1. NAME OF THE MEDICINAL PRODUCT

Lyumjev 100 units/mL solution for injection in vial
Lyumjev 100 units/mL solution for injection in cartridge
Lyumjev 100 units/mL KwikPen solution for injection in pre-filled pen
Lyumjev 100 units/mL Junior KwikPen solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 100 units of insulin lispro (as zinc crystals)* (equivalent to 3.5 mg).

Lyumjev 100 units/mL solution for injection in vial

Each vial contains 1000 units insulin lispro (as zinc crystals) in 10 mL solution.

Lyumjev 100 units/mL solution for injection in cartridge

Each cartridge contains 300 units of insulin lispro (as zinc crystals) in 3 mL solution.

Lyumjev 100 units/mL KwikPen solution for injection in pre-filled pen

Each pre-filled pen contains 300 units of insulin lispro (as zinc crystals) in 3 mL solution.
Each pre-filled pen delivers 1 - 60 units in steps of 1 unit in a single injection.

Lyumjev 100 units/mL Junior KwikPen solution for injection in pre-filled pen

Each pre-filled pen contains 300 units of insulin lispro in 3 mL solution.
Each Junior KwikPen delivers 0.5 - 30 units in steps of 0.5 units in a single injection.

*produced in *E.coli* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

4.2 Posology and method of administration

Posology

Lyumjev is a mealtime insulin for subcutaneous injection and should be administered zero to two minutes before the start of the meal (see section 5.1).

Due to its rapid onset of activity, Lyumjev can be administered up to 20 minutes after starting a meal. To achieve the most optimal glycemic control, the bolus injection after the start of the meal should be given only in exceptional cases.

Lyumjev 100 units/mL is suitable for continuous subcutaneous insulin infusion (CSII) and is used for both the bolus and basal insulin requirement.

The initial dose should take into account the type of diabetes, weight of the patient and their blood glucose levels.

The early onset of action must be considered when prescribing Lyumjev (see section 5.1). Continued adjustment of the dose of Lyumjev should be based on the patient's metabolic needs, blood glucose monitoring results, and glycaemic control goal. Dose adjustments may be needed, when switching from another insulin, with changes in physical activity, changes in concomitant medicinal products, 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 to minimize the risk of hypoglycaemia or hyperglycaemia (see sections 4.4 and 4.5).

Switching from another mealtime insulin medicinal product

If converting from another mealtime insulin to Lyumjev, the change can be done on a unit-to-unit basis. The potency of insulin analogues, including Lyumjev, is expressed in units. One (1) unit of Lyumjev corresponds to 1 international unit (IU) of human insulin or 1 unit of other fast-acting insulin analogues.

Missed doses

Patients who forget a mealtime dose should monitor their blood glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.

Special populations

Elderly
The safety and efficacy of Lyumjev has been established in elderly patients aged 65 to 75 years. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see sections 4.8, 5.1 and 5.2). The therapeutic experience in patients ≥ 75 years of age is limited.

Renal impairment
Insulin requirements may be reduced in the presence of renal impairment. In patients with renal impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis.

Hepatic impairment
Insulin requirements may be reduced in patients with hepatic impairment due to reduced capacity for gluconeogenesis and reduced insulin breakdown. In patients with hepatic impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis.

Paediatric population

Lyumjev can be used safely and effectively in adolescents and children (see section 5.1). Lyumjev is recommended to be administered zero to two minutes before the start of the meal.

Method of administration

Patients should be trained on proper use and injection technique before initiating Lyumjev. Patients should be told to:

- Always check insulin labels before administration.

- Inspect Lyumjev visually before use and discard for particulate matter or discolouration.
- Injection or infusion sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).
- Carry a spare or alternative administration method in case their delivery system breaks.

Subcutaneous injection

Lyumjev should be injected subcutaneously into the abdomen, upper arm, thigh or buttocks (see section 5.2).

Lyumjev should generally be used in combination with an intermediate or long-acting insulin. A different injection site should be used if injecting at the same time as another insulin.

When injecting a blood vessel should not be entered.

Devices should be discarded if any part looks broken or damaged.

The needle should be discarded after each injection.

