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

**DOSE AND ADMINISTRATION**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- Never share an insulin lispro KwikPen, cartridge, reusable pen compatible with Lilly 3 mL cartridges, or syringe between patients, even if the needle is changed. (5.1)

Adverse reactions associated with insulin lispro include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. (5.3)

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

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

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

Revised: 12/2018

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**INDICATIONS AND USAGE**

Insulin lispro injection for subcutaneous or intravenous use

Initial U.S. Approval: 1996

**CONTRAINDICATIONS**

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

Insulin lispro 100 units/mL (U-100) is available as:

- Do not mix insulin lispro U-200 with any other insulin. (2.4)

**Dosage Forms and Strengths**

Insulin lispro 100 units/mL (U-100) is available as:

- 10 mL vials
- 3 mL Insulin Lispro KwikPen® (prefilled)

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- Never share an insulin lispro KwikPen, cartridge, reusable pen compatible with Lilly 3 mL cartridges, or syringe between patients, even if the needle is changed. (5.1)

- Hyper- or Hypoglycemia with Changes in Insulin Regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)
- Hypoglycemia: May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3, 7, 8.6, 8.7)
- HypoglycemiaDue to Medication Errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. Do not transfer insulin lispro U-200 from the Insulin Lispro KwikPen to a syringe as overdosage and severe hypoglycemia can result. (5.4)
- Hypersensitivity Reactions: May be life-threatening. Discontinue insulin lispro, monitor and treat if indicated. (5.5)
- Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
- Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)
- Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction: Monitor glucose and administer insulin lispro U-100 by subcutaneous injection if pump malfunction occurs. (5.8)

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**USE IN SPECIFIC POPULATIONS**

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

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

Revised: 12/2018

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Insulin lispro is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
• Always check insulin labels before administration [see Warnings and Precautions (5.4)].
• Inspect insulin lispro visually before use. It should appear clear and colorless. Do not use insulin lispro if particulate matter or coloration is seen.
• Use Insulin Lispro KwikPens with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
• Do NOT mix insulin lispro U-100 with other insulins when administering using a continuous subcutaneous infusion pump.
• Do NOT transfer insulin lispro U-200 from the KwikPen to a syringe for administration [see Warnings and Precautions (5.4)].
• Do NOT mix insulin lispro U-100 with any other insulins.
• Do NOT administer insulin lispro U-200 using a continuous subcutaneous infusion pump (i.e., insulin pump).
• Do NOT administer insulin lispro U-200 intravenously.

2.2 Route of Administration
Subcutaneous Injection: Insulin Lispro U-100 or U-200
• Administer the dose of insulin lispro U-100 or insulin lispro U-200 within fifteen minutes before a meal or immediately after a meal by injection into the subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks. To reduce the risk of lipodystrophy, rotate the injection site within the same region from one injection to the next [see Adverse Reactions (6)].
• Insulin lispro administered by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
• The Insulin Lispro U-100 KwikPen and Insulin Lispro U-200 KwikPen each dial in 1 unit increments.
• The Insulin Lispro U-100 Junior KwikPen dials in 0.5 unit increments.

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

Intravenous Administration: Insulin Lispro U-100 ONLY
• Do NOT administer insulin lispro U-200 intravenously.
• Dilute insulin lispro U-100 to concentrations from 0.1 unit/mL to 1.0 unit/mL using 0.9% sodium chloride.
• Administer insulin lispro U-100 intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [see Warnings and Precautions (5.3, 5.6) and How Supplied/Storage and Handling (16.4)].

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

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

| Insulin lispro U-100 subcutaneous injection route | • Insulin lispro U-100 may be mixed with NPH insulin preparations ONLY.
| • If insulin lispro U-100 is mixed with NPH insulin, insulin lispro U-100 should be drawn into the syringe first. Injection should occur immediately after mixing. |
| Insulin lispro U-100 continuous subcutaneous infusion route (Insulin Pump) | • Do NOT mix insulin lispro U-100 with any other insulin. |
| Insulin lispro U-200 subcutaneous injection route | • Do NOT mix with any other insulin. |

3 DOSAGE FORMS AND STRENGTHS
Insulin lispro 100 units per mL (U-100) is available as:
• 10 mL vials
• 3 mL Insulin Lispro KwikPen (prefilled)

4 CONTRAINDICATIONS
Insulin lispro is contraindicated:
• during episodes of hypoglycemia
• in patients who are hypersensitive to insulin lispro or to any of its excipients.

