HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LYUMJEV safely and effectively. See full prescribing information for LYUMJEV.

LYUMJEV (insulin lispro-aabc) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2020

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1) 10/2022

---------- INDICATIONS AND USAGE ----------
LYUMJEV® is a rapid-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus. (1)

----------DOSAGE AND ADMINISTRATION----------
- See Full Prescribing Information for important administration instructions. (2.1, 2.2)
- Subcutaneous Injection (2.2):
  - Administer LYUMJEV U-100 or U-200 at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks.
  - Rotate injection sites within the same region to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
  - Should generally be used in regimens with an intermediate or long-acting insulin.
- Continuous subcutaneous infusion (Insulin Pump) (2.2):
  - Refer to the insulin infusion pump user manual to see if LYUMJEV can be used. Use in accordance with the insulin pump instructions for use.
  - Administer LYUMJEV U-100 by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis.
  - Do not administer LYUMJEV U-200 by continuous subcutaneous infusion.
- Intravenous Infusion (2.2):
  - Administer LYUMJEV U-100 intravenously only under medical supervision. DO NOT administer LYUMJEV U-200 by intravenous infusion.
  - Dilute LYUMJEV U-100 to a concentration of 1 unit/mL.
- Individualize and adjust the dosage of LYUMJEV based on the patient's metabolic needs, glucose monitoring results, and glycemic control goal. (2.3)
- Dose adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., amount and type of food, timing of food intake), changes in renal or hepatic function, or during acute illness. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 units/mL (U-100) available as:
- 10 mL multiple-dose vial (3)
- 3 mL single-patient-use KwikPen® (3)
- 3 mL single-patient-use Junior KwikPen® (3)
- 3 mL single-patient-use Tempo Pen® (3)
- 3 mL single-patient-use cartridges (3)

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

---------- CONTRAINDICATIONS ----------
- During episodes of hypoglycemia. (4)
- Hypersensitivity to insulin lispro-aabc or any of the excipients in LYUMJEV. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Never share* a LYUMJEV prefilled pen or cartridge 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 glucose monitoring. (5.2)
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or 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. Do not transfer LYUMJEV U-200 from the LYUMJEV KwikPen to a syringe as overdosage and severe hypoglycemia can result. (5.4)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. (5.5)
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LYUMJEV, monitor, 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 of TZD if heart failure occurs. (5.7)
- *Hyperglycemia and ketoacidosis due to insulin pump device malfunction:* Monitor glucose and administer LYUMJEV by subcutaneous injection if pump malfunction occurs. (5.8)

----------ADVERSE REACTIONS----------
Adverse reactions observed with LYUMJEV include hypoglycemia, injection/infusion site reactions, allergic reactions, rash, pruritus, lipodystrophy, and weight gain. (6.1)

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

---------- DRUG INTERACTIONS ----------
- *Drugs that Increase Hypoglycemia Risk or Increase or Decrease Blood Glucose Lowering Effect:* Adjustment of dosage may be needed; closely monitor blood glucose. (7)
- *Drugs that Blunt Hypoglycemia Signs and Symptoms (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Increased frequency of glucose monitoring may be required. (7)

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

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LYUMJEV® is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin labels before administration *[see Warnings and Precautions (5.4)]*.
- Inspect LYUMJEV visually before use. It should appear clear and colorless. Do not use LYUMJEV if particulate matter and discoloration is seen.
- Use LYUMJEV prefilled pens with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- Do not perform dose conversion when using any LYUMJEV U-100 or U-200 prefilled pens. **The dose window of LYUMJEV prefilled pens shows the number of units of LYUMJEV to be delivered and no conversion is needed**.
- Do not transfer LYUMJEV U-200 from the prefilled pen to a syringe for administration *[see Warnings and Precautions (5.4)]*.
- Do not mix LYUMJEV with any other insulin products.
- Do not administer LYUMJEV U-200 using continuous subcutaneous infusion insulin pump.
- Do not administer LYUMJEV U-200 intravenously.

2.2 Route of Administration Instructions

Subcutaneous Injection for LYUMJEV U-100 or U-200

- Administer LYUMJEV at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks.
- Rotate injection sites 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 Adverse Reactions (6.1, 6.2)]*.
- LYUMJEV given by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin.
- The LYUMJEV U-100 KwikPen, LYUMJEV U-100 Tempo Pen, and LYUMJEV U-200 KwikPen each dial in 1 unit increments and deliver a maximum dose of 60 units per injection.
- The LYUMJEV U-100 Junior KwikPen dials in 0.5 unit increments and delivers a maximum dose of 30 units per injection.

Continuous Subcutaneous Insulin Infusion (Insulin Pump) for LYUMJEV U-100 Only

- Do not administer LYUMJEV U-200 using an insulin pump.
- Refer to the continuous subcutaneous insulin infusion pump user manual to see if LYUMJEV can be used with the insulin pump. Use LYUMJEV in accordance with the insulin pump system's instructions for use.
- Administer LYUMJEV U-100 by continuous subcutaneous infusion in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not infuse into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

- Train patients using continuous subcutaneous insulin infusion (CSII) therapy to administer insulin by injection and have alternate insulin therapy available in case of insulin pump failure *[see Warnings and Precautions (5.8)]*.
- Change LYUMJEV U-100 in the pump reservoir at least every 9 days or according to the pump user manual, whichever is shorter.
- Change the infusion sets and the infusion set insertion site according to the manufacturer's user manual.
- Do not dilute or mix LYUMJEV U-100 when administering by CSII.
- Do not expose LYUMJEV in the pump reservoir to temperatures greater than 98.6°F (37°C).

