

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **INSULIN LISPRO PROTAMINE AND INSULIN LISPRO MIX75/25 safely and effectively. See full prescribing information for INSULIN LISPRO PROTAMINE AND INSULIN LISPRO MIX75/25.**

**INSULIN LISPRO PROTAMINE AND INSULIN LISPRO injectable suspension Mix75/25, for subcutaneous use**

**Initial U.S. Approval: 1999**

This product is HUMALOG® Mix75/25™ (insulin lispro protamine and insulin lispro).

### INDICATIONS AND USAGE

Insulin Lispro Protamine and Insulin Lispro Mix75/25™ is a mixture 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 adults 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 preparation and administration instructions. (2.1)
- Inject Insulin Lispro Protamine and Insulin Lispro Mix75/25 subcutaneously within 15 minutes before a meal in abdominal wall, thigh, upper arm, or buttocks and rotate injection sites to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. (2.1, 2.2)
- Individualize and adjust dosage based on metabolic needs, blood glucose monitoring results and glycemic control goal. (2.2)
- Do not administer Insulin Lispro Protamine and Insulin Lispro Mix75/25 intravenously or by a continuous subcutaneous insulin infusion pump. (2.1)
- Insulin Lispro Protamine and Insulin Lispro Mix75/25 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: 100 units/mL (U-100) of Insulin Lispro Protamine and Insulin Lispro Mix75/25, 75% insulin lispro protamine and 25% insulin lispro available as: (3)

- 3 mL single-patient-use KwikPen® prefilled pen

### CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to Insulin Lispro Protamine and Insulin Lispro Mix75/25 or any of its excipients. (4)

### WARNINGS AND PRECAUTIONS

- *Never share* an Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 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](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

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

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

Revised: 07/2023

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Insulin Lispro Protamine and Insulin Lispro Mix75/25 is indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use:

The proportions of rapid-acting and intermediate-acting insulins in Insulin Lispro Protamine and Insulin Lispro Mix75/25 are fixed and do not allow for basal versus prandial dose adjustments.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Preparation and Administration Instructions

##### Preparation Instructions

- Always check insulin labels before administration. This product is HUMALOG Mix75/25 [see *Warnings and Precautions (5.4)*].
- Insulin Lispro Protamine and Insulin Lispro Mix75/25 is a suspension that must be resuspended immediately before use. Resuspension is easier when the insulin has reached room temperature.
- 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.
- Inspect Insulin Lispro Protamine and Insulin Lispro Mix75/25 visually before use. Do not use if discoloration or particulate matter is seen.

##### Administration Instructions

- After resuspension, immediately administer Insulin Lispro Protamine and Insulin Lispro Mix75/25 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)*].
- The Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen dials in 1 unit increments. Use Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- Do not administer Insulin Lispro Protamine and Insulin Lispro Mix75/25 intravenously or by a continuous subcutaneous insulin infusion pump.
- Do not mix Insulin Lispro Protamine and Insulin Lispro Mix75/25 with any other insulins or diluents.

#### 2.2 Dosage Recommendations

- Individualize and adjust the dosage of Insulin Lispro Protamine and Insulin Lispro Mix75/25 based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Inject Insulin Lispro Protamine and Insulin Lispro Mix75/25 subcutaneously within 15 minutes before a meal.
- Insulin Lispro Protamine and Insulin Lispro Mix75/25 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)*].
- When switching from another insulin to Insulin Lispro Protamine and Insulin Lispro Mix75/25, a different dosage of Insulin Lispro Protamine and Insulin Lispro Mix75/25 may be needed.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring [see *Warnings and Precautions (5.2)*].

#### 2.3 Dosage Modifications for Drug Interactions

Dosage modification may be needed when Insulin Lispro Protamine and Insulin Lispro Mix75/25 is used concomitantly with certain drugs [see *Drug Interactions (7)*].

### 3 DOSAGE FORMS AND STRENGTHS

Injectable Suspension: 100 units/mL (U-100) of Insulin Lispro Protamine and Insulin Lispro, 75% insulin lispro protamine and 25% insulin lispro is a white and cloudy suspension available as:

- 3 mL single-patient-use KwikPen prefilled pen

## 4 CONTRAINDICATIONS

Insulin Lispro Protamine and Insulin Lispro Mix75/25 is contraindicated:

- during episodes of hypoglycemia [see *Warnings and Precautions (5.3)*]
- in patients who have had hypersensitivity reactions to Insulin Lispro Protamine and Insulin Lispro Mix75/25 or to any of its excipients. [see *Warnings and Precautions (5.5)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Never Share an Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen Between Patients

Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPens must never be shared between patients, even if the needle is changed. 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 insulins, including Insulin Lispro Protamine and Insulin Lispro Mix75/25. 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.

#### Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulins, the glucose lowering effect time course of Insulin Lispro Protamine and Insulin Lispro Mix75/25 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see *Clinical Pharmacology (12.2)*]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions (7)*]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations (8.6, 8.7)*].

#### Risk Mitigation Strategies for Hypoglycemia

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

### 5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 insulins, including Insulin Lispro Protamine and Insulin Lispro Mix75/25. If hypersensitivity reactions occur, discontinue Insulin Lispro Protamine and Insulin Lispro Mix75/25; treat per standard of care and monitor until symptoms and signs resolve. Insulin Lispro Protamine

and Insulin Lispro Mix75/25 is contraindicated in patients who have had hypersensitivity reactions to Insulin Lispro Protamine and Insulin Lispro Mix75/25 or any of its excipients [see *Contraindications (4)*].

## 5.6 Hypokalemia

All insulins, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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)*]
- Hypoglycemia Due to Medication Errors [see *Warnings and Precautions (5.4)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.5)*]
- Hypokalemia [see *Warnings and Precautions (5.6)*]

### Adverse Reactions from Clinical Studies or Postmarketing Reports

The following adverse reactions have been identified during post-marketing use of Insulin Lispro Protamine and Insulin Lispro Mix75/25. 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25.

#### *Hypokalemia*

Insulin Lispro Protamine and Insulin Lispro Mix75/25 can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia.

#### *Injection site reactions*

Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25.

#### *Lipodystrophy*

Administration of insulin subcutaneously, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 have been identified during postapproval use.

### Peripheral Edema

Insulins, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 insulins, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

### Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The incidence of antibody formation with Insulin Lispro Protamine and Insulin Lispro Mix75/25 is unknown.

## 7 DRUG INTERACTIONS

Table 1 below presents clinically significant drug interactions with Insulin Lispro Protamine and Insulin Lispro Mix75/25.

**Table 1: Clinically Significant Drug Interactions with Insulin Lispro Protamine and Insulin Lispro Mix75/25**

| <b>Drugs that May Increase the Risk of Hypoglycemia</b>  |   |
|--|---|
| <i>Drugs:</i>  | 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.  |
| <i>Intervention:</i>   | Dose adjustment and increased frequency of glucose monitoring may be required when Insulin Lispro Protamine and Insulin Lispro Mix75/25 is co-administered with these drugs.  |
| <b>Drugs that May Decrease the Blood Glucose Lowering Effect of Insulin Lispro Protamine and Insulin Lispro Mix75/25</b>             |   |
| <i>Drugs:</i>  | 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. |
| <i>Intervention:</i>   | Dose adjustment and increased frequency of glucose monitoring may be required when Insulin Lispro Protamine and Insulin Lispro Mix75/25 is co-administered with these drugs.  |
| <b>Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of Insulin Lispro Protamine and Insulin Lispro Mix75/25</b> |   |
| <i>Drugs:</i>  | Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.   |
| <i>Intervention:</i>   | Dose adjustment and increased frequency of glucose monitoring may be required when Insulin Lispro Protamine and Insulin Lispro Mix75/25 is co-administered with these drugs.  |
| <b>Drugs that May Blunt Signs and Symptoms of Hypoglycemia</b>   |   |
| <i>Drugs:</i>  | Beta-blockers, clonidine, guanethidine, and reserpine.  |
| <i>Intervention:</i>   | Increased frequency of glucose monitoring may be required when Insulin Lispro Protamine and Insulin Lispro Mix75/25 is co-administered with these drugs.  |

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

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

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

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

### Clinical Considerations

#### *Disease-associated maternal and/or embryo/fetal risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25. However, subcutaneous reproduction and teratology studies have been conducted with insulin lispro (a component of Insulin Lispro Protamine and Insulin Lispro Mix75/25). In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 1, 5, and 20 units/kg/day (0.2, 0.8, and 3 times the human subcutaneous dose of 1 unit insulin lispro/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.2 times the human subcutaneous dose of 1 unit insulin lispro/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

## **8.2 Lactation**

### Risk Summary

Available data from published literature suggests that exogenous human insulin products, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, are transferred to human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 or from the underlying maternal condition.

