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.

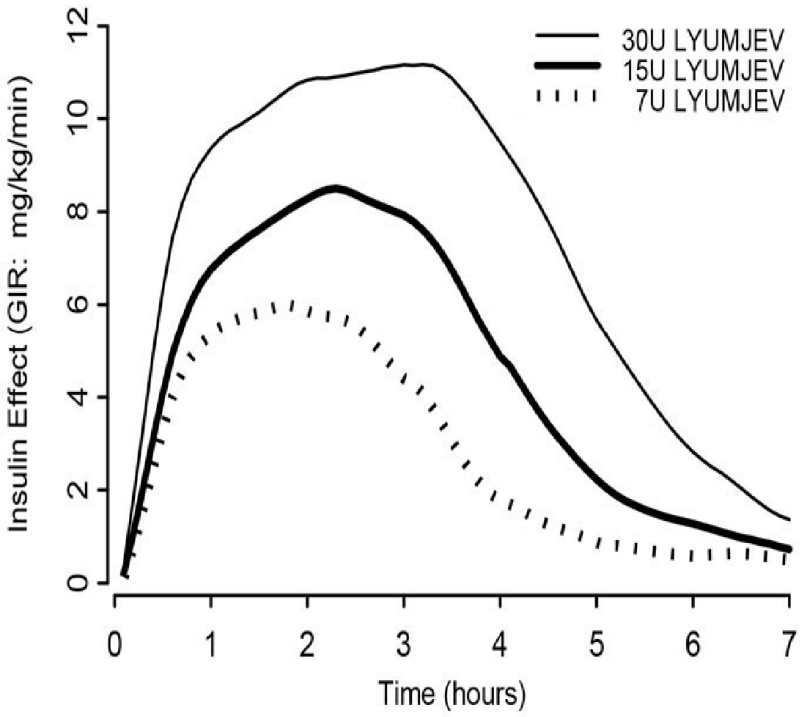

Figure 1. Mean Insulin Effect Over Time After Subcutaneous Administration of 7, 15, and 30 units of LYUMJEV in Healthy Subjects.

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}).

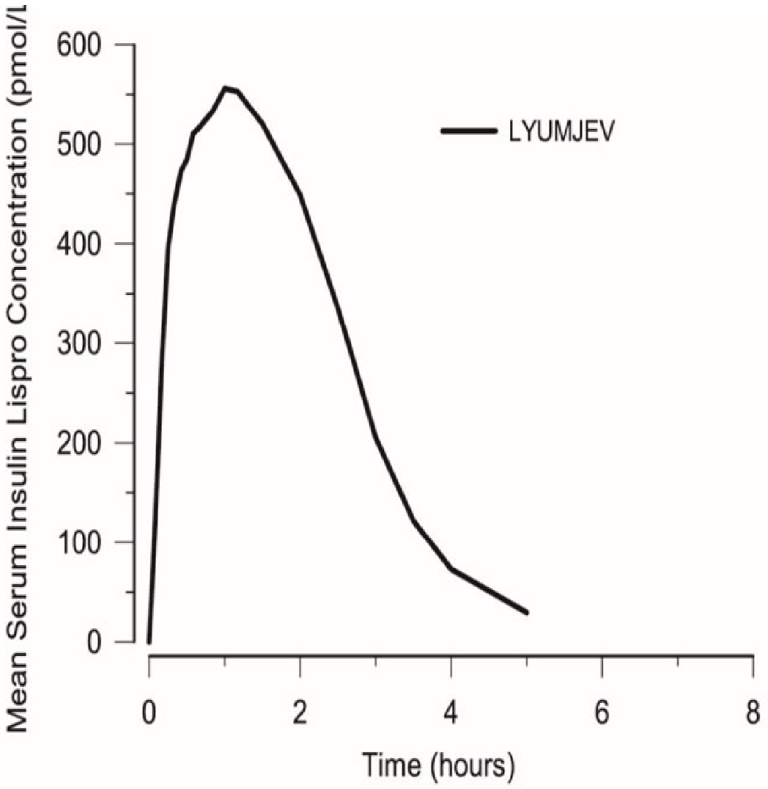

Figure 2. Mean Serum Insulin Lispro-aabc After Subcutaneous Injection of LYUMJEV (15 unit dose) in Healthy Subjects

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.