HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMALOG MIX50/50 safely and effectively. See full prescribing information for HUMALOG MIX50/50.

HUMALOG MIX50/50 (insulin lispro protamine and insulin lispro injectable suspension), for subcutaneous use

Initial U.S. Approval: 1999

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2.1)	11/2019
Warnings and Precautions (5.2)	11/2019

---------- INDICATIONS AND USAGE ----------

HUMALOG® Mix50/50™ is a mixture1 of insulin lispro protamine, an intermediate-acting human insulin analog, and insulin lispro, a rapid-acting human insulin analog indicated to improve glycemic control in patients with diabetes mellitus. (1)

Limitations of Use:

The proportions of rapid-acting and intermediate-acting insulins are fixed and do not allow for basal versus prandial dose adjustments. (1)

----------DOSAGE AND ADMINISTRATION----------

- See Full Prescribing Information for important administration instructions. (2.1)
- Inject subcutaneously in abdominal wall, thigh, upper arm, or buttocks and rotate injection sites to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. (2.1)
- Individualize and adjust dosage based on metabolic needs, blood glucose monitoring results and glycemic control goal. (2.2)
- Inject HUMALOG Mix50/50 subcutaneously within 15 minutes before a meal. (2.2)
- Do not administer HUMALOG Mix50/50 intravenously or by a continuous subcutaneous insulin infusion pump. (2.1)
- HUMALOG Mix50/50 is typically dosed twice daily (with each dose intended to cover 2 meals or a meal and a snack). (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injectable suspension: HUMALOG Mix50/50 is 100 units per mL (U-100), 50% insulin lispro protamine and 50% insulin lispro available as: (3)

- 10 mL multiple-dose vial
- 3 mL single-patient-use KwikPen® (prefilled)

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

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to HUMALOG Mix50/50 or any of its excipients. (4)

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

- *Never share* a HUMALOG Mix50/50 KwikPen 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. Increase frequency of blood glucose monitoring with changes to insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3)
- *Hypoglycemia Due to Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- Hypersensitivity Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue HUMALOG Mix50/50, 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 reductions or discontinuation if heart failure occurs. (5.7)

----------ADVERSE REACTIONS----------

Adverse reactions observed with HUMALOG Mix50/50 include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, weight gain, edema, pruritus, and rash. (6)

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: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Administration Instructions
- 2.2 Dosage Information
- 2.3 Dosage Adjustment Due to Drug Interactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Never Share a HUMALOG Mix50/50 KwikPen or Syringe Between Patients
- 5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen
- 5.3 Hypoglycemia
- 5.4 Hypoglycemia Due to Medication Errors
- 5.5 Hypersensitivity Reactions
- 5.6 Hypokalemia
- 5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HUMALOG Mix50/50 is indicated to improve glycemic control in patients with diabetes mellitus.

Limitations of Use:

The proportions of rapid-acting and intermediate-acting insulins in HUMALOG Mix50/50 are fixed and do not allow for basal versus prandial dose adjustments.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin labels before administration *[see Warnings and Precautions (5.4)]*.
- HUMALOG Mix50/50 is a suspension that must be resuspended immediately before use. Resuspension is easier when the insulin has reached room temperature.
- To resuspend vial, carefully invert the vial at least 10 times until the suspension appears uniformly white and cloudy. Inject immediately.
- To resuspend KwikPen, gently roll the KwikPen at least 10 times and then carefully invert the KwikPen at least 10 times until the suspension appears uniformly white and cloudy. Inject immediately.
- Inspect HUMALOG Mix50/50 visually before use. Do not use if discoloration or particulate matter is seen.
- Administer HUMALOG Mix50/50 by subcutaneous injection into the abdominal wall, thigh, upper arm, or buttocks.
- Rotate the injection site within the same region from one injection to the next 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)]*.
- The HUMALOG Mix50/50 KwikPen dials in 1 unit increments.
- Use HUMALOG Mix5050 KwikPen with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- Do not administer HUMALOG Mix50/50 intravenously, intramuscularly or by a continuous subcutaneous insulin infusion pump.
- Do not mix HUMALOG Mix50/50 with any other insulins or diluents.

2.2 Dosage Information

- Individualize and adjust the dosage of HUMALOG Mix50/50 based on the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal.
- Inject HUMALOG Mix50/50 subcutaneously within 15 minutes before a meal.
- HUMALOG Mix50/50 is typically dosed twice-daily (with each dose intended to cover 2 meals or a meal and a snack)
- 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)]*.
- Dosage adjustment may be needed when switching from another insulin to HUMALOG Mix50/50.