## **8.4 Pediatric Use**

Safety and effectiveness of Insulin Lispro Protamine and Insulin Lispro Mix75/25 in pediatric patients have not been established.

## **8.5 Geriatric Use**

Clinical studies of Insulin Lispro Protamine and Insulin Lispro Mix75/25 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In patients aged 65 and over 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 has not been studied. Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 has not been studied. Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent Insulin Lispro Protamine and Insulin Lispro Mix75/25 dose adjustment and more frequent glucose monitoring [see *Warnings and Precautions (5.3)*].

## 10 OVERDOSAGE

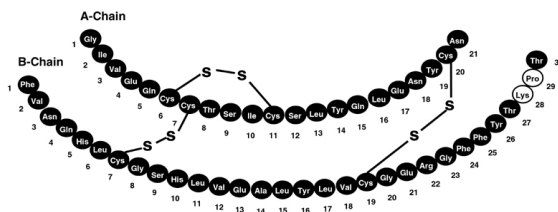
Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with a glucagon product for emergency use or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately [see *Warnings and Precautions (5.3, 5.6)*].

## 11 DESCRIPTION

Insulin lispro is a rapid-acting insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analog and has the empirical formula  $C_{257}H_{383}N_{65}O_{77}S_6$  and a molecular weight of 5.808 kDa, both identical to that of human insulin.

Insulin Lispro Protamine and Insulin Lispro Mix75/25 is a mixture of 75% insulin lispro protamine, an intermediate-acting human insulin analog, and 25% insulin lispro, a rapid-acting human insulin analog. 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:



Insulin Lispro Protamine and Insulin Lispro Mix75/25 injectable suspension is a white and cloudy, sterile suspension for subcutaneous use.

Each mL of Insulin Lispro Protamine and Insulin Lispro Mix75/25 contains 100 units of insulin lispro; dibasic sodium phosphate (2.0 mg), glycerin (16 mg), metacresol (1.76 mg), phenol (0.715 mg), protamine sulfate (0.28 mg), zinc oxide content adjusted to provide zinc ion (0.025 mg), and Water for Injection, USP. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid is added during manufacture to adjust the pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The primary activity of insulin, including Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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.

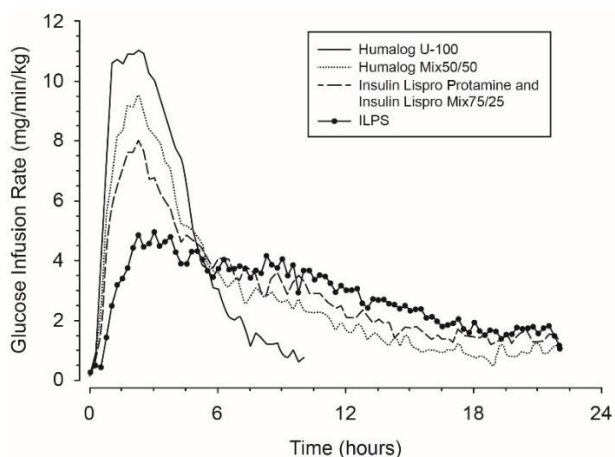
### 12.2 Pharmacodynamics

In a glucose clamp study performed in 30 healthy subjects, the onset of action and glucose-lowering activity of HUMALOG, HUMALOG® Mix50/50™, Insulin Lispro Protamine and Insulin Lispro 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25. The median maximum pharmacologic effect of Insulin Lispro Protamine and Insulin Lispro Mix75/25 after administration of a 0.3 unit/kg dose to healthy subjects occurred at approximately 2 hours (range: 1-6 hours); glucose lowering activity was detectable for a median of 22 hours (range: 13 to 22 hours), which was the end of the clamp.

