALOG include:

- low blood sugar (hypoglycemia), allergic reactions, including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy), itching, and rash.

These are not all of the possible side effects from HUMALOG. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of HUMALOG KwikPen.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use HUMALOG for a condition for which it was not prescribed. **Do not** give HUMALOG to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about HUMALOG KwikPen. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about HUMALOG that is written for healthcare providers. For more information go to www.humalog.com or call 1-800-LillyRx (1-800-545-5979).

What are the ingredients in HUMALOG U-200?

Active ingredient: insulin lispro.

Inactive ingredient: glycerin, tromethamine, metacresol, zinc oxide (zinc ion), trace amounts of phenol and water for injection.

Humalog® and Humalog KwikPen® are registered trademarks of Eli Lilly and Company.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

For more information, go to www.humalog.com.

Patient Information issued: Month Year

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This Patient Information has been approved by the U.S. Food and Drug Administration

Instructions for Use

HUMALOG KwikPen®

insulin lispro injection

200 units/mL, 3 mL pen

DO NOT TRANSFER TO A SYRINGE
SEVERE OVERDOSE CAN RESULT

Read the Instructions for Use before you start taking HUMALOG® and each time you get another KwikPen®. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

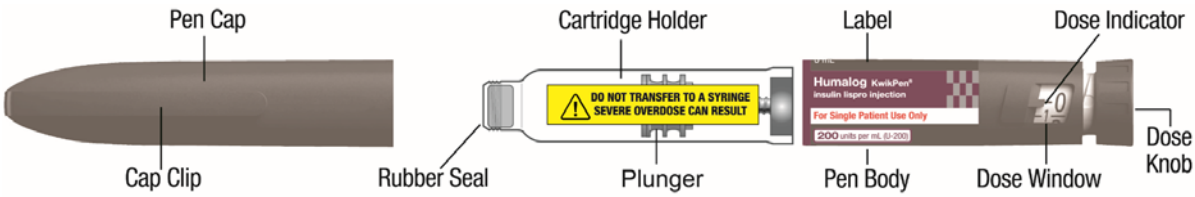
Do not share your HUMALOG KwikPen with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

HUMALOG KwikPen 200 units/mL ("Pen") is a disposable prefilled pen containing 600 units of HUMALOG. You can give yourself more than 1 dose from the Pen. Each turn (click) of the Dose Knob dials 1 unit of insulin. You can give from 1 to 60 units in a single injection. **If your dose is more than 60 units, you will need to give yourself more than 1 injection.** The Plunger only moves a little with each injection, and you may not notice that it moves. The Plunger will only reach the end of the cartridge when you have used all 600 units in the Pen.

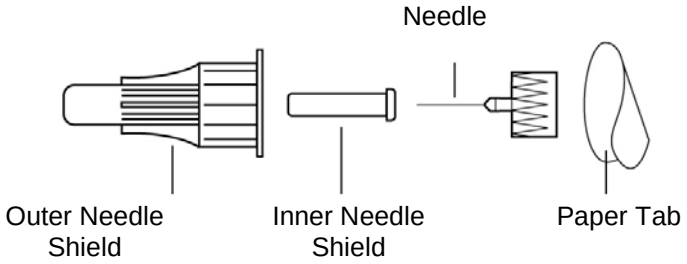
HUMALOG KwikPen is available in 2 strengths, 100 units/mL and 200 units/mL. Inject HUMALOG 200 units/mL only with your Pen. Do not transfer insulin from your Pen to a syringe. Syringes will not measure 200 units/mL insulin correctly. A severe overdose can result, causing very low blood sugar which may put your life in danger.

This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.

KwikPen Parts



Pen Needle Parts
(Needles Not Included)



Dose Knob

How to recognize your HUMALOG 200 units/mL KwikPen

- Pen color: Dark grey
- Dose Knob: Dark grey with burgundy ring on the end
- Label: Burgundy label with “200 units per mL (U-200)” in white stripe and a grey and burgundy checker board design.