2.3 Dosage Adjustment Due to Drug Interactions

- Dosage adjustment may be needed when HUMALOG Mix50/50 is coadministered with certain drugs *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

HUMALOG Mix50/50 injectable suspension 100 units per mL (U-100) is 50% insulin lispro protamine and 50% insulin lispro, a white and cloudy suspension available as:

- 10 mL multiple-dose vial
- 3 mL single-patient-use KwikPen (prefilled)

4 CONTRAINDICATIONS

HUMALOG Mix50/50 is contraindicated:

- during episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*

- in patients who have had hypersensitivity reactions to HUMALOG Mix50/50 or to any of its excipients *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a HUMALOG Mix50/50 KwikPen or Syringe Between Patients

HUMALOG Mix50/50 KwikPens must never be shared between patients, even if the needle is changed. Patients using HUMALOG Mix50/50 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 anti-diabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with all insulin therapies, including HUMALOG Mix50/50. Severe hypoglycemia can cause seizures, may lead to unconsciousness, 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.

<u>Risk Factors for Hypoglycemia</u>

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 Mix50/50 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)]*.

<u>Risk Mitigation Strategies for Hypoglycemia</u>

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 HUMALOG Mix50/50 and other insulin products have been reported. To avoid medication errors between HUMALOG Mix50/50 and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG Mix50/50. If hypersensitivity reactions occur, discontinue HUMALOG Mix50/50; treat per standard of care and monitor until symptoms and signs resolve. HUMALOG Mix50/50 is contraindicated in patients who have had hypersensitivity reactions to HUMALOG Mix50/50 or any of its excipients *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, including HUMALOG Mix50/50, 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 Mix50/50, 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

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

Adverse Reactions from Clinical Studies or Postmarketing Reports

The following adverse reactions have been identified during post-marketing use of HUMALOG Mix50/50. Because some of 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.

Adverse reactions associated with insulin initiation and glucose control intensification

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. Over the long-term, improved glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Hypersensitivity reactions

Severe, life-threatening, generalized allergy, including anaphylaxis.

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in HUMALOG Mix50/50.

Hypokalemia

HUMALOG Mix50/50 can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia.

Injection site reactions

HUMALOG Mix50/50 can cause local injection site reactions including redness, swelling, or itching at the site of injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation. Localized reactions and generalized myalgias have been reported with the use of meta-cresol, which is an excipient in HUMALOG Mix50/50.

Lipodystrophy

Administration of insulin subcutaneously, including HUMALOG Mix50/50, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) *[see Dosage and Administration (2.1)]* in some patients.

Localized cutaneous amyloidosis

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.

Medication Errors

Medication errors in which other insulins have been accidentally substituted for HUMALOG Mix50/50 have been identified during postapproval use.

Peripheral Edema

Insulin, including HUMALOG Mix50/50, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Weight gain

Weight gain can occur with insulin therapy, including HUMALOG Mix50/50, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Immunogenicity

As with all therapeutic peptides, insulin administration may cause anti-insulin antibodies to form. The incidence of antibody formation with HUMALOG Mix50/50 is unknown.

7 DRUG INTERACTIONS

Table 1: Clinically Significant Drug Interactions with HUMALOG Mix50/50

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 Mix50/50 is co-administered with these drugs.
Drugs that May Decrease the Blood Glucose Lowering Effect of HUMALOG Mix50/50	

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 Mix50/50 is co-administered with these drugs.
Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of HUMALOG Mix50/50	
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 Mix50/50 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 Mix50/50 is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with HUMALOG Mix50/50 in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. 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, still birth, 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

Animal reproduction studies have not been performed with HUMALOG Mix50/50. However, subcutaneous reproduction and teratology studies have been conducted with insulin lispro (a component of HUMALOG Mix50/50). 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

There are no data on the presence of HUMALOG Mix50/50 in human milk, the effects on the breastfed infant, or the effect on milk production. One small published study reported that exogenous insulin was present in human milk. However, there is insufficient information to determine the effects of HUMALOG Mix50/50 on the breastfed infant and no available information on the effects of HUMALOG Mix50/50 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 Mix50/50 or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of HUMALOG Mix50/50 in patients less than 18 years of age has not been established.

8.5 Geriatric Use

Clinical studies of Humalog Mix50/50 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)].*

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of HUMALOG Mix50/50 has not been studied. Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG Mix50/50 dose adjustment and more frequent glucose monitoring *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of HUMALOG Mix50/50 has not been studied. Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG Mix50/50 dose adjustment and more frequent glucose monitoring *[see Warnings and Precautions (5.3)]*.