Intravenous Administration for LYUMJEV U-100 Only

- Do not administer LYUMJEV U-200 intravenously.
- Administer LYUMJEV U-100 intravenously only under medical supervision with close monitoring of glucose and potassium levels to avoid hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.5)]*.
- Dilute LYUMJEV U-100 to a concentration of 1 unit/mL using 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP infusion solutions. Dilutions to concentrations below 1 unit/mL are not recommended.
- Diluted LYUMJEV may be stored for up to 4 days when refrigerated or up to 12 hours at room temperature *[see HOW SUPPLIED/STORAGE AND HANDLING (16.2)]*.

2.3 General Dosage Instructions

- Individualize and adjust the dosage of LYUMJEV based on the patient's metabolic needs, glucose monitoring results, and glycemic control goal.
- If converting from another mealtime insulin to LYUMJEV, the change can be done on a unit-to-unit basis.
- Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.2, 5.3), Drug Interactions (7) and Use in Specific Populations (8.6, 8.7)]*.
- During changes to a patient's insulin regimen, increase the frequency of glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Instruct patients who forget a mealtime dose to monitor their glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) clear and colorless solution available as:

- 10 mL multiple-dose vial
- 3 mL single-patient-use LYUMJEV KwikPen
- 3 mL single-patient-use LYUMJEV Junior KwikPen
- 3 mL single-patient-use LYUMJEV Tempo Pen
- 3 mL single-patient-use cartridges

Injection: 200 units/mL (U-200) clear and colorless solution available as:

- 3 mL single-patient-use LYUMJEV KwikPen

4 CONTRAINDICATIONS

LYUMJEV is contraindicated:

- during episodes of hypoglycemia.
- in patients with hypersensitivity to insulin lispro-aabc or any of the excipients in LYUMJEV.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a LYUMJEV Prefilled Pen, Cartridge, or Syringe Between Patients

LYUMJEV prefilled pens or cartridges should never be shared between patients, even if the needle is changed. Patients using LYUMJEV vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin, 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 (6.1)]*.

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 insulins, including LYUMJEV *[see Adverse Reactions (6.1)]*. 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). LYUMJEV, or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

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. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulins, the glucose lowering effect time course of LYUMJEV 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 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 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 LYUMJEV and other insulins, instruct patients to always check the insulin label before each injection.

Do not transfer LYUMJEV U-200 from the LYUMJEV 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 Hypokalemia

All insulins, including LYUMJEV, 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).

5.6 Hypersensitivity Reactions

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

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 LYUMJEV, 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

Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of LYUMJEV 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 Dosage and Administration (2.2), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

Adverse Reaction Database – Adult Patients with Type 1 and Type 2 Diabetes

The data in Table 1 reflect the exposure of 780 adult patients with type 1 diabetes to LYUMJEV with a mean exposure duration of 26 weeks *[see Clinical Studies (14.2)]*. The mean age was 44 years, the mean duration of diabetes was 19 years, 55% were male, 77% were White, 2% were Black or African American, and 9% were Hispanic. The mean BMI was 26.6 kg/m^2 and the mean HbA_{1c} at baseline was 7.3%.

The data in Table 2 reflect the exposure of 336 adult patients with type 2 diabetes to LYUMJEV with a mean exposure duration of 26 weeks *[see Clinical Studies (14.3)]*. The mean age was 60 years, the mean duration of diabetes was 16 years, 55% were male, 69% were White, 4% were Black or African American, and 24% were Hispanic. The mean BMI was 32.1 kg/m^2 and the mean HbA_{1c} at baseline was 7.3%.

The data in Table 3 reflect the exposure of 215 adult patients with type 1 diabetes to LYUMJEV via CSII administration with a mean exposure duration of 16 weeks *[see Clinical Studies (14.4)]*. The mean age was 48 years, the mean duration of diabetes was 26 years, 44% were male, 94% were White, 3% were Black or African American, and 8% were Hispanic. The mean BMI was 27.0 kg/m^2 and the mean HbA_{1c} at baseline was 7.6%.

Common adverse reactions, excluding hypoglycemia, were defined as events that occurred in ≥5% and at the same rate or greater for LYUMJEV-treated patients than HUMALOG-treated patients.

Table 1. Adverse Reactions That Occurred in ≥5% of LYUMJEV-Treated Adult Patients with Type 1 Diabetes

	Mealtime LYUMJEV + basal insulin (N=451) %	**Postmeal LYUMJEV + basal insulin (N=329) %**
Nasopharyngitis	14.2	14.6

Table 2. Adverse Reactions That Occurred in ≥5% of LYUMJEV-Treated Adult Patients with Type 2 Diabetes

	Mealtime LYUMJEV + basal insulin (N=336) %
Nasopharyngitis	12.5
Upper Respiratory Tract Infection	7.4

Table 3. Adverse Reactions That Occurred in ≥5% of LYUMJEV-Treated Adult Patients with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion

	CSII LYUMJEV administration (N=215) %
Infusion site reaction	19.1
Infusion site pain	15.8
Nasopharyngitis	6.0

Adverse Reaction Database – Pediatric Patients with Type 1 Diabetes

The data in Table 4 reflect the exposure of 418 pediatric patients with type 1 diabetes to LYUMJEV with a mean exposure duration of 26 weeks *[see Clinical Studies (14.5)]*. The mean age was 12 years; 50% were male, 91% were White, 1% were Black or African American; and 24% of the US subpopulation in this trial were Hispanic. The mean BMI was 20.5 kg/m^2, the mean duration of diabetes was 5 years, and the mean HbA_{1c} at baseline was 7.8%. Common adverse reactions, excluding hypoglycemia, were defined as events that occurred in ≥5% and at the same rate or greater for LYUMJEV-treated patients than HUMALOG-treated patients.