5 WARNINGS AND PRECAUTIONS
5.1 Never Share an Insulin Lispro KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges1, or Syringe Between Patients
Insulin Lispro KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using insulin lispro vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

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

5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction associated with insulins, including insulin lispro. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).
Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions (7)], or in patients who experience recurrent hypoglycemia.
Risk Factors for Hypoglycemia

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

Risk Mitigation Strategies for Hypoglycemia

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

5.4 Hypoglycemia Due to Medication Errors

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

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

5.5 Hypersensitivity Reactions

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

5.6 Hypokalemia

All insulin products, including insulin lispro, 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, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction

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

6 ADVERSE REACTIONS

Observed with Insulin Lispro U-100

The following adverse reactions are discussed elsewhere:

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

6.1 Clinical Trial Experience

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

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

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus

(adverse events with frequency ≥5%)
### Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

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

---

**Insulin initiation and intensification of glucose control**

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

**Lipodystrophy**

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

**Weight gain**

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

**Peripheral Edema**

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

**Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII) — Insulin Lispro U-100**

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

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

<table>
<thead>
<tr>
<th>Events</th>
<th>Insulin Lispro U-100 (n=38)</th>
<th>Regular human insulin (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter occlusions/month</td>
<td>0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>2.6% (1/38)</td>
<td>2.6% (1/39)</td>
</tr>
</tbody>
</table>
In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy — As with any insulin therapy, patients taking insulin lispro may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of insulin lispro. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy — Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including insulin lispro. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

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

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

Antibody Production

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

6.2 Postmarketing Experience

Insulin Lispro U-100

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

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

7 DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

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

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of Insulin Lispro

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

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of Insulin Lispro

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

7.4 Drugs That May Blunt Signs and Symptoms of Hypoglycemia

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

8 USE IN SPECIFIC POPULATIONS

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

Although there are limited clinical studies of the use of insulin lispro in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

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

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

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

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

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

8.5 Geriatric Use
Of the total number of subjects (n=2834) in eight clinical studies of insulin lispro, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of insulin lispro action have not been performed.

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

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

10 OVERDOSAGE
Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION
Insulin lispro injection is a rapid-acting human insulin analog used to lower blood glucose. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analog and has the empirical formula C_{257}H_{383}N_{65}O_{77}S_{6} and a molecular weight of 5808, both identical to that of human insulin.
Insulin lispro has the following primary structure:

![Insulin Lispro Primary Structure Diagram]

Insulin lispro is a sterile, aqueous, clear, and colorless solution. Each milliliter of insulin lispro U-100 contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%. Each milliliter of insulin lispro U-200 contains insulin lispro 200 units, 16 mg glycerin, 5 mg tromethamine, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.046 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Insulin lispro has been shown to be equipotent to human insulin on a molar basis. One unit of insulin lispro has the same glucose-lowering effect as one unit of regular human insulin. Studies in normal volunteers and patients with diabetes demonstrated that insulin lispro has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

The time course of action of insulin and insulin analogs, such as insulin lispro, may vary considerably in different individuals or within the same individual. The parameters of insulin lispro activity (time of onset, peak time, and duration) as designated in Figure 1 should be considered only as general guidelines. The rate of insulin absorption, and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables [see Warnings and Precautions (5.2)].

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

\(^a\) Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.
Intravenous Administration of Insulin Lispro U-100 — The glucose lowering effect of intravenously administered insulin lispro was tested in 21 patients with type 1 diabetes. For the study, the patients’ usual doses of insulin were held and blood glucose concentrations were allowed to reach a stable range of 200 to 260 mg/dL during a one to three hours run-in phase. The run-in phase was followed by a 6-hour assessment phase. During the assessment phase, patients received intravenous insulin lispro at an initial infusion rate of 0.5 units/hour. The infusion rate of insulin lispro could be adjusted at regular timed intervals to achieve and maintain blood glucose concentrations between 100 to 160 mg/dL.