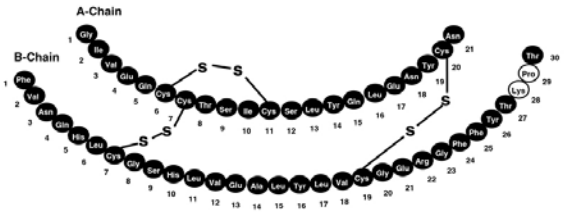
10 OVERDOSAGE

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 or 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 *[see Warnings and Precautions (5.3, 5.6)].*

11 DESCRIPTION

HUMALOG Mix50/50 (insulin lispro protamine and insulin lispro injectable suspension) is a mixture of 50% insulin lispro protamine, an intermediate-acting human insulin analog, and 50% insulin lispro, a rapid-acting human insulin analog. 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. Insulin lispro protamine suspension is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:



HUMALOG Mix50/50 vials and KwikPens contain a white and cloudy, sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of HUMALOG Mix50/50 injection contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

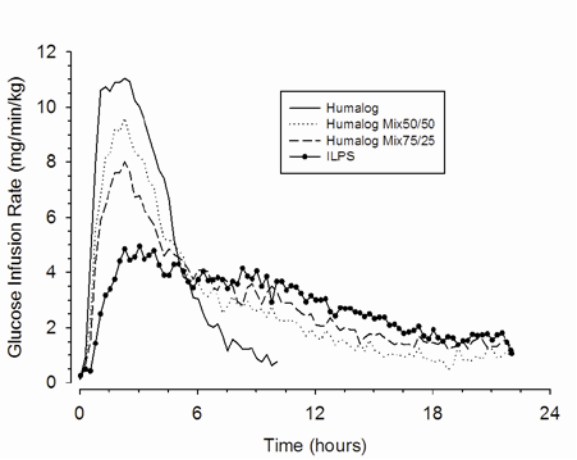
The primary activity of insulin including HUMALOG Mix50/50 is the regulation of glucose metabolism. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

In a glucose clamp study performed in 30 healthy subjects, the onset of action and glucose-lowering activity of HUMALOG, HUMALOG Mix50/50, HUMALOG® Mix75/25™, and insulin lispro protamine suspension (ILPS) were compared (*see* Figure 1). Graphs of mean glucose infusion rate versus time showed a distinct insulin activity profile for each formulation. The rapid onset of glucose-lowering activity characteristic of HUMALOG was maintained in HUMALOG Mix50/50. The median maximum pharmacologic effect of HUMALOG Mix50/50 after administration of a 0.3 unit/kg dose to healthy subjects occurred at 2 hours (range: 1-5 hours); glucose lowering activity was detectable for a median of 22 hours (range: 11 to 22 hours), which was the end of the clamp.

Figure 1 should be considered only as a representative example since the time course of action of insulin and insulin analogs, may vary in different individuals or within the same individual.

Figure 1: Mean Insulin Activity Versus Time Profiles After Injection of 0.3 units/kg of HUMALOG, HUMALOG Mix50/50, HUMALOG Mix75/25, or Insulin Lispro Protamine Suspension (ILPS) in 30 Healthy Subjects.



12.3 Pharmacokinetics

Absorption — HUMALOG Mix50/50 has two phases of absorption. The early phase represents insulin lispro and its distinct characteristics of rapid onset. The late phase represents the prolonged absorption of insulin lispro protamine suspension.

In 30 healthy subjects given subcutaneous doses (0.3 unit/kg) of HUMALOG Mix50/50, the median peak serum concentration occurred at 60 minutes (range: 45 minutes to 13.5 hours) after dosing. In patients with type 1 diabetes, the median peak serum concentration occurred at 60 minutes (range: 45 minutes to 2 hours) after dosing.

Metabolism — Human metabolism studies of HUMALOG Mix50/50 have not been conducted. However, studies in animals indicate that the metabolism of HUMALOG, the rapid-acting component of HUMALOG Mix50/50, is identical to that of regular human insulin.

Elimination — Because of the absorption-rate limited kinetics of insulin mixtures, a true half-life cannot be accurately estimated from the terminal slope of the concentration versus time curve.

Specific Populations

The effects of age, race, obesity, pregnancy, smoking, or renal or hepatic impairment on the pharmacokinetics of HUMALOG Mix50/50 have not been studied.