Table 4. Adverse Reactions That Occurred in ≥5% of LYUMJEV-Treated Pediatric Patients with Type 1 Diabetes

	Mealtime LYUMJEV + basal insulin (N=280) %	Postmeal LYUMJEV + basal insulin (N=138) %
Nasopharyngitis	8.2	5.1
Upper Respiratory Tract Infection	5.4	1.4

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LYUMJEV. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for LYUMJEV with the incidence of hypoglycemia for other products may be misleading and also may not be representative of hypoglycemia rates that occur in clinical practice.

Incidence rates for severe hypoglycemia in adults with type 1 and type 2 diabetes mellitus and pediatric patients with type 1 diabetes mellitus treated with LYUMJEV in clinical trials are shown in Table 5 *[see Clinical Studies (14)]*.

Table 5. Proportion of Patients with Type 1 Diabetes and Type 2 Diabetes Who Experienced at Least One Episode of Severe Hypoglycemia in Adult and Pediatric Clinical Trials

	PRONTO-T1D (Adult Type 1)		PRONTO-T2D (Adult Type 2)	PRONTO-Pump-2 (Adult Type 1 CSII)	PRONTO-Peds (Pediatric Type 1)	
	Mealtime LYUMJEV + basal insulin (N=451) %	Postmeal LYUMJEV + basal insulin (N=329) %	Mealtime LYUMJEV + basal insulin (N=336) %	LYUMJEV (N=215) %	Mealtime LYUMJEV + basal insulin (N=280) %	Postmeal LYUMJEV + basal insulin (N=298) %
Severe hypoglycemia[a]	5.5	4.6	0.9	1.4	1.1	0

[a] Severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LYUMJEV, and may be life threatening. Generalized hypersensitivity reactions such as skin rashes and hypersensitivity were reported in adult patients treated with LYUMJEV: eczema (0.4%), rash (0.4%), dermatitis (0.3%), hypersensitivity (0.2%), and pruritus (0.2%).

Generalized hypersensitivity reactions reported in more than 1 pediatric patient treated with LYUMJEV included: rhinitis (0.7%), dermatitis (0.7%), rash (0.5%), and hypersensitivity (0.5%).

Lipodystrophy

Administration of insulin, including LYUMJEV, has resulted in lipohypertrophy (enlargement or thickening of tissue) and lipoatrophy (depression in the skin). Lipodystrophy was reported in 0.2% of adult and pediatric patients treated with LYUMJEV *[see Dosage and Administration (2.2)]*.

Injection/Infusion Site Reactions

Injection or infusion site reactions can occur with insulin therapy. With LYUMJEV, adult and pediatric patients have experienced rash, redness, inflammation, pain, bruising, or itching at the site of LYUMJEV injection or infusion. LYUMJEV contains treprostinil sodium and sodium citrate dihydrate as inactive ingredients *[see Description (11)]* which have been associated with infusion and injection site reactions with other non-insulin products.

Subcutaneous Injection Site-Related Reactions:

In studies PRONTO-T1D and PRONTO-T2D, injection site-related reactions occurred in 2.7% of adult patients treated with LYUMJEV (mild in 2.2% and moderate in 0.5%). with <0.1% of patients discontinuing from treatment due to injection site-related reactions.

In Study PRONTO-Peds, injection site-related reactions occurred in 6.2% of pediatric patients treated with LYUMJEV (mild in 5.7% and moderate in 0.5%), with <0.5% of patients discontinuing from treatment due to injection site-related reactions.

Continuous Subcutaneous Insulin Infusion (CSII) Site-Related Reactions:

In Study PRONTO-Pump-2, infusion site-related reactions were reported in 37.7% of adult patients treated with LYUMJEV (mild in 27.9%, moderate in 7.9%, and severe in 1.9%), with 3.3% of patients discontinuing from treatment due to infusion site-related reactions. See Table 4.

Weight Gain

Weight gain can occur with insulin therapy, including LYUMJEV, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. Adult patients with type 1 diabetes treated with LYUMJEV gained an average of 0.6 kg and patients with type 2 diabetes treated with LYUMJEV gained an average of 1.5 kg.

Peripheral Edema

Insulin, including LYUMJEV, may cause sodium retention and edema, particularly if previous poor metabolic control is improved by intensified insulin therapy. Peripheral edema occurred in 0.2% of adult patients treated with LYUMJEV.

6.2 Postmarketing Experience

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.

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

7 DRUG INTERACTIONS

Table 6 includes clinically significant drug interactions with LYUMJEV.

Table 6. Clinically Significant Drug Interactions with LYUMJEV

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when LYUMJEV is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of LYUMJEV	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines,

	progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when LYUMJEV is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of LYUMJEV	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when LYUMJEV is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when LYUMJEV 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% to 10% in women with pre-gestational diabetes with a HbA_{1c}>7 and has been reported to be as high as 20% to 25% in women with a HbA_{1c}>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% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

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

Data

Human Data

Published data from retrospective studies and meta-analyses do not report an association with insulin lispro and major birth defects, 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 LYUMJEV. However, subcutaneous reproduction and teratology studies have been conducted with insulin lispro. In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 1, 5, and 20 units/kg/day (0.2, 0.8, and 3 times the human subcutaneous dose of 1 unit insulin lispro/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of LYUMJEV to improve glycemic control in pediatric patients with diabetes mellitus have been established. Use of LYUMJEV for this indication is supported by evidence from an adequate and well-controlled study in 716 pediatric patients with type 1 diabetes mellitus aged 1 year and older, and from studies in adult and pediatric patients with diabetes mellitus *[see Clinical Pharmacology (12.3) and Clinical Studies (14.5)]*.