Supplies needed to give your injection

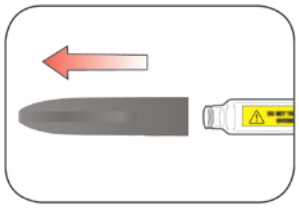
- HUMALOG KwikPen
- KwikPen compatible Needle (Becton, Dickinson and Company Pen Needles recommended)
- Alcohol swab
- Gauze

Preparing your Pen

- Wash your hands with soap and water.
- Check your Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the Label or for more than 28 days after you first start using the Pen.
- **Always use a new needle for each injection to help prevent infections and blocked needles. Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.**

Step 1:

- Pull the Pen Cap straight off.
  - **Do not** remove the Pen Label.
- Wipe the Rubber Seal with an alcohol swab.



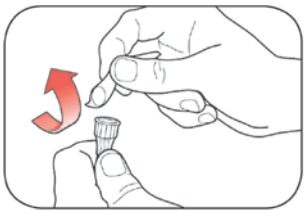
Step 2:

- **Check the liquid in the Pen.**

  HUMALOG should look clear and colorless. **Do not** use if it is cloudy, colored, or has particles or clumps in it.

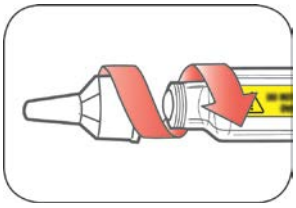
Step 3:

- Select a new Needle.
- Pull off the Paper Tab from the Outer Needle Shield.



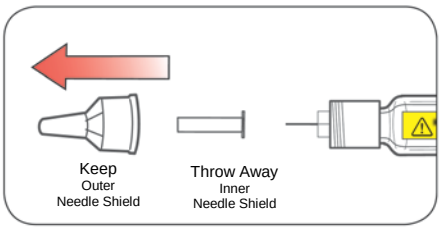
Step 4:

- Push the capped Needle straight onto the Pen and twist the Needle on until it is tight.



Step 5:

- Pull off the Outer Needle Shield. **Do not** throw it away.
- Pull off the Inner Needle Shield and throw it away.



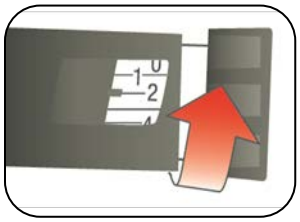
Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the Needle and Cartridge that may collect during normal use and ensures that the Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6:

- To prime your Pen, turn the Dose Knob to **select 2 units**.



Step 7:

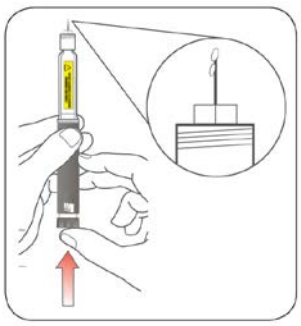
- Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.

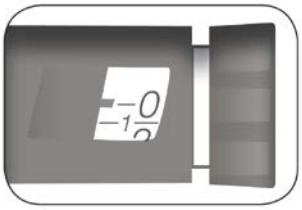
Step 8:

- Continue holding your Pen with Needle pointing up. Push the Dose Knob in until it stops, and "**0**" is seen in the Dose Window. Hold the Dose Knob in and **count to 5 slowly**.

  You should see insulin at the tip of the Needle.
  - If you **do not** see insulin, repeat priming steps 6 to 8, no more than 8 times.
  - If you **still do not** see insulin, change the Needle and repeat priming steps 6 to 8.

Small air bubbles are normal and will not affect your dose.





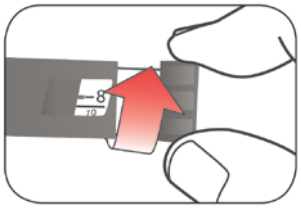
Selecting your dose

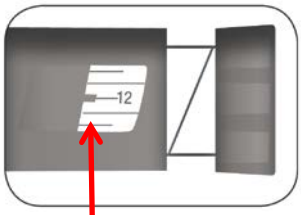
This Pen has been made to deliver the dose that is shown in the Dose Window. Dial your usual dose as instructed by your healthcare provider.

- You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give more than 1 injection.
  - If you need help with dividing up your dose the right way, ask your healthcare provider.
  - Use a new Needle for each injection and repeat the priming step.