Gender — Pharmacokinetic and pharmacodynamic comparisons between men and women administered HUMALOG Mix50/50 showed no gender differences.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed with HUMALOG Mix50/50. In Fischer 344 rats, a 12-month repeat-dose toxicity study was conducted with insulin lispro (a component of HUMALOG Mix50/50) at subcutaneous doses of 20 and 200 units/kg/day (approximately 3 and 32 times the human subcutaneous dose of 1 unit insulin lispro/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 insulin lispro/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 insulin lispro/kg/day, based on units/body surface area), mating and fertility were not adversely affected in either gender at any dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMALOG Mix50/50 injectable suspension 100 units per mL (U-100) is 50% insulin lispro protamine and 50% insulin lispro, a white and cloudy suspension available as:

10 mL multiple-dose vial	NDC 0002-7512-01
3 mL single-patient-use KwikPen (prefilled)	NDC 0002-8798-59

HUMALOG Mix50/50 KwikPens must never be shared between patients, even if the needle is changed. Patients using HUMALOG Mix50/50 vials must never share needles or syringes with another person. Always use a new disposable syringe or needle for each injection to prevent contamination.

The HUMALOG Mix50/50 KwikPen dials in 1 unit increments.

16.2 Storage and Handling

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

Do not use after the expiration date. Protect from direct heat and light. Do not freeze. See storage table below:

	Not In-Use (Unopened) Refrigerated (36° to 46°F [2° to 8°C])	**Not In Use (unopened) Room Temperature (Below 86°F [30°C])**	**In-Use (Opened) Room Temperature, (Below 86°F [30°C])**
10 mL multiple-dose vial	Until expiration date	28 days	28 days, refrigerated/room temperature
3 mL single-patient-use KwikPen	Until expiration date	10 days	10 days, room temperature. Do not refrigerate.

17 PATIENT COUNSELING INFORMATION

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

Never Share a HUMALOG Mix50/50 KwikPen or Syringe Between Patients

Advise patients using Humalog Mix50/50 vials or Humalog Mix50/50 KwikPen not to share needles, syringes, or KwikPen with another person. Sharing poses a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of HUMALOG Mix50/50 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 *[see Warnings and Precautions (5.3)].*

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.

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 label before each injection to avoid mix-ups between insulin products *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with HUMALOG Mix50/50. Inform patients on the symptoms of hypersensitivity reactions and to seek medical attention if they occur *[see Warnings and Precautions (5.5)]*.

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

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Patient Information
HUMALOG® (HU-ma-log) Mix50/50™
(insulin lispro protamine and insulin lispro injectable suspension)
for subcutaneous use

Do not share your HUMALOG Mix50/50 KwikPen, needles or syringes 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 Mix50/50?

- HUMALOG Mix50/50 is a man-made insulin that is used to control high blood sugar in people with diabetes mellitus.
- It is not known if HUMALOG Mix50/50 is safe and effective in children under 18 years of age.

Who should not take HUMALOG Mix50/50?
Do not take HUMALOG Mix50/50 if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to HUMALOG Mix50/50 or any of the ingredients in HUMALOG Mix50/50. See the end of this Patient Information leaflet for a complete list of ingredients in Humalog Mix50/50.

What should I tell my healthcare provider before taking Humalog Mix50/50?
Before taking HUMALOG Mix50/50, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- take any 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 Mix50/50.
- are pregnant or plan to become pregnant. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. Talk with your healthcare provider about the best way to feed your baby while taking HUMALOG Mix50/50.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.
Before you start taking HUMALOG Mix50/50, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take HUMALOG Mix50/50?

- Read the **Instructions for Use** that comes with your HUMALOG Mix50/50.
- Take HUMALOG Mix50/50 exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much HUMALOG Mix50/50 to take and when to take it.
- **HUMALOG Mix50/50 starts acting fast. Inject HUMALOG Mix50/50 within 15 minutes before you eat a meal.**
- Know the type, strength, and amount of insulin you take. **Do not** change the type or amount of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- Check your insulin label each time you give your injection to make sure you are taking the correct insulin.
- Inject Humalog Mix50/50 under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs or upper arms. **Do not** inject HUMALOG Mix50/50 into your vein (intravenously) or muscle (intramuscularly) or use in an insulin infusion pump.
- **Change (rotate) your injection sites within the area you choose with each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
  - **Do not** use the exact same spot for each injection.
  - **Do not** inject where the skin has pits, is thickened, or has lumps.
  - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** mix Humalog Mix50/50 with other insulins or liquids.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Keep HUMALOG Mix50/50 and all medicines out of reach of children.

Your dose of HUMALOG Mix50/50 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 taking HUMALOG Mix50/50?
While taking HUMALOG Mix50/50 do not:

- drive or operate heavy machinery until you know how HUMALOG Mix50/50 affects you.
- drink alcohol or take prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of HUMALOG Mix50/50?

HUMALOG Mix50/50 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 light-headedness
  - sweating
  - confusion
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability or mood changes
  - hunger

Your healthcare provider may prescribe a glucagon emergency kit so that someone else can give you glucagon if your blood sugar becomes too low (severe hypoglycemia) and you are unable to take sugar by mouth.