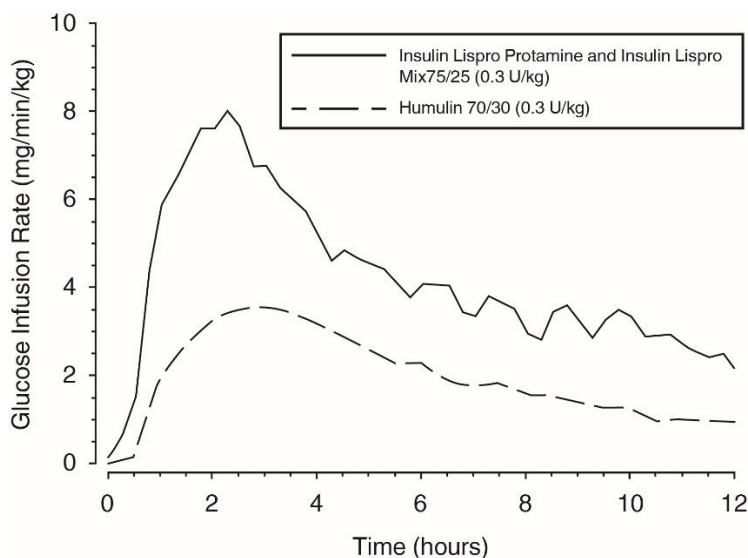
In separate glucose clamp studies performed in healthy subjects, pharmacodynamics of Insulin Lispro Protamine and Insulin Lispro Mix75/25 and HUMALIN® 70/30 were assessed and are presented in Figure 2. Insulin Lispro Protamine and Insulin Lispro Mix75/25 has a duration of activity similar to that of HUMALIN 70/30.

Figures 1 and 2 should be considered only as representative examples 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, Insulin Lispro Protamine and Insulin Lispro Mix75/25, or Insulin Lispro Protamine Suspension (ILPS) in 30 Healthy Subjects.**



**Figure 2: Mean Insulin Activity Versus Time Profiles After Injection of 0.3 units/kg of Insulin Lispro Protamine and Insulin Lispro Mix75/25 or HUMALIN 70/30 in Healthy Subjects.**



### 12.3 Pharmacokinetics

**Absorption** — Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 31 healthy subjects given subcutaneous doses (0.3 unit/kg) of Insulin Lispro Protamine and Insulin Lispro Mix75/25, the median peak serum concentration was 60 minutes (range: 30 minutes to 4 hours) after dosing. Identical results were found in patients with type 1 diabetes. The rapid absorption characteristics of HUMALOG are maintained with Insulin Lispro Protamine and Insulin Lispro Mix75/25. Insulin Lispro Protamine and Insulin Lispro Mix75/25 has a more rapid absorption than HUMALIN 70/30, which has been confirmed in patients with type 1 diabetes.



**Metabolism** — Human metabolism studies of Insulin Lispro Protamine and Insulin Lispro Mix75/25 have not been conducted. However, studies in animals indicate that the metabolism of HUMALOG, the rapid-acting component of Insulin Lispro Protamine and Insulin Lispro Mix75/25, 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 have not been studied.

**Gender** — Pharmacokinetic and pharmacodynamic comparisons between men and women administered Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25. In Fischer 344 rats, a 12-month repeat-dose toxicity study was conducted with insulin lispro (a component of Insulin Lispro Protamine and Insulin Lispro Mix75/25) 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**

Insulin Lispro Protamine and Insulin Lispro, injectable suspension, is a white and cloudy suspension of 100 units/mL (U-100) of 75% insulin lispro protamine and 25% insulin lispro available as:

|   |                  |
|---|------------------|
| 3 mL single-patient-use KwikPen prefilled pen | NDC 0002-8233-05 |
|---|------------------|

Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPens must never be shared between patients, even if the needle is changed. Always use a new needle for each injection to prevent contamination.

The Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen dials in 1 unit increments.

#### **16.2 Storage and Handling**

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

Protect from direct heat and light. Do not freeze and do not use if it has been frozen. See storage table below:

|                                 | <b>Not In-Use (Unopened)<br/>Refrigerated<br/>(36° to 46°F [2° to 8°C])</b> | <b>Not In Use (Unopened)<br/>Room Temperature<br/>(up to 86°F [30°C])</b> | <b>In-Use (Opened)<br/>(see temperature below)</b>       |
|---------------------------------|---|---|--|
| 3 mL single-patient-use KwikPen | Until expiration date   | 10 days   | 10 days<br>Room temperature only<br>(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 an Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPen Between Patients**

Advise patients using Insulin Lispro Protamine and Insulin Lispro Mix75/25 KwikPens not to share needles or KwikPens 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25 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 Insulin Lispro Protamine and Insulin Lispro Mix75/25. Inform patients on the symptoms of hypersensitivity reactions and to seek medical attention if they occur [see *Warnings and Precautions (5.5)*].

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