RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	LYUMJEV™
Generic Name	insulin lispro
Drug Manufacturer	Eli Lilly and Company

New Drug Approval

LYUMJEV™ is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

FDA Approval date: June 15, 2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. Symptoms often include frequent urination, increased thirst, and increased appetite. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, damage to the eyes and cognitive impairment.

Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are two main types of diabetes mellitus:

- Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown.
- Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop. This form was previously referred to as "non-insulin dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is a combination of excessive body weight and insufficient exercise.
- Gestational diabetes is hyperglycaemia with blood glucose values above normal but below those diagnostic of diabetes. Gestational diabetes occurs during pregnancy.

New in 2020, the report features trends in prevalence and incidence estimates over time. Key findings include:

- 34.2 million Americans—just over 1 in 10—have diabetes.
- 88 million American adults—approximately 1 in 3—have prediabetes.
- New diabetes cases were higher among non-Hispanic blacks and people of Hispanic origin than non-Hispanic Asians and non-Hispanic whites.

Efficacy

The safety and efficacy of LYUMJEV™ was evaluated in 2 randomized, active controlled trials of 26 weeks in adult patients with type 1 diabetes (N=780) or type 2 diabetes (N=336).

- Type 1 Diabetes – Efficacy of LYUMJEV™ was evaluated in 1222 patients with type 1 diabetes. Patients were randomized to either blinded mealtime LYUMJEV™ (N=451), blinded mealtime HUMALOG (N=442),

or open-label post meal LYUMJEV™ (N=329), all in combination with either insulin glargine or insulin degludec. 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/m2. Insulin doses were similar in both treatment groups at baseline and at 26 weeks.

At week 26, treatment with mealtime LYUMJEV™ provided a mean reduction in HbA1c that met the pre-specified noninferiority margin (0.4%). In addition, post meal LYUMJEV™ met the prespecified non-inferiority margin (0.4%) compared to mealtime HUMALOG.

- Type 2 Diabetes – Efficacy of LYUMJEV™ was evaluated in 673 patients with type 2 diabetes who at study entry were on up to three oral antidiabetic medications (OAMs), basal insulin and at least one prandial insulin injection or premixed insulin with at least two injections daily. 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. 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/m2. Insulin doses were similar in both treatment groups at baseline and at 26 weeks.

  At week 26, treatment with mealtime LYUMJEV™ provided a mean reduction of HbA1c from baseline that met the prespecified non-inferiority margin (0.4%) compared to mealtime HUMALOG.

Safety

ADVERSE EVENTS

Adverse reactions observed with LYUMJEV™ include hypoglycemia, injection site reactions, allergic reactions, rash, pruritus, lipodystrophy, and weight gain.

WARNINGS & PRECAUTIONS

- 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.
- 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.
- 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.
- Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
- Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LYUMJEV™, monitor, and treat if indicated.
- 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.
- Never share a LYUMJEV™ prefilled pen or cartridge between patients, even if the needle is changed.

CONTRAINDICATIONS

- During episodes of hypoglycemia.
- Hypersensitivity to insulin lispro-aabc or one of the excipients in LYUMJEV™.

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

Insulin lispro can be administered as follow.

- Intermittent subcutaneous dosage: 0.4 to 1 unit/kg/day 15 minutes before or immediately after a meal. Insulin lispro is used along with basal insulin.
- Continuous subcutaneous infusion dosage: With the help of continuous subcutaneous infusion pump, use insulin lispro 100 units/mL only.
- Intravenous dosage: Infusions prepared with insulin lispro 100 units/mL only. Do not administer Humalog 200 units/mL intravenously.

PEDIATRICS

The safety and effectiveness of LYUMJEV™ in pediatric patients have not been established.

GERIATRICS

No overall differences in safety or effectiveness were observed in clinical trials, between elderly patients and younger adult patients.

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.

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.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 units/mL (U-100) available as:

- 10 mL multiple-dose vial
- 3 mL single-patient-use KwikPen®
- 3 mL single-patient-use Junior KwikPen®

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- 3 mL single-patient-use Tempo Pen™
- 3 mL single-patient-use cartridges

Injection: 200 units/mL (U-200) available as:

- 3 mL single-patient-use KwikPen®