- **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
  - trouble breathing
  - fast heartbeat
  - sweating
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with HUMALOG Mix50/50 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 Mix50/50. Your healthcare provider should monitor you closely while you are taking TZDs with HUMALOG Mix50/50. 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 Mix50/50 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency medical help if you have:

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

The most common side effects of HUMALOG Mix50/50 include:

- low blood sugar (hypoglycemia)
- reactions at your injection site
- skin thickening or pits at the injection site (lipodystrophy)
- weight gain
- swelling in your hands or feet
- itching
- rash

These are not all the possible side effects of HUMALOG Mix50/50. 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 Mix50/50.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take HUMALOG Mix50/50 for a condition for which it was not prescribed. Do not give HUMALOG Mix50/50 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 Mix50/50. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about HUMALOG Mix50/50 that is written for health professionals.

What are the ingredients in HUMALOG Mix50/50?

Active ingredients: insulin lispro

Inactive ingredients: protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, zinc oxide (zinc ion), phenol and water for injection.

Humalog®, Humalog® Mix50/50™ and Humalog® Mix50/50™ KwikPen® are trademarks of Eli Lilly and Company.
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For more information, go to www.humalog.com or call 1-800-545-5979.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:November 2019

Instructions for Use

HUMALOG® (HU-ma-log) Mix50/50™ KwikPen®

(insulin lispro protamine and insulin lispro injectable suspension)

for subcutaneous use

3 mL single-patient-use pen (100 units/mL)

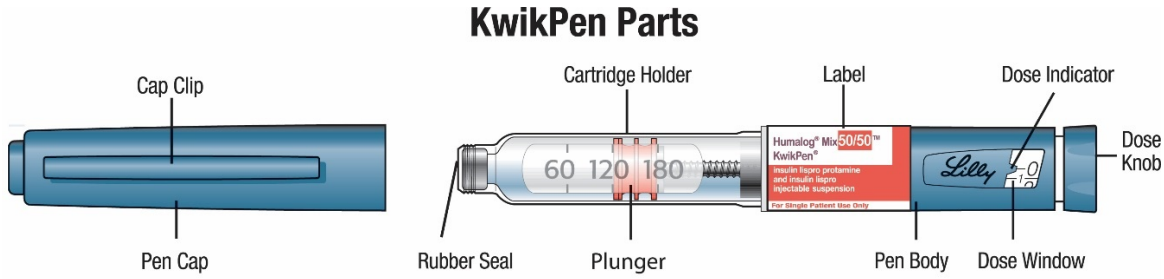
Read this Instructions for Use before you start taking HUMALOG Mix50/50 and each time you get another KwikPen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your HUMALOG Mix50/50 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.

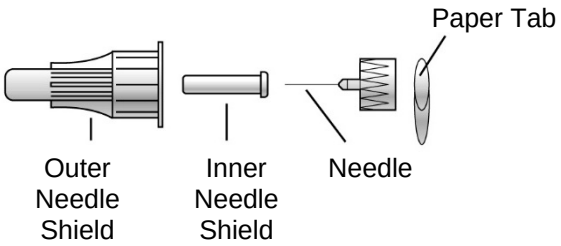
HUMALOG Mix50/50 KwikPen ("Pen") is a disposable single-patient-use prefilled pen containing 300 units of HUMALOG Mix50/50.

- You can give yourself more than 1 dose from the Pen.
- By turning the Dose Knob, you can dial doses from 1 to 60 units in 1 unit increments.
- **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 300 units in the Pen.

People who are blind or have vision problems should not use this Pen without help from a person trained to use the Pen.



Pen Needle Parts
(Needles Not Included)



How to recognize your HUMALOG Mix50/50 KwikPen

- Pen color: Dark blue
- Dose Knob: Dark blue
- Labels: White label with red stripe

Supplies you will need to give your injection

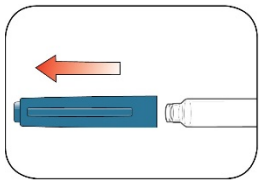
- HUMALOG Mix50/50 KwikPen
- KwikPen compatible Needle (Becton, Dickinson and Company Pen Needles recommended)
- Alcohol swab
- Gauze

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.
- **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.**

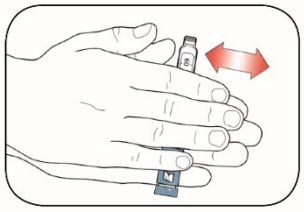
Step 1:

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



Step 2:

- Gently roll the Pen between your hands at least 10 times.

