CLINICAL UPDATE

Brand Name	Humalog Tempo Pen™
Generic Name	insulin lispro injection
Drug Manufacturer	Eli Lilly and Company

Clinical Update

TYPE OF CLINICAL UPDATE

New Dosage form

FDA APPROVAL DATE

November 15, 2019

LAUNCH DATE

November 17, 2022

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Biologic License Application (BLA): 020563

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Humalog Tempo Pen™ is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

MECHANISMS 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.

DOSAGE FORM(S) AND STRENGTH(S)

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

- 10 mL multiple-dose vial
- 3 mL multiple-dose vial
- 3 mL single-patient-use Humalog KwikPen®
- 3 mL single-patient-use Humalog Tempo Pen™
- 3 mL single-patient-use Humalog® Junior KwikPen®
- 3 mL single-patient-use cartridges

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

- 3 mL single-patient-use Humalog KwikPen®

CLINICAL UPDATE

DOSE & ADMINISTRATION

Subcutaneous injection

- Administer Humalog® U-100 or U-200 by subcutaneous injection into the abdominal wall, thigh, upper arm, or buttocks within 15 minutes before a meal or immediately after a meal.
- Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.

Continuous subcutaneous infusion (Insulin Pump)

- Administer Humalog® U-100 by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer.
- Administer Humalog® U-100 by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer.
- Rotate infusion sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
- Do not administer Humalog® U-200 by continuous subcutaneous infusion.

Intravenous Infusion

- Administer Humalog® U-100 by intravenous infusion only after dilution and under medical supervision. Do not administer Humalog® U-200 by intravenous infusion.
- The dosage of Humalog® must be individualized based on the route of administration and the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Do not perform dose conversion when using the Humalog® U-100 or U-200 prefilled pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.
- Do not mix Humalog® U-200 with any other insulin.

EFFICACY

The safety and efficacy of Humalog® 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).

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 Humalog® (n=81) compared with Humulin® R [insulin human injection (100 units per mL)] (n=86). Humalog® 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 Humalog® 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 1: Type 1 Diabetes Mellitus – Adults and Adolescents

Treatment Duration Treatment in Combination with:	12 months Humulin® U	
	Humalog®	Humulin® R
N	81	86
Baseline HbA_{1c} (%)[a]	8.2 ± 1.4	8.3 ± 1.7
Change from baseline HbA_{1c} (%)[a]	-0.1 ± 0.9	0.1 ± 1.1

Treatment Difference in HbA_{1c} Mean (95% confidence interval)	0.4 (0.0, 0.8)	
Baseline short-acting insulin dose (units/kg/day)	0.3 ± 0.1	0.3 ± 0.1
End-of-Study short-acting insulin dose (units/kg/day)	0.3 ± 0.1	0.3 ± 0.1
Change from baseline short-acting insulin dose (units/kg/day)	0.0 ± 0.1	0.0 ± 0.1
Baseline Body weight (kg)	72 ± 12.7	71 ± 11.3
Weight change from baseline (kg)	1.4 ± 3.6	1.0 ± 2.6
Patients with severe hypoglycemia (n, %)[b]	14 (17%)	18 (21%)

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

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 Humalog® for 3 months followed by Humulin® R for 3 months or the reverse sequence. Humalog® 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 4week 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 HbA_{1c} 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.

Table 2: Type 2 Diabetes Mellitus—Adults

		End point	
	Baseline	**Humalog® + Basal**	**Humulin® R + Basal**
HbA_{1c} (%)[a]	8.9 ± 1.7	8.2 ± 1.3	8.2 ± 1.4
Change from baseline HbA_{1c} (%)[a]	—	-0.7 ± 1.4	-0.7 ± 1.3
Short-acting insulin dose (units/kg/day)[a]	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2
Change from baseline short-acting insulin dose (units/kg/day)[a]	—	0.0 ± 0.1	0.0 ± 0.1
Body weight (kg)[a]	80 ± 15	81 ± 15	81 ± 15
Weight change from baseline	—	0.8 ± 2.7	0.9 ± 2.6
Patients with severe hypoglycemia (n, %)[b]	—	15 (2%)	16 (2%)

[a] Values are Mean ± SD

[b] Severe hypoglycemia refers to hypoglycemia for which patients were not able to self-treat.

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: Humalog® or Humulin® R, both administered with Humulin® N (NPH human insulin) as the basal insulin. Humalog® achieved glycemic control comparable to Humulin® R, as measured by HbA_{1c} ,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, Humalog® administered immediately before meals, Humalog® administered immediately after meals and Humulin® R administered 30

minutes before meals resulted in similar glycemic control, as measured by HbA_{1c}, and incidence of hypoglycemia, regardless of treatment group.

Table 3: Pediatric Subcutaneous Administration of Humalog® in Type 1 Diabetes			
		End point	
	Baseline	Humalog® + NPH	Humulin® R + NPH
HbA_{1c} (%)[a]	8.6 ± 1.5	8.7 ± 1.5	8.7 ± 1.6
Change from baseline HbA_{1c} (%)[a]	—	0.1 ± 1.1	0.1 ± 1.3
Short-acting insulin dose (units/kg/day)[a]	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
Change from baseline short-acting insulin dose (units/kg/day)[a]	—	0.01 ± 0.1	-0.01 ± 0.1
Body weight (kg)[a]	59.1 ± 13.1	61.1 ± 12.7	61.4 ± 12.9
Weight change from baseline (kg)[a]	—	2.0 ± 3.1	2.3 ± 3.0
Patients with severe hypoglycemia (n, %)[b]	—	5 (1.1%)	5 (1.1%)
Diabetic ketoacidosis (n, %)	—	11 (2.4%)	9 (1.9%)

[a] Values are Mean ± SD

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

Type 1 Diabetes – Adults Continuous Subcutaneous Insulin Infusion

To evaluate the administration of Humalog® 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 Humalog® or regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.8% to 7.2% in the Humalog® -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 Humalog® or buffered regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.7% to 7.4% in the Humalog® -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.

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 Humalog® U-100 (n=100). These two treatments resulted in comparable changes from baseline in HbA_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment.Infusion site reactions were similar between groups.

Table 8: Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)		
	Humalog®	Aspart
N	100	198
Baseline HbA_{1c} (%)[a]	8.2 ± 0.8	8.0 ± 0.9
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.7	-0.1 ± 0.8
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	0.1 (-0.3, 0.1)	
Baseline insulin dose (units/kg/24 hours)[a]	0.9 ± 0.3	0.9 ± 0.3
End-of-Study insulin dose (units/kg/24 hours)[a]	0.9 ± 0.2	0.9 ± 0.2
Patients with severe hypoglycemia (n, %)[b]	8 (8%)	19 (10%)
Diabetic ketoacidosis (n, %)	0 (0)	1 (0.5%)

Baseline body weight (kg)[a]	55.5 ± 19.0	54.1 ± 19.7
Weight Change from baseline (kg)[a]	1.6 ± 2.1	1.8 ± 2.1

[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.