LYUMJEV-treated pediatric patients reported a higher incidence of subcutaneous injection site-related reactions compared to LYUMJEV-treated adults *[see Adverse Reactions (6.1)].* It is expected that LYUMJEV-treated pediatric patients who receive continuous subcutaneous insulin infusion (CSII) are more likely to have infusion site-related adverse reactions than those who receive subcutaneous injections *[see Adverse Reactions (6.1)]*. Monitor injection and infusion sites closely when initiating therapy with LYUMJEV in pediatric patients. If persistent injection or infusion site reactions occur, discontinue LYUMJEV and initiate therapy with an alternative insulin.

8.5 Geriatric Use

Of the total number of LYUMJEV-treated patients in clinical studies for type 1 or type 2 diabetes (PRONTO-T1D and PRONTO-T2D, respectively), 17% (187/1,116) were 65 years of age and older, while 2% (18/1,116) were 75 years of age and older *[see Clinical Studies (14.2, 14.3)]*.

No overall differences in safety or effectiveness of LYUMJEV have been observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent LYUMJEV dose adjustment and more frequent glucose monitoring *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent LYUMJEV dose adjustment and more frequent glucose monitoring *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

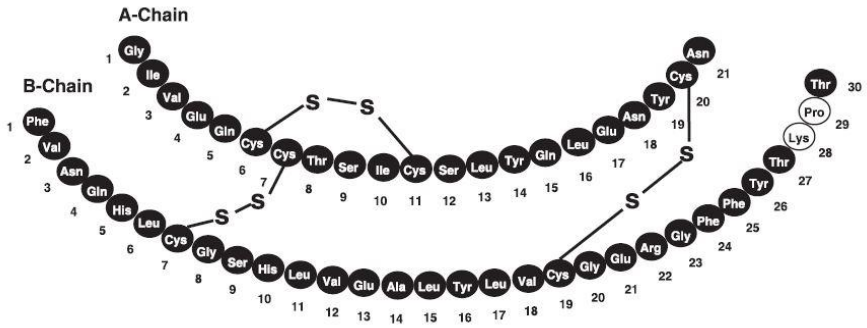
10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.5)]*. 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 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-aabc is a rapid-acting human insulin analog used to lower blood glucose. Insulin lispro-aabc is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro-aabc 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 daltons, both identical to that of human insulin.

Insulin lispro-aabc has the following primary structure:



LYUMJEV (insulin lispro-aabc) injection is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous administration. Each mL of LYUMJEV U-100 contains 100 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 39 mcg zinc ion), and Water for Injection, USP.

Each mL of LYUMJEV U-200 contains 200 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 52 mcg zinc ion), and Water for Injection, USP.

Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. LYUMJEV has a pH of 7.0 to 7.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of LYUMJEV is the regulation of glucose metabolism. Insulins, including insulin lispro-aabc, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers 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

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals or within the same individual. The average pharmacodynamic profile [i.e., glucose lowering effect measured as glucose infusion rate (GIR) in a euglycemic clamp study] for subcutaneous administration of 7, 15, and 30 units of LYUMJEV in 42 healthy subjects is shown in Figure 1 and key characteristics of the timing of the effect are described in Table 7 below.

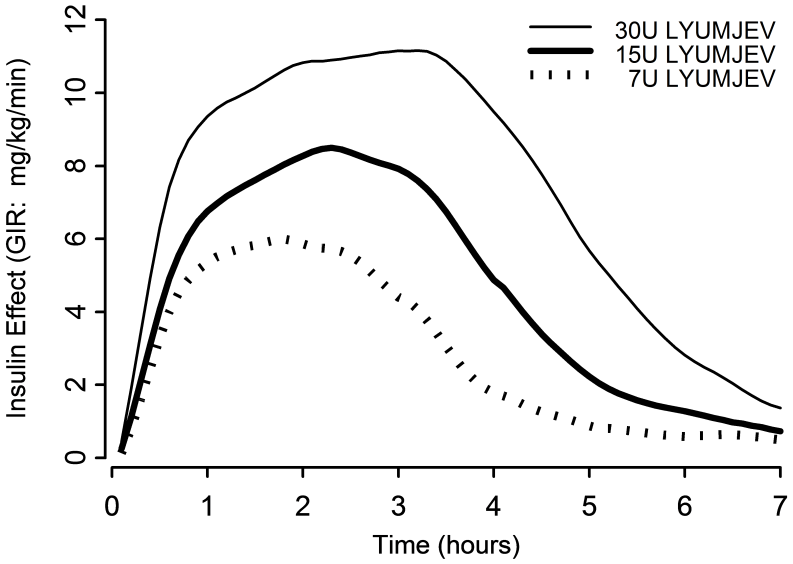


Figure 1. Mean Insulin Effect Over Time After Subcutaneous Administration of 7, 15, and 30 units of LYUMJEV in Healthy Subjects.

Table 7. Timing of Insulin Effect (i.e., Mean Pharmacodynamic Effect) After Subcutaneous Administration of 7, 15, and 30 Units of LYUMJEV in Healthy Subjects (N=42) and Corresponding to the Data Shown in Figure 1

Parameter for Insulin Effect	LYUMJEV 7 units	LYUMJEV 15 units	LYUMJEV 30 units
Time to first measurable effect	~17 minutes	~17 minutes	~15 minutes
Time to peak effect	~120 minutes	~138 minutes	~174 minutes
Time for effect to return to baseline	~4.6 hours	~6.2 hours	~7.3 hours

On average, the pharmacodynamic effects of LYUMJEV, measured as area under the glucose infusion rate-time curve (AUC_{GIR}), was 1080 mg/kg, 1860 mg/kg, and 3030 mg/kg following administration of 7, 15, and 30 units of LYUMJEV in healthy subjects.