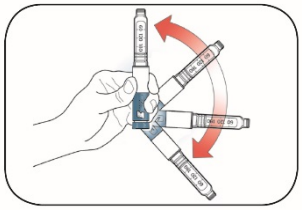


Step 3:

- Move the Pen up and down (invert) at least 10 times.

  Mixing by rolling and inverting the Pen is important to make sure you get the right dose.

  After mixing HUMALOG Mix50/50, inject your dose right away. If you wait to inject your dose, the insulin will need to be mixed again.

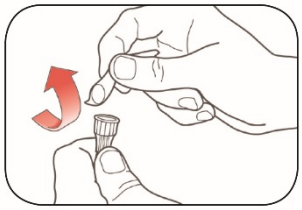


Step 4:

- **Check the liquid in the Pen.**
  HUMALOG Mix50/50 should look white and cloudy after mixing. **Do not** use if it looks clear or has any lumps or particles in it.

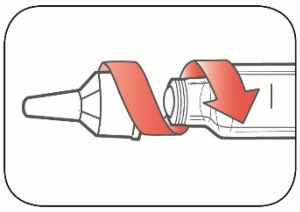
Step 5:

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



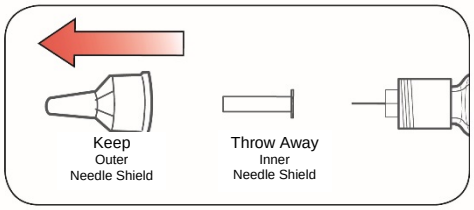
Step 6:

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



Step 7:

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



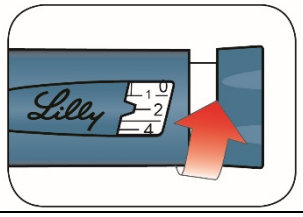
Priming your Pen

Prime your Pen 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.

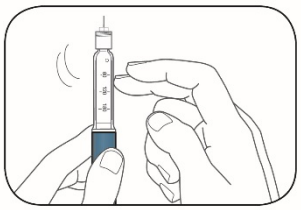
Step 8:

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



Step 9:

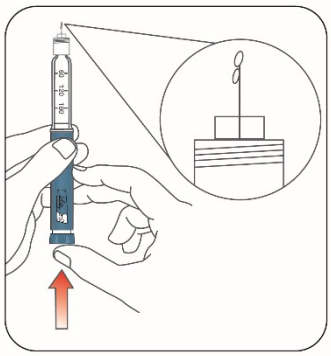
- Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.

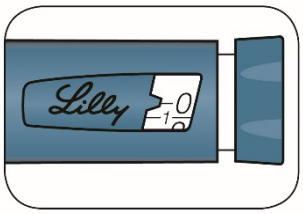


Step 10:

- 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 8 to 10, no more than 4 times.
  - If you **still do not** see insulin, change the Needle and repeat priming steps 8 to 10.

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



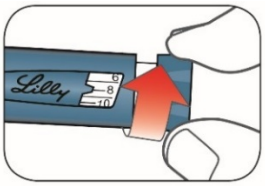


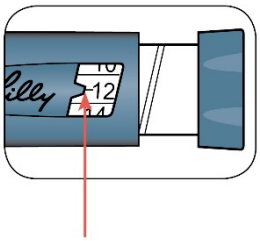
Selecting your dose

- 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 one 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 steps.

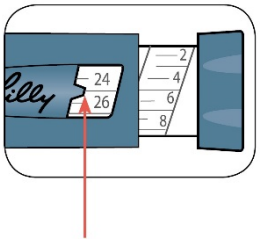
Step 11:

- 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 too 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.

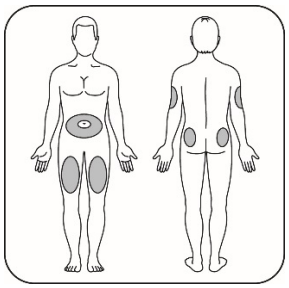
Giving your injection

- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** try to change your dose while injecting.

Step 12:

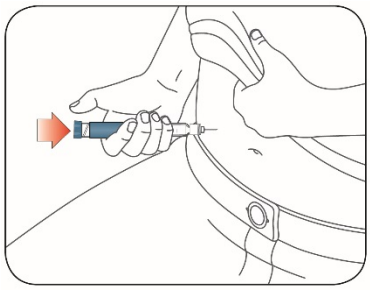
- Choose your injection site.

  HUMALOG Mix50/50 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 13:

- 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.

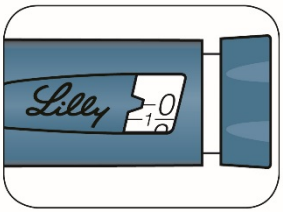


Do not try to inject your insulin by turning the Dose Knob. You will **not** receive your insulin by turning the Dose Knob.