Lyumjev vials
If subcutaneous administration by syringe is necessary, a vial should be used.

The appropriate syringe must have 100 unit markings.

Patients using vials must never share needles or syringes.

Lyumjev cartridges
Lyumjev in cartridges is only suitable for subcutaneous injections from a Lilly reusable pen.

Lyumjev cartridges should not be used with any other reusable pen as the dosing accuracy has not been established with other pens.

The instructions with each individual pen must be followed for loading the cartridge, attaching the needle and administering the insulin injection.

To prevent the possible transmission of disease, each cartridge must be used by one patient only, even if the needle on the delivery device is changed.

Lyumjev KwikPens
The KwikPen and Junior KwikPen are only suitable for subcutaneous injections.

The KwikPen delivers 1 - 60 units in steps of 1 unit in a single injection.
The Lyumjev 100 units/mL Junior KwikPen delivers 0.5 - 30 units in steps of 0.5 units in a single injection.

The number of insulin units is shown in the dose window of the pen regardless of concentration and no dose conversion should be done when transferring a patient to a new concentration or to a pen with a different dose step.

Lyumjev 100 units/mL Junior KwikPen is suitable for patients who may benefit from finer insulin dose adjustments.

For detailed user instructions, please refer to the instructions for use provided with the package leaflet.

To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

CSII (insulin pump)
Use a pump suitable for insulin infusion. Fill the pump reservoir from a Lyumjev 100 units/mL vial.

Patients using a pump should follow the instructions provided with the pump and infusion set.
Use the correct reservoir and catheter for the pump.

When filling the pump reservoir avoid damaging it by using the correct needle length on the filling system. The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

A pump malfunction or obstruction of the infusion set can result in a rapid rise in glucose levels (see section 4.4).

Intravenous use

Lyumjev 100 units/mL is available in vials if administration of intravenous injection is necessary. This medicinal product must not be mixed with any other insulin or any other medicinal product except those mentioned in section 6.6.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Intravenous administration of Lyumjev 100 units/mL must be performed under medical supervision.

4.3 Contraindications

Hypoglycaemia.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypoglycaemia

Hypoglycaemia is the most common adverse reaction of insulin therapy (see section 4.8). The timing of hypoglycaemia usually reflects the time-action profile of the administered insulin formulations. Hypoglycaemia may occur earlier after an injection/infusion when compared to other mealtime insulins due to the earlier onset of action of Lyumjev (see section 5.1).

Hypoglycaemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Severe hypoglycaemia can cause seizures, may lead to unconsciousness, may be life-threatening, or cause death. Symptomatic awareness of hypoglycaemia may be less pronounced in patients with longstanding diabetes.

Hyperglycaemia

The use of inadequate doses or discontinuation of treatment, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Patients should be educated to recognize the signs and symptoms of ketoacidosis and to get immediate help when ketoacidosis is suspected.

Injection technique

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A

sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Insulin requirements and dose adjustments

Changes in insulin, insulin concentration, manufacturer, type, or method of administration may affect glycaemic control and predispose to hypoglycaemia or hyperglycaemia. These changes should be made cautiously under close medical supervision and the frequency of glucose monitoring should be increased. For patients with type 2 diabetes, dose adjustments in concomitant anti-diabetic treatment may be needed (see sections 4.2 and 4.5).

In patients with renal or hepatic impairment, glucose monitoring should be intensified and dose adjusted on an individual basis (see section 4.2).

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of dose may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

Hyperglycaemia and ketoacidosis due to insulin pump device malfunction

Malfunction of the insulin pump or insulin infusion set can rapidly lead to hyperglycaemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis is necessary. Interim subcutaneous injections with Lyumjev may be required.

Thiazolidinediones (TZDs) used in combination with insulin

TZDs 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 and a TZD should be observed for signs and symptoms of heart failure. If heart failure develops, consider discontinuation of the TZD.

Hypersensitivity and allergic reactions

Severe, life-threatening, generalised allergy, including anaphylaxis, can occur with insulin medicinal products, including Lyumjev (see section 4.8). If hypersensitivity reactions occur, discontinue Lyumjev.

Medication errors

Lyumjev should not be used by patients with visual impairment without help of a trained person.