Similar pharmacodynamic profiles were observed in separate studies conducted in 40 patients with type 1 diabetes and 38 patients with type 2 diabetes given LYUMJEV subcutaneously as a single 15 unit dose.

The onset and total glucose lowering were similar when LYUMJEV was administered in the abdomen, deltoid, or thigh. The day-to-day variability [percent coefficient of variation (CV%)] within subjects in the glucose-lowering-effect of LYUMJEV was 24% for the early glucose lowering (AUC_{GIR}, 0-1h), 27% for the total glucose lowering (AUC_{GIR}, 0-10h), and 19% for maximum glucose lowering effect (GIR_{max}).

Postprandial Glucose Lowering

When given at the start of a meal or 20 minutes after the start of the meal, LYUMJEV reduced postprandial glucose during a standardized test meal over the complete 5-hour period [change from premeal AUC(0-5h)] in patients with type 1 or type 2 diabetes.

The maximum and total glucose lowering were comparable for a single 15 unit dose of LYUMJEV 200 units/mL or LYUMJEV 100 units/mL when administered subcutaneously to healthy subjects. The insulin time action profile with LYUMJEV 200 units/mL was the same as observed with LYUMJEV 100 units/mL.

12.3 Pharmacokinetics

Absorption

Absorption of insulin lispro-aabc was evaluated in healthy subjects (see Figure 2) and patients with diabetes following subcutaneous injection of LYUMJEV.

- Insulin lispro-aabc appeared in circulation approximately 1 minute after injection of LYUMJEV.
- Time to 50% maximum insulin lispro-aabc concentration was 13 minutes.
- Time to maximum insulin lispro-aabc concentration was achieved at 57 minutes.

In healthy subjects, the day-to-day variability [CV%] within subjects of LYUMJEV was 10% for total exposure (AUC, 0-10h) and 16% for maximum insulin lispro-aabc concentration (C_{max}).

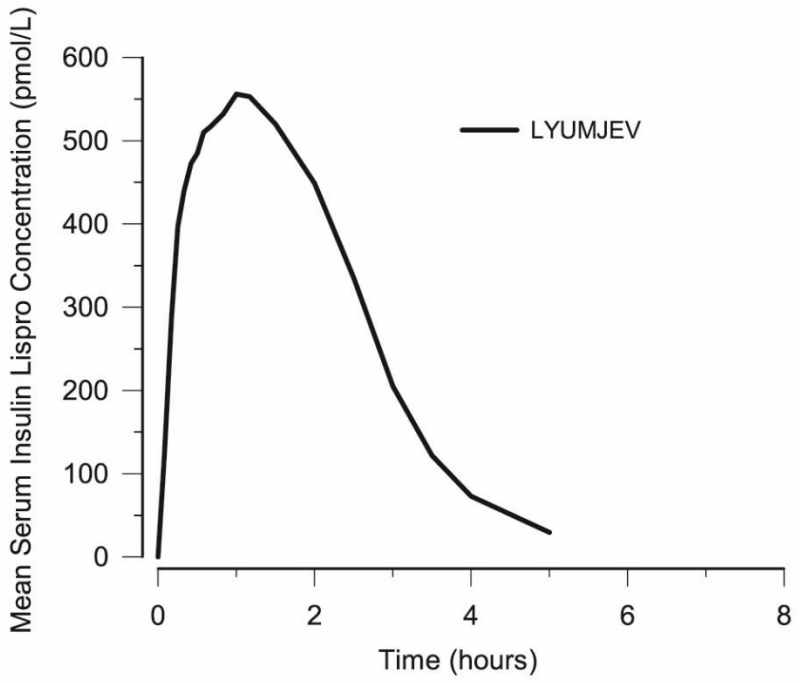


Figure 2. Mean Serum Insulin Lispro-aabc After Subcutaneous Injection of LYUMJEV (15 unit dose) in Healthy Subjects

The absolute bioavailability of insulin lispro-aabc after subcutaneous administration of LYUMJEV in the abdomen, deltoid, and thigh was approximately 65%. The rate of absorption of insulin lispro-aabc is maintained regardless of injection site. Maximum concentration and time to maximum concentration were comparable for the abdomen and upper arm regions; time to maximum concentration was longer and maximum concentration was lower for the thigh.

Total insulin lispro-aabc exposure and maximum insulin lispro-aabc concentration increased proportionally with increasing subcutaneous doses of LYUMJEV within the therapeutic dose range.

The results of a study in healthy subjects demonstrated that LYUMJEV 200 units/mL is bioequivalent to LYUMJEV 100 units/mL following administration of a single 15 unit dose for the area under the serum insulin lispro-aabc concentration-time curve from time zero to infinity and maximum insulin lispro-aabc concentration. The rate of insulin lispro-aabc absorption after administration of LYUMJEV 200 units/mL was similar as observed with LYUMJEV 100 units/mL.

Distribution

Following a 15 unit intravenous bolus injection of LYUMJEV in healthy subjects, the geometric mean (CV%) volume of distribution of insulin lispro-aabc (Vd) was 34 L (30%).

Elimination

Following a 15 unit intravenous bolus injection of LYUMJEV in healthy subjects, the geometric mean (CV%) clearance of insulin lispro-aabc was 32 L/hour (22%) and the median half-life of insulin lispro-aabc was 44 minutes.

Specific Populations

Age, biological sex, and race did not affect the pharmacokinetics and pharmacodynamics of LYUMJEV.

Patients with Renal and Hepatic Impairment

Renal and hepatic impairment is not known to impact the pharmacokinetics of insulin lispro-aabc. Insulin requirements may be reduced in the presence of renal or hepatic impairment.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of insulin lispro-aabc or of other insulin lispro products.