Step 14:

- 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.



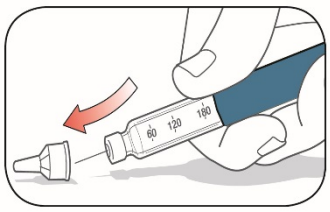
The Plunger only moves a little with each injection, and you may not notice that it moves.

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

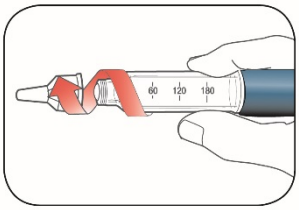
Step 15:

- Carefully replace the Outer Needle Shield.



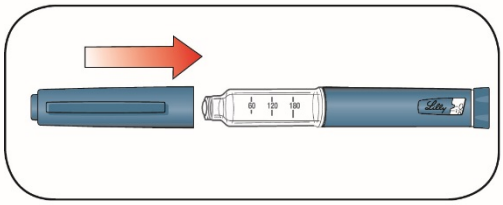
Step 16:

- 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 17:

- 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 HUMALOG Mix50/50 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.
- Unused Pens stored at room temperature, below 86°F (30°C), should be thrown away after 10 days.

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 Mix50/50 Pen you are using after 10 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 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 Mix50/50 KwikPen, contact Lilly at 1-800-LillyRx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMALOG Mix50/50 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.

HUMALOG® Mix50/50™ and HUMALOG® Mix50/50™ KwikPen® are trademarks of Eli Lilly and Company.

Revised: November 2019

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

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HUMALOG Mix50/50 KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1.

Instructions for Use

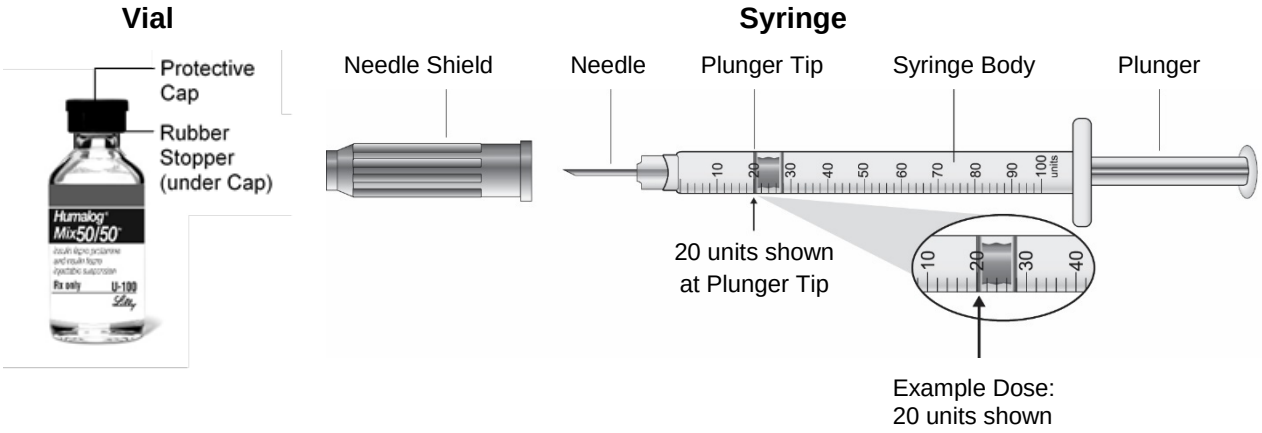
HUMALOG® (HU-ma-log) Mix50/50™
(insulin lispro protamine and insulin lispro injectable suspension)
for subcutaneous use
10 mL multiple-dose vial (100 units/mL)

Read this Instructions for Use before you start taking HUMALOG Mix50/50 and each time you get a new vial. 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 needles or syringes 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.

Supplies needed to give your injection

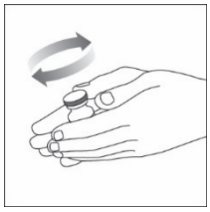
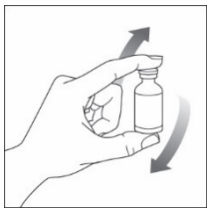
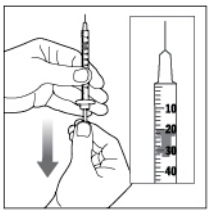
- a multiple-dose HUMALOG Mix50/50 vial
- a U-100 insulin syringe and needle
- 2 alcohol swabs
- gauze
- 1 sharps container for throwing away used needles and syringes. See **"Disposing of used needles and syringes"** at the end of these instructions.