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

<table>
<thead>
<tr>
<th>Time from Start of Infusion (minutes)</th>
<th>Mean Blood Glucose (mg/dL) Intravenous*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>224 ± 16</td>
</tr>
<tr>
<td>30</td>
<td>205 ± 21</td>
</tr>
<tr>
<td>60</td>
<td>195 ± 20</td>
</tr>
<tr>
<td>120</td>
<td>165 ± 26</td>
</tr>
<tr>
<td>180</td>
<td>140 ± 26</td>
</tr>
<tr>
<td>240</td>
<td>123 ± 20</td>
</tr>
<tr>
<td>300</td>
<td>120 ± 27</td>
</tr>
<tr>
<td>360</td>
<td>122 ± 25</td>
</tr>
</tbody>
</table>

* Results shown as mean ± SD

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

12.3 Pharmacokinetics

Absorption and Bioavailability — Studies in healthy volunteers and patients with diabetes demonstrated that insulin lispro is absorbed more quickly than regular human insulin. In healthy volunteers given subcutaneous doses of insulin lispro ranging from 0.1 to 0.4 unit/kg, peak serum levels were seen 30 to 90 minutes after dosing. When healthy volunteers received equivalent doses of regular human insulin, peak insulin levels occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes (see Figure 2).
Insulin lispro U-100 was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 unit/kg at abdominal, deltoid, or femoral subcutaneous sites. After insulin lispro was administered in the abdomen, serum drug levels were higher and the duration of action was slightly shorter than after deltoid or thigh administration. Bioavailability of insulin lispro is similar to that of regular human insulin. The absolute bioavailability after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

The results of a study in healthy subjects demonstrated that insulin lispro U-200 is bioequivalent to insulin lispro U-100 following administration of a single 20 unit dose. The mean observed area under the serum insulin concentration-time curve from time zero to infinity was 2360 pmol hr/L and 2390 pmol hr/L for insulin lispro U-200 and insulin lispro U-100, respectively. The corresponding mean peak serum insulin concentration was 795 pmol/L and 909 pmol/L for insulin lispro U-200 and insulin lispro U-100, respectively. The median time to maximum concentration was 1.0 hour for both formulations.

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

**Metabolism** — Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of insulin lispro is identical to that of regular human insulin.

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

### Specific Populations

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

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

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

### NONCLINICAL TOXICOLOGY

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

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

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

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

#### 13.2 Animal Toxicology and/or Pharmacology

In standard biological assays in fasted rabbits, 0.2 unit/kg of insulin lispro injected subcutaneously had the same glucose-lowering effect and had a more rapid onset of action as 0.2 unit/kg of regular human insulin.
The safety and efficacy of insulin lispro U-100 were studied in children, adolescent, and adult patients with type 1 diabetes (n=789) and adult patients with type 2 diabetes (n=722).

14.1 Type 1 Diabetes – Adults and Adolescents

A 12-month, randomized, parallel, open-label, active-controlled study was conducted in patients with type 1 diabetes to assess the safety and efficacy of insulin lispro (n=81) compared with Humulin® R [insulin human injection (100 units per mL)] (n=86). Insulin lispro was administered by subcutaneous injection immediately prior to meals and Humulin R was administered 30 to 45 minutes before meals. Humulin® U [ULTRALENTE® human insulin (rDNA origin) extended zinc suspension] was administered once or twice daily as the basal insulin. There was a 2- to 4-week run-in period with Humulin R and Humulin U before randomization. Most patients were Caucasian (97%). Forty-seven percent of the patients were male. The mean age was 31 years (range 12 to 70 years). Glycemic control, the total daily doses of insulin lispro and Humulin R, and the incidence of severe hypoglycemia (as determined by the number of events that were not self-treated) were similar in the two treatment groups. There were no episodes of diabetic ketoacidosis in either treatment group.