To avoid medication errors between Lyumjev and other insulins, patients need to always check the insulin label before each injection.

Patients should always use a new needle for each injection to prevent infections and a blocked needle. In the event of a blocked needle it should be replaced with a new needle.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The following substances may reduce insulin requirement: Antidiabetic medicinal products (oral or injectable), salicylates, sulphonamides, certain antidepressants (monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blocking agents, or somatostatin analogues.

The following substances may increase insulin requirement: oral contraceptives, corticosteroids, thyroid hormones, danazol, sympathomimetic agents, diuretics, or growth hormone.

Alcohol may increase or decrease the blood glucose lowering effect of Lyumjev. Consumption of large amounts of ethanol concomitantly with insulin use may lead to severe hypoglycaemia.

Beta-blockers may blunt the signs and symptoms of hypoglycaemia.

TZDs can cause dose-related fluid retention, particularly when used in combination with insulin, and exacerbate heart failure (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data available on use in pregnant patients.

There are no available data with Lyumjev in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. 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.

It is essential to maintain good control of an insulin-treated (insulin-dependent or gestational) diabetes patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control is essential in pregnant patients with diabetes.

Breast-feeding

There are no available data with Lyumjev in Breast-feeding women.

Fertility

Insulin lispro did not induce fertility impairment in animal studies.

4.7 Effects on ability to drive and use machines

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving, this is particularly important in those patients who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions during treatment are hypoglycaemia (very common) and infusion site reactions in patients using CSII system (very common) (see sections 4.2, 4.4 and 4.9).

The following related adverse reactions from clinical trials are listed below as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000; very rare: < 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

MedDRA system organ class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders	Hypoglycaemia			
General disorders and administration site conditions	Infusion site reactions[a]	Allergic reactions [b]	Oedema	
		Injection site reactions [c]		
Skin and subcutaneous tissue disorders			Lipodystrophy	Cutaneous amyloidosis
			Rash	
			Pruritus	

[a]Reported in PRONTO-Pump-2
[b]See section 4.8 Description of selected adverse reactions
[c]Reported in PRONTO-T1D, PRONTO-T2D and PRONTO-Peds

Description of selected adverse reactions

Hypoglycaemia

Hypoglycaemia is the most commonly observed adverse reaction in patients using insulin. The incidence of severe hypoglycaemia in the 26 week phase 3 adult clinical studies was 5.5% in patients with type 1 diabetes mellitus and 0.9% in patients with type 2 diabetes (see tables 2 and 3). In study PRONTO-Peds, severe hypoglycaemia was reported in 0.7% of paediatric patients treated with Lyumjev.

The symptoms of hypoglycaemia usually occur suddenly. They may include listlessness, confusion, palpitations, sweating, vomiting, and headache.

There were no clinically significant differences in the frequency of hypoglycaemia with administration of Lyumjev or the comparator (another medicinal product containing insulin lispro) across all studies. In studies where Lyumjev and the comparator were administered at different times relative to meals, there were no clinically relevant differences in the frequency of hypoglycaemia.

Hypoglycaemia may occur earlier after an injection/infusion of Lyumjev compared to other mealtime insulins due to the earlier onset of action.

Allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including Lyumjev.

Injection/Infusion site reactions

Lyumjev contains treprostinil sodium and sodium citrate dihydrate as inactive ingredients which have been associated with infusion and injection site reactions with other non-insulin products.

As with other insulin therapy, patients may experience rash, redness, inflammation, pain, bruising or itching at the site of Lyumjev injection or infusion.

In studies PRONTO-T1D and PRONTO-T2D (multiple-dose injection [MDI] administration), injection site reactions occurred in 2.7% of adult patients treated with Lyumjev. These reactions were usually mild and normally disappeared during continued treatment. Of the 1,116 patients who received Lyumjev, 1 discontinued treatment due to injection site reactions (< 0.1%).

In study PRONTO-Peds, injection site reactions occurred in 6.2% of paediatric patients treated with Lyumjev. These events were mild or moderate. Of the 418 patients treated with Lyumjev, 2 discontinued treatment due to injection site reactions (< 0.5%).