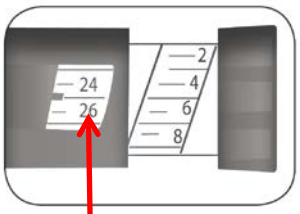
Step 9:

- Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.
  - The Pen dials 1 unit at a time.
  - The Dose Knob clicks as you turn it.
  - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to you getting to much insulin or not enough insulin.
  - The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator.
  - The **even** numbers (for example, 12) are printed on the dial.
  - The **odd** numbers, (for example, 25) after the number 1, are shown as full lines.
- **Always check the number in the Dose Window to make sure you have dialed the correct dose.**





(Example: 12 units shown in the Dose Window)



(Example: 25 units shown in the Dose Window)

- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

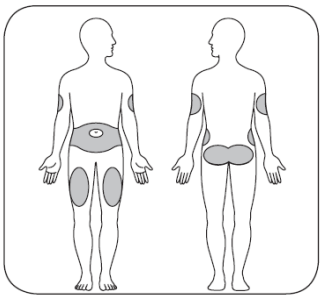
  or
  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you can not inject. **Do not transfer this to a syringe. Severe overdose can result.**

Giving your injection

- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

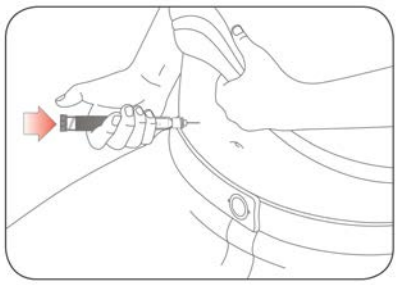
Step 10:

- Choose your injection site.
  HUMALOG is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.
- Wipe your skin with an alcohol swab, and let your skin dry before you inject your dose.



Step 11:

- Insert the Needle into your skin.
- Push the Dose Knob all the way in.



- Continue to hold the Dose Knob in and **slowly count to 5** before removing the Needle.

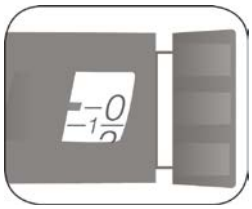
Do not try to inject your insulin by turning the Dose Knob. You will **not** receive your insulin by turning the Dose Knob.

Step 12:

- Pull the Needle out of your skin.
  - A drop of insulin at the Needle tip is normal. It will not affect your dose.
- Check the number in the Dose Window
  - If you see “0” in the Dose Window, you have received the full amount you dialed.
  - If you do not see “0” in the Dose Window, **do not** redial. Insert the Needle into your skin and finish your injection.
  - If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat the injection.** Monitor your blood glucose as instructed by your healthcare provider.
  - If you normally need to give 2 injections for your full dose, be sure to give your second injection.

The Plunger only moves a little with each injection, and you may not notice that it moves.

If you see blood after you take the Needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



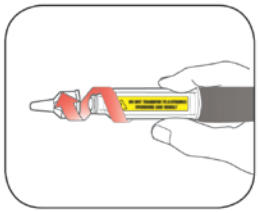
After your injection

Step 13:

- Carefully replace the Outer Needle Shield.

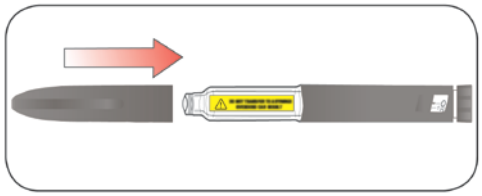
Step 14:

- Unscrew the capped Needle and throw it away(see **Disposing of Pens and Needles** section).
- **Do not** store the Pen with the Needle attached to prevent leaking, blocking the Needle, and air from entering the Pen.



Step 15:

- Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.



Disposing of Pens and Needles

- Put your used needles in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- The used Pen may be discarded in your household trash after you have removed the needle.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze your insulin. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the Label, if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature [up to 86°F (30°C)]. Keep away from heat and light.
- Throw away the HUMALOG Pen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you can not remove the Pen Cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the Dose Knob is hard to push:
  - Pushing the Dose Knob more slowly will make it easier to inject.
  - Your Needle may be blocked. Put on a new Needle and prime the Pen.
  - You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your HUMALOG KwikPen, contact Lilly at 1-800-LillyRx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMALOG KwikPen and insulin, go to www.humalog.com.

Scan this code to launch

www.humalog.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Revised: Month DD, YYYY

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

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HUMALOG KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2014.