Table 5: Type 1 Diabetes Mellitus – Adults and Adolescents

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>Treatment in Combination with:</th>
<th>Insulin Lispro</th>
<th>Humulin U</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>Humulin U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>81</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>$8.2 \pm 1.4$</td>
<td>$8.3 \pm 1.7$</td>
<td></td>
</tr>
<tr>
<td>Change from baseline HbA1c (%)</td>
<td>$-0.1 \pm 0.9$</td>
<td>$0.1 \pm 1.1$</td>
<td></td>
</tr>
<tr>
<td>Treatment Difference in HbA1c Mean (95% confidence interval)</td>
<td>$0.4 (0.0, 0.8)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline short-acting insulin dose (units/kg/day)</td>
<td>$0.3 \pm 0.1$</td>
<td>$0.3 \pm 0.1$</td>
<td></td>
</tr>
<tr>
<td>End-of-Study short-acting insulin dose (units/kg/day)</td>
<td>$0.3 \pm 0.1$</td>
<td>$0.3 \pm 0.1$</td>
<td></td>
</tr>
<tr>
<td>Change from baseline short-acting insulin dose (units/kg/day)</td>
<td>$0.0 \pm 0.1$</td>
<td>$0.0 \pm 0.1$</td>
<td></td>
</tr>
<tr>
<td>Baseline Body weight (kg)</td>
<td>$72 \pm 12.7$</td>
<td>$71 \pm 11.3$</td>
<td></td>
</tr>
<tr>
<td>Weight change from baseline (kg)</td>
<td>$1.4 \pm 3.6$</td>
<td>$1.0 \pm 2.6$</td>
<td></td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)</td>
<td>$14 (17%)$</td>
<td>$18 (21%)$</td>
<td></td>
</tr>
</tbody>
</table>

* Values are Mean ± SD

14.2 Type 2 Diabetes – Adults

A 6-month randomized, crossover, open-label, active-controlled study was conducted in insulin-treated patients with type 2 diabetes (n=722) to assess the safety and efficacy of insulin lispro for 3 months followed by Humulin R for 3 months or the reverse sequence. Insulin lispro was administered by subcutaneous injection immediately before meals and Humulin R was administered 30 to 45 minutes before meals. Humulin® N [NPH human insulin (rDNA origin) isophane suspension] or Humulin U was administered once or twice daily as the basal insulin. All patients participated in a 2- to 4-week run-in period with Humulin R and Humulin N or Humulin U. Most of the patients were Caucasian (88%), and the numbers of men and women in each group were approximately equal. The mean age was 58.6 years (range 23.8 to 85 years). The average body mass index (BMI) was 28.2 kg/m$^2$. During the study, the majority of patients used Humulin N (84%) compared with Humulin U (16%) as their basal insulin. The reductions from baseline in HbA1c and the incidence of severe hypoglycemia (as determined by the number of events that were not self-treated) were similar between the two treatments from the combined groups (see Table 6).

Table 6: Type 2 Diabetes Mellitus — Adults

<table>
<thead>
<tr>
<th>End point</th>
<th>Baseline</th>
<th>Insulin Lispro + Basal</th>
<th>Humulin R + Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>$8.9 \pm 1.7$</td>
<td>$8.2 \pm 1.3$</td>
<td>$8.2 \pm 1.4$</td>
</tr>
<tr>
<td>Change from baseline HbA1c (%)</td>
<td>—</td>
<td>$-0.7 \pm 1.4$</td>
<td>$-0.7 \pm 1.3$</td>
</tr>
<tr>
<td>Short-acting insulin dose (units/kg/day)</td>
<td>$0.3 \pm 0.2$</td>
<td>$0.3 \pm 0.2$</td>
<td>$0.3 \pm 0.2$</td>
</tr>
<tr>
<td>Change from baseline short-acting insulin dose (units/kg/day)</td>
<td>—</td>
<td>$0.0 \pm 0.1$</td>
<td>$0.0 \pm 0.1$</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>$80 \pm 15$</td>
<td>$81 \pm 15$</td>
<td>$81 \pm 15$</td>
</tr>
<tr>
<td>Weight change from baseline</td>
<td>—</td>
<td>$0.8 \pm 2.7$</td>
<td>$0.9 \pm 2.6$</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)</td>
<td>—</td>
<td>$15 (2%)$</td>
<td>$16 (2%)$</td>
</tr>
</tbody>
</table>

* Values are Mean ± SD

Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.
14.3 Type 1 Diabetes – Pediatric and Adolescents

An 8-month, crossover study of adolescents with type 1 diabetes (n=463), aged 9 to 19 years, compared two subcutaneous multiple-dose treatment regimens: insulin lispro or Humulin R, both administered with Humulin N (NPH human insulin) as the basal insulin. Insulin lispro achieved glycemic control comparable to Humulin R, as measured by HbA1c (see Table 7), and both treatment groups had a comparable incidence of hypoglycemia. In a 9-month, crossover study of prepubescent children (n=60) with type 1 diabetes, aged 3 to 11 years, insulin lispro administered immediately before meals, insulin lispro administered immediately after meals and Humulin R administered 30 minutes before meals resulted in similar glycemic control, as measured by HbA1c, and incidence of hypoglycemia, regardless of treatment group.