In a 26-week trial in adult patients with type 1 diabetes (Study PRONTO-T1D) *[see Clinical Studies (14.2)]*, 49% of LYUMJEV-treated patients were anti-drug (insulin lispro-aabc) antibody (ADA)-positive at baseline, 91% of whom had cross-reactive antibodies with native insulin. During this 26-week period in this trial, 33% of LYUMJEV-treated patients had treatment-emergent ADA post-baseline (i.e., either new ADA or a 57% increase in assay signal over baseline), 75% of whom had cross-reactive antibodies with native insulin.

In a 26-week trial in adult patients with type 2 diabetes (Study PROTO-T2D) *[see Clinical Studies (14.3)]*, 35% of LYUMJEV-treated patients were ADA-positive at baseline, 81% of whom had cross-reactive antibodies with native insulin. During this 26-week period in this trial, 31% of LYUMJEV-treated patients had treatment-emergent ADA post-baseline (i.e., either new ADA or a 57% increase in assay signal over baseline), 68% of whom had cross-reactive antibodies with native insulin.

In a 26-week trial in pediatric patients with type 1 diabetes (Study-PRONTO-PEDS) *[see Clinical Studies (14.5)]*, 73% of LYUMJEV-treated patients were ADA-positive at baseline. Of these ADA-positive patients, 97% had cross-reactive antibodies with native insulin. During this 26-week period in this trial, 31% of LYUMJEV-treated patients had treatment-emergent ADA post-baseline (i.e., either new ADA or a 57% increase in assay signal over baseline). Of these treatment-emergent ADA-positive patients, 84% had cross-reactive antibodies with native insulin.

In these clinical trials, there were no identified clinically significant effects of ADA on safety or effectiveness (measured by HbA1c) of LYUMJEV over the treatment duration of 26-weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Male fertility was not compromised when male rats given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area) for 6 months were mated with untreated female rats. In a combined fertility, perinatal, and postnatal study in male and female rats given 1, 5, and 20 units/kg/day subcutaneously (0.2, 0.8, and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area), mating and fertility were not adversely affected in either gender at any dose.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The effectiveness of LYUMJEV was evaluated in:

- Two randomized, active controlled trials of 26 weeks in adults with type 1 diabetes (N=780) or type 2 diabetes (N=336) (PRONTO-T1D and PRONTO-T2D, respectively) *[see Clinical Studies (14.2, 14.3)]*.
- A randomized, active controlled 16-week trial in adults with type 1 diabetes using continuous subcutaneous insulin infusion (N=432) (PRONTO-Pump-2) *[see Clinical Studies (14.4)]*.
- A randomized, active controlled 26-week trial in pediatric patients with type 1 diabetes (N=716) (PRONTO-Peds) *[see Clinical Studies (14.5)]*.

14.2 Adults with Type 1 Diabetes

PRONTO-T1D (NCT03214367) was a 26 week, randomized (4:4:3), active controlled, treat-to-target, multinational trial that evaluated the efficacy of LYUMJEV in 1222 adult patients with type 1 diabetes. Patients were randomized to either blinded mealtime LYUMJEV (N=451), blinded mealtime HUMALOG (N=442), or open-label postmeal LYUMJEV (N=329), all in combination with either insulin glargine or insulin degludec. Mealtime LYUMJEV or HUMALOG was injected 0 to 2 minutes before the meal and postmeal LYUMJEV was injected 20 minutes after the start of the meal.

Patients had a mean age of 44 years; mean duration of diabetes of 19 years; 56% were male; race: 77% White, 19% Asian, and 2% Black or African American. Eight percent of the randomized patients were Hispanic. The mean BMI was 26.6 kg/m^2.

At week 26, treatment with mealtime LYUMJEV provided a mean reduction in HbA_{1c} that met the pre-specified non-inferiority margin (0.4%) (see Table 8). In addition, postmeal LYUMJEV met the prespecified non-inferiority margin (0.4%) compared to mealtime HUMALOG. Insulin doses were similar in all treatment groups at baseline and at 26 weeks.

Table 8. Results from Study PRONTO-T1D: 26 Week Trial of Mealtime LYUMJEV and Postmeal LYUMJEV compared with Mealtime HUMALOG, all in Combination with Basal Insulin in Adults with Type 1 Diabetes

	Mealtime LYUMJEV + basal insulin	Mealtime HUMALOG + basal insulin	Postmeal LYUMJEV + basal insulin
Number of randomized subjects (N)	451	442	329
HbA_{1c} (%) (mean)[a]			
Baseline	7.3	7.3	7.4
Adjusted mean change from baseline[b]	-0.12	-0.04	0.1
Estimated treatment difference versus HUMALOG [95% CI]	-0.08 [-0.16, 0.00][c]		0.14 [0.05, 0.22]

[a] Analysis population: all randomized subjects regardless of adherence to treatment or availability of post-baseline assessment. Missing data at Week 26 were imputed by return to baseline approach. At week 26, primary efficacy assessment was missing for 3.8%, 4.8%, and 5.2% of subjects, for mealtime LYUMJEV, mealtime HUMALOG, and postmeal LYUMJEV, respectively.

[b] Least-squares (LS) mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Tested for non-inferiority.