In study PRONTO-Pump-2, infusion site reactions were reported in 38% of patients treated with Lyumjev, compared to 12.5% of patients treated with Humalog. Of the 215 patients treated with Lyumjev, 7 discontinued treatment due to infusion site reactions (3.3%). The majority of these events were mild.

Immunogenicity

Administration of insulin can cause formation of insulin antibodies. The presence of anti-drug antibodies did not have a clinically meaningful effect on the pharmacokinetics, efficacy, or safety of Lyumjev.

Skin and subcutaneous tissue disorders

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Oedema

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

Paediatric population

Safety and efficacy have been investigated in a therapeutic confirmatory trial in children with type 1 diabetes aged 3 to < 18 years. In the trial, 418 patients were treated with Lyumjev. The frequency, type and severity of adverse reactions observed in the paediatric population is consistent with the safety profile in adult patients.

Other special populations

Based on results from clinical trials with insulin lispro in general, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population. The safety information in very elderly patients (≥ 75 years) or patients with moderate to severe renal impairment or hepatic impairment is limited (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Overdose causes hypoglycaemia with accompanying symptoms that include listlessness, confusion, palpitations, sweating, vomiting, and headache.

Hypoglycaemia may occur as a result of an excess of insulin lispro relative to food intake, energy expenditure, or both. Mild episodes of hypoglycaemia usually can be treated with oral glucose. 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 hypoglycaemia may recur after apparent clinical recovery. Adjustments in medicinal product dose, meal patterns, or exercise may be needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes, insulins and analogues for injection, fast-acting, ATC code: A10AB04

Mechanism of action

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

Lyumjev is a formulation of insulin lispro that contains citrate and treprostinil. Citrate increases local vascular permeability and treprostinil induces local vasodilation to achieve accelerated absorption of insulin lispro.

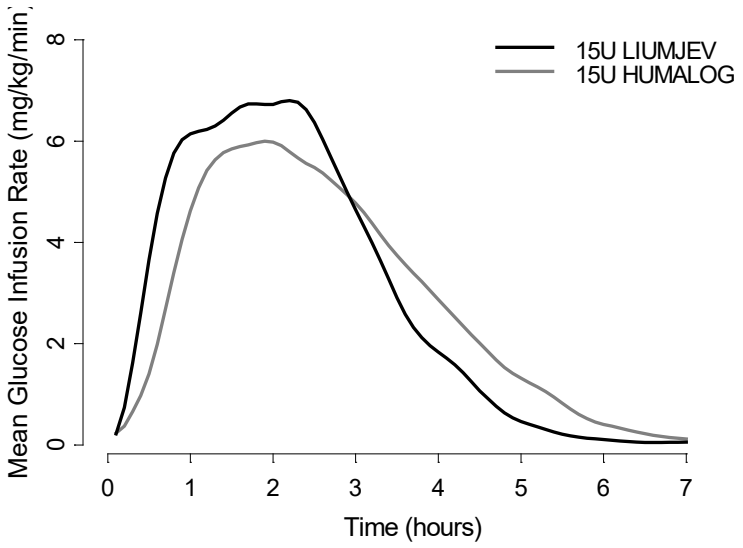
Pharmacodynamic effects

Early and late insulin action

A glucose clamp study was conducted in 40 type 1 diabetes patients given Lyumjev and Humalog subcutaneously as a single 15 unit dose. Results are provided in Figure 1. Lyumjev has been shown to be equipotent to Humalog on a unit for unit basis but its effect is more rapid with a shorter duration of action.

- Onset of action of Lyumjev was 20 minutes post dose, 11 minutes faster than Humalog.
- During the first 30 minutes post dose, Lyumjev had a 3-fold greater glucose lowering effect compared to Humalog.
- Maximum glucose-lowering effect of Lyumjev occurred between 1 and 3 hours after injection.
- The late insulin action, from 4 hours until the end of the glucose clamp, was 54% lower with Lyumjev than observed with Humalog.
- The duration of action of Lyumjev was 5 hours, 44 minutes shorter than Humalog.
- The total glucose infused during the clamp was comparable between Lyumjev and Humalog.

Figure 1. Mean glucose infusion rate (GIR) in patients with type 1 diabetes after subcutaneous injection of Lyumjev or Humalog (15 