Table 7: Pediatric Subcutaneous Administration of Insulin Lispro in Type 1 Diabetes

<table>
<thead>
<tr>
<th>End point</th>
<th>Baseline</th>
<th>Insulin Lispro + NPH</th>
<th>Humulin R + NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.6 ± 1.5</td>
<td>8.7 ± 1.5</td>
<td>8.7 ± 1.6</td>
</tr>
<tr>
<td>Change from baseline HbA1c (%)</td>
<td>—</td>
<td>0.1 ± 1.1</td>
<td>0.1 ± 1.3</td>
</tr>
<tr>
<td>Short-acting insulin dose (units/kg/day)</td>
<td>0.5 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Change from baseline short-acting insulin dose (units/kg/day)</td>
<td>—</td>
<td>0.01 ± 0.1</td>
<td>-0.01 ± 0.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59.1 ± 13.1</td>
<td>61.1 ± 12.7</td>
<td>61.4 ± 12.9</td>
</tr>
<tr>
<td>Weight change from baseline (kg)</td>
<td>—</td>
<td>2.0 ± 3.1</td>
<td>2.3 ± 3.0</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)</td>
<td>—</td>
<td>5 (1.1%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (n, %)</td>
<td>—</td>
<td>11 (2.4%)</td>
<td>9 (1.9%)</td>
</tr>
</tbody>
</table>

* Values are Mean ± SD

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

14.4 Type 1 Diabetes – Adults Continuous Subcutaneous Insulin Infusion

To evaluate the administration of insulin lispro U-100 via external insulin pumps, two open-label, crossover design studies were performed in patients with type 1 diabetes. One study involved 39 patients, ages 19 to 58 years, treated for 24 weeks with insulin lispro or regular human insulin. After 12 weeks of treatment, the mean HbA1c values decreased from 7.8% to 7.2% in the insulin lispro-treated patients and from 7.8% to 7.5% in the regular human insulin-treated patients. Another study involved 60 patients (mean age 39, range 15 to 58 years) treated for 24 weeks with either insulin lispro or buffered regular human insulin. After 12 weeks of treatment, the mean HbA1c values decreased from 7.7% to 7.4% in the insulin lispro-treated patients and remained unchanged from 7.7% in the buffered regular human insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in both studies.

14.5 Type 1 Diabetes – Pediatric Continuous Subcutaneous Insulin Infusion

A randomized, 16-week, open-label, parallel design, study of children and adolescents with type 1 diabetes (n=298) aged 4 to 18 years compared two subcutaneous infusion regimens administered via an external insulin pump: insulin aspart (n=198) or insulin lispro U-100 (n=100). These two treatments resulted in comparable changes from baseline in HbA1c and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 8). Infusion site reactions were similar between groups.

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

<table>
<thead>
<tr>
<th>End point</th>
<th>Insulin Lispro</th>
<th>Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td>198</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.2 ± 0.8</td>
<td>8.0 ± 0.9</td>
</tr>
<tr>
<td>Change from Baseline HbA1c (%)</td>
<td>-0.1 ± 0.7</td>
<td>-0.1 ± 0.8</td>
</tr>
<tr>
<td>Treatment Difference in HbA1c, Mean (95% confidence interval)</td>
<td>0.1 (-0.3, 0.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline insulin dose (units/kg/24 hours)</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>End-of-Study insulin dose (units/kg/24 hours)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Patients with severe hypoglycemia (n, %)</td>
<td>8 (8%)</td>
<td>19 (10%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (n, %)</td>
<td>0 (0)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Baseline body weight (kg)</td>
<td>55.5 ± 19.0</td>
<td>54.1 ± 19.7</td>
</tr>
<tr>
<td>Weight Change from baseline (kg)</td>
<td>1.6 ± 2.1</td>
<td>1.8 ± 2.1</td>
</tr>
</tbody>
</table>

a Values are Mean ± SD

b Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.
16  HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Insulin lispro is available as:

<table>
<thead>
<tr>
<th>Insulin Lispro</th>
<th>Total Volume</th>
<th>Concentration</th>
<th>Total Units Available in Presentation</th>
<th>NDC Number</th>
<th>Max Dose per Injection</th>
<th>Dose Increment</th>
<th>Package Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 vial</td>
<td>10 mL</td>
<td>100 units/mL</td>
<td>1000 units</td>
<td>66733-773-01</td>
<td>n/a</td>
<td>n/a</td>
<td>1 vial</td>
</tr>
<tr>
<td>U-100 KwikPen</td>
<td>3 mL</td>
<td>100 units/mL</td>
<td>300 units</td>
<td>66733-822-59</td>
<td>60 units</td>
<td>1 unit</td>
<td>5 pens</td>
</tr>
</tbody>
</table>

Each prefilled KwikPen is for use by a single patient. Insulin Lispro KwikPens must never be shared between patients, even if the needle is changed. Patients using insulin lispro vials must never share needles or syringes with another person.

16.2 Storage and Handling

Do not use after the expiration date.

Unopened insulin lispro should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use insulin lispro if it has been frozen. In-use insulin lispro vials and Insulin Lispro KwikPens should be stored at room temperature, below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain insulin lispro. Protect from direct heat and light. See table below:

<table>
<thead>
<tr>
<th></th>
<th>Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])</th>
<th>Not In-Use (Unopened) Refrigerated</th>
<th>In-Use (Opened) Room Temperature, (Below 86°F [30°C])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Lispro U-100</td>
<td>28 days</td>
<td>Until expiration date</td>
<td>28 days, refrigerated/room temperature</td>
</tr>
<tr>
<td>10 mL vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mL Insulin Lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KwikPen (prefilled)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

16.3 Preparation and Handling

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

16.4 Admixture for Intravenous Administration

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

17  PATIENT COUNSELING INFORMATION

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

17.1 Never Share an Insulin Lispro KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges, or Syringe Between Patients

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

17.2 Hypoglycemia

Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of insulin lispro therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or
skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia.

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

17.3 Hypersensitivity Reactions
Advise patients that hypersensitivity reactions have occurred with insulin lispro. Inform patients on the symptoms of hypersensitivity reactions [see Warnings and Precautions (5.5)].

17.4 Medication Errors
Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.
Inform patients that insulin lispro U-200 contains 2 times as much insulin in 1 mL as insulin lispro U-100.
Inform patients that the Insulin Lispro U-200 KwikPen dose window shows the number of units of insulin lispro U-200 to be injected and that no dose conversion is required.
Instruct patients to NOT transfer insulin lispro U-200 from the Insulin Lispro KwikPen to a syringe. The markings on the syringe will not measure the dose correctly and this can result in overdosage and severe hypoglycemia.

17.5 Administration Instruction for Insulin Lispro U-200
Instruct patients to NOT mix insulin lispro U-200 with any other insulin.

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

17.7 Instructions For Patients Using Continuous Subcutaneous Insulin Pumps
Patients using external pump infusion therapy should be trained appropriately.
The following insulin pumps have been tested in insulin lispro clinical trials conducted by Eli Lilly and Company.
- Disetronic® H-Tron® plus V100, D-Tron® and D-Tronplus® with Disetronic Rapid infusion sets
- MiniMed® Models 506, 507 and 508 and Polyfin® infusion sets

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

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

Insulin exposed to temperatures higher than 98.6°F (37°C) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematosus, pruritic, or thickened should be reported to the healthcare professional, and a new site selected because continued infusion may increase the skin reaction or alter the absorption of insulin lispro.
Pump or infusion set malfunctions or insulin degradation can lead to rapid hyperglycemia and ketosis. This is especially pertinent for rapid acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their healthcare professionals [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)].

1 3 mL cartridge is for use in Eli Lilly and Company’s HumaPen® Luxura® HD insulin delivery device, and Disetronic D-TRON® and D-TRONplus® pumps.
2 Disetronic®, H-Tron®, D-Tron®, and D-Tronplus® are registered trademarks of Roche Diagnostics GmbH.
3 MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

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