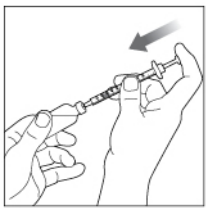
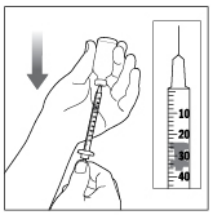
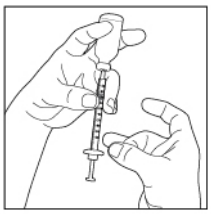
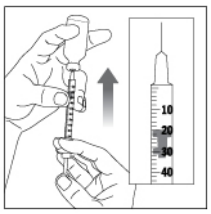
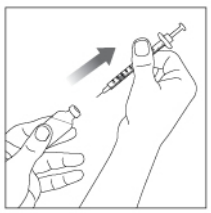


Preparing your HUMALOG Mix50/50 dose

- Wash your hands with soap and water.
- Check the HUMALOG Mix50/50 label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- HUMALOG Mix50/50 is easier to mix when it is at room temperature.
- After mixing HUMALOG Mix50/50, inject your dose right away. If you wait to inject your dose, the insulin will need to be mixed again.

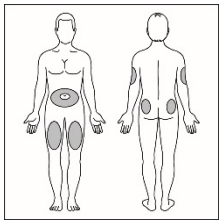
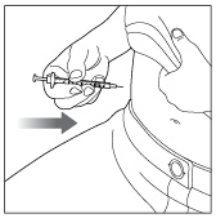
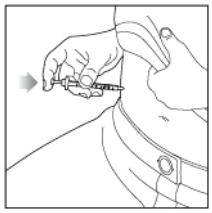
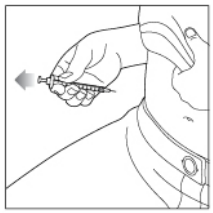
- **Always use a new syringe and needle for each injection to help prevent infections and blocked needles. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.**

Step 1: Gently roll the vial between the palms of your hands at least 10 times.	
Step 2: **Gently** move the vial up and down (invert) at least 10 times. **Mixing is important** to make sure you get the right dose. Humalog Mix50/50 should look white and cloudy after mixing. **Do not** use it if it looks clear or contains any lumps or particles.	
Step 3: If you are using a new vial, pull off the plastic Protective Cap, but **do not** remove the Rubber Stopper.	
Step 4: Wipe the Rubber Stopper with an alcohol swab.	
Step 5: Remove the Needle Shield from the syringe by pulling the Needle Shield straight off. Hold the syringe with the needle pointing up. Pull down on the Plunger until the Plunger Tip reaches the line for the number of units for your prescribed dose.	 (Example Dose: 20 units shown)

Step 6: Push the needle through the Rubber Stopper of the vial.	
Step 7: Push the Plunger all the way in. This puts air into the vial.	
Step 8: Turn the vial and syringe upside down and slowly pull the Plunger down until the Plunger Tip is a few units past the line for your prescribed dose. If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top.	 (Example Dose: 20 units Plunger Tip is shown at 24 units) 
Step 9: Slowly push the Plunger up until the Plunger Tip reaches the line for your prescribed dose. Check the syringe to make sure that you have the right dose.	 (Example Dose: 20 units shown)
Step 10: Pull the syringe out of the Rubber Stopper of the vial.	

Giving your HUMALOG Mix50/50 Injection

- Inject your insulin exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you should pinch the skin before injecting.
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Step 11: Choose your injection site. HUMALOG Mix50/50 is injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs or upper arms. Wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose.	
Step 12: Insert the needle into your skin.	
Step 13: Push down on the Plunger to inject your dose. The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your insulin dose.	
Step 14: Pull the needle out of your skin. • If you see blood after you take the needle out of your skin, press the injection site with a piece of gauze or an alcohol swab. **Do not** rub the area. • **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.	

Disposing of used needles and syringes

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes 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.

How should I store HUMALOG Mix50/50?

All unopened vials:

- Store all unopened vials in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze. **Do not** use if HUMALOG Mix50/50 has been frozen.
- Keep away from heat and out of direct light.
- Unopened vials can be used until the expiration date on the carton and label, if they have been stored in the refrigerator.
- Unopened vials should be thrown away after 28 days, if they are stored at room temperature.

After vials have been opened:

- Store opened vials in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
- Keep vials away from heat and out of direct light.
- Throw away all opened vials after 28 days of use, even if there is insulin left in the vial.

Keep HUMALOG Mix50/50 vials, syringes, needles, and all medicines out of the reach of children.

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

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