14.3 Adults with Type 2 Diabetes

PRONTO-T2D (NCT03214380) was a 26-week, randomized (1:1), active controlled, treat-to-target, multinational trial that evaluated the efficacy of LYUMJEV in 673 adult patients with type 2 diabetes who at study entry were on multiple daily injections with either basal insulin and at least one prandial insulin injection or premixed insulin with at least two injections daily. Patients may also have been treated with up to three oral anti-diabetic medications (OAMs) in addition to insulin. Patients were allowed to continue on metformin and/or a SGLT2 inhibitor and were randomized to either mealtime LYUMJEV (N=336) or to mealtime HUMALOG (N=337), both in combination with insulin glargine or insulin degludec in a basal-bolus regimen. Mealtime LYUMJEV or mealtime HUMALOG was injected 0-2 minutes before the meal.

Patients had a mean age of 61 years; mean duration of diabetes of 17 years; 53% were male; race: 69% White, 24% Asian, and 5% Black or African American. Twenty-three percent of the randomized patients were Hispanic. The mean BMI was 32.3 kg/m^2.

At week 26, treatment with mealtime LYUMJEV provided a mean reduction of HbA_{1c} from baseline that met the pre-specified non-inferiority margin (0.4%) compared to mealtime HUMALOG (see Table 9). Insulin doses were similar in both treatment groups at baseline and at 26 weeks.

Table 9. Results from Study PRONTO-T2D: 26 Week Trial of Mealtime LYUMJEV Compared with Mealtime HUMALOG, both in Combination with Basal Insulin in Adults with Type 2 Diabetes

	Mealtime LYUMJEV + basal insulin	Mealtime HUMALOG + basal insulin
Number of randomized subjects (N)	336	337
HbA_{1c} (%)[a]		

Baseline mean	7.3	7.3
Adjusted mean change from baseline[b]	-0.36	-0.38
Estimated treatment difference versus HUMALOG [95% CI][c]	0.03 [-0.08, 0.13]	

[a] Analysis population: all randomized subjects regardless of adherence to treatment or availability of post-baseline assessment. Missing data at Week 26 were imputed by return to baseline approach. At week 26, primary efficacy assessment was missing for 4.8% of subjects for mealtime LYUMJEV and for 4.5% mealtime HUMALOG.

[b] Least-squares (LS) mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Tested for non-inferiority.

14.4 Adults with Type 1 Diabetes – Continuous Subcutaneous Insulin Infusion (CSII)

PRONTO-Pump-2 (NCT03830281) was a 16 week randomized (1:1), active controlled, treat-to-target, multinational trial that evaluated the efficacy of LYUMJEV in 432 adult patients with type 1 diabetes currently using continuous subcutaneous insulin infusion. Patients were randomized to either blinded LYUMJEV (N=215) or blinded HUMALOG (N= 217). Mealtime LYUMJEV or HUMALOG boluses were initiated 0 to 2 minutes before the meal.

Patients had a mean age of 46 years; mean duration of diabetes of 26 years; 45% were male; race: 95% White, 3% Black or African American, and 0.5% Asian. Eight percent of the randomized patients were Hispanic. The mean BMI was 27.1 kg/m^2.

At week 16, treatment with LYUMJEV provided a mean reduction in HbA_{1c} that met the pre-specified non-inferiority margin (0.4%) compared to mealtime HUMALOG (see Table 10). Total daily insulin doses were similar for both treatment groups at baseline and at 16 weeks.

Table 10. Results from Study PRONTO-Pump-2: 16 Week Trial of LYUMJEV compared with HUMALOG in Adults with Type 1 Diabetes

	LYUMJEV	**HUMALOG**
Number of randomized subjects (N)	215	217
HbA_{1c} (%)[a]		
Baseline mean	7.6	7.5
Adjusted mean change from baseline[b]	-0.06	-0.09
Estimated treatment difference versus HUMALOG [95% CI][c]	0.03 [-0.05, 0.11]	

[a] Analysis population: all randomized subjects regardless of adherence to treatment or availability of post-baseline assessment. Missing data at Week 16 were imputed by return to baseline approach. At week 16, primary efficacy assessment was missing for 7% and 4.6% of subjects, for LYUMJEV and HUMALOG, respectively.

[b] Least-squares (LS) mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Tested for non-inferiority.

14.5 Pediatric Patients with Type 1 Diabetes

PRONTO-Peds (NCT03740919) was a 26-week, randomized (2:2:1), active controlled, treat-to-target, multinational trial that evaluated the efficacy of LYUMJEV in 716 pediatric patients with type 1 diabetes. Patients were randomized to either blinded mealtime LYUMJEV (N=280), blinded mealtime HUMALOG (N=298), or open-label postmeal LYUMJEV (N=138), all in combination with basal insulin (insulin glargine, insulin degludec or insulin detemir). Mealtime LYUMJEV or HUMALOG was injected 0 to 2 minutes before the meal and postmeal LYUMJEV was injected within 20 minutes after the start of the meal.

Patients had a mean age of 12 years (3-17 years); 51% were male; race: 89% White, 6% Asian, and 2% Black or African American. In the U.S. subpopulation in this trial, 24% of the randomized patients were Hispanic. The mean BMI was 20.4 kg/m^2 and the mean duration of diabetes was 5 years.

At week 26, treatment with mealtime LYUMJEV provided a mean change in HbA1c that met the pre-specified non-inferiority margin (0.4%) (see Table 11). In addition, postmeal LYUMJEV met the prespecified non-inferiority margin (0.4%) compared to mealtime HUMALOG. Insulin doses were similar in all treatment groups at baseline and at 26 weeks.

Table 11. Results from Study PRONTO-Peds: 26 Week Trial of Mealtime LYUMJEV and Postmeal LYUMJEV compared with Mealtime HUMALOG, all in Combination with Basal Insulin in Pediatric Patients with Type 1 Diabetes

	Mealtime LYUMJEV + basal insulin	Mealtime HUMALOG + basal insulin	Postmeal LYUMJEV + basal insulin
Number of randomized subjects (N)	280	298	138
HbA_{1c} (%) (mean) [a]			
Baseline	7.8	7.8	7.8
Adjusted mean change from baseline[b]	0.06	0.06	0.06
Estimated treatment difference versus HUMALOG [95% CI][c]	-0.01 [-0.15, 0.14]		-0.00 [-0.18, 0.18]

[a] Analysis population: all randomized subjects regardless of adherence to treatment or availability of post-baseline assessment. Missing data at Week 26 were imputed by return to baseline approach. At week 26, primary efficacy assessment was missing for 5.4%, 7.1%, and 5.1% of subjects, for mealtime LYUMJEV, mealtime HUMALOG, and postmeal LYUMJEV, respectively.

[b] Least-squares (LS) mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Tested for non-inferiority.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LYUMJEV (insulin lispro-aabc) injection is a clear and colorless solution available as shown in Table 12.

Table 12. How Supplied

LYUMJEV	NDC Number	Concentration	Total Units in Presentation	Dose Increment	Package Size
U-100 multiple-dose 10 mL vial	0002-7728-01	100 units/mL	1,000 units	n/a	1 vial
U-100 single-patient-use 3 mL cartridge[a]	0002-7726-05	100 units/mL	300 units	n/a	5 cartridges
U-100 single-patient-use 3 mL KwikPen	0002-8207-05	100 units/mL	300 units	1 unit	5 pens
U-100 single-patient-use 3 mL Junior KwikPen	0002-8351-05	100 units/mL	300 units	0.5 unit	5 pens
U-100 single-patient-use 3 mL Tempo Pen[b]	0002-8235-05	100 units/mL	300 units	1 unit	5 pens
U-200 single-patient-use 3 mL KwikPen	0002-8228-27	200 units/mL	600 units	1 unit	2 pens

[a] 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Luxura® HD insulin delivery device. Patients need to check their device manual to determine if the LYUMJEV cartridge is compatible for use in other devices.

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

16.2 Storage and Handling

- Dispense in the original sealed carton with the enclosed Instructions for Use.
- Refrigerate unopened LYUMJEV vials, pens, and cartridges between 36°F to 46°F (2°C to 8°C) until time of use and keep in the original carton to protect from light. Do not freeze or use LYUMJEV if it has been frozen. Do not expose to direct heat. Discard opened or unopened LYUMJEV vials, pens, and cartridges stored at room temperature below 86°F (30°C) after 28 days.

The storage conditions for vials, pens, and cartridges are summarized in Table 13.

Table 13. Storage Conditions for Vials, Pens, and Cartridges

LYUMJEV Presentation	Not In-use (Unopened)		In-use (Opened)	
	Room Temperature (below 86°F [30°C])	Refrigerated (36°F to 46°F [2°C to 8°C])	Room Temperature (below 86°F [30°C])	Refrigerated (36°F to 46°F [2°C to 8°C])
10 mL vial[a,b]	28 days	Until expiration date	28 days	28 days
3 mL cartridge[b]	28 days	Until expiration date	28 days	Do not refrigerate
3 mL LYUMJEV KwikPen (U-100 and U-200)[b]	28 days	Until expiration date	28 days	Do not refrigerate
3 mL LYUMJEV Junior KwikPen[b]	28 days	Until expiration date	28 days	Do not refrigerate
3 mL LYUMJEV Tempo Pen[b]	28 days	Until expiration date	28 days	Do not refrigerate

[a] In-use (opened) vials, whether or not refrigerated, must be used within 28 days.

[b] When stored at room temperature, LYUMJEV can only be used for a total of 28 days including both not in-use (unopened) and in-use (opened) storage time.

Storage of LYUMJEV in Insulin Pump

Change the LYUMJEV U-100 in the pump reservoir at least every 9 days, or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 98.6°F (37°C).

Storage of LYUMJEV in Intravenous Infusion Fluids

Diluted LYUMJEV may be stored for up to 4 days when refrigerated at 36°F to 46°F (2°C to 8°C) until time of use. The same solution may be stored up to 12 hours at room temperature at 68°F to 77°F (20°C to 25°C) *[see Dosage and Administration (2.2)].*

17 PATIENT COUNSELING INFORMATION

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

Never Share a LYUMJEV Prefilled Pen, Cartridge, or Syringe Between Patients

Advise patients that they must never share a LYUMJEV prefilled pen or cartridge with another person, even if the needle is changed. Advise patients using LYUMJEV vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or Hypoglycemia

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 LYUMJEV therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia.

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

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

Hypoglycemia due to Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

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

Instruct patients to not transfer LYUMJEV U-200 from the LYUMJEV U-200 KwikPen to a syringe *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with LYUMJEV. Inform patients on the symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.6)]*.

Instructions for Patients Using Continuous Subcutaneous Infusion (Insulin Pump)

- Do not use LYUMJEV U-200 in an insulin pump.
- Train patients in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.
- Instruct patients to follow healthcare provider recommendations when setting pump basal rates and bolus settings.
- Refer to the continuous subcutaneous infusion pump user manual to see if LYUMJEV can be used with the pump. See recommended reservoir and infusion sets in the insulin pump user manual.
- Instruct patients to replace insulin in the reservoir at least every 9 days, or according to the pump user manual whichever is shorter. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin preservative.
- Instruct patients to discard insulin exposed to temperatures higher than 98.6°F (37°C).
- Instruct patients to inform healthcare provider and select a new site for infusion if infusion site becomes erythematous, pruritic, or thickened.
- Instruct patients on the risk of rapid hyperglycemia and ketosis due to pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Instruct patients on the risk of hypoglycemia from pump malfunction. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their healthcare provider *[see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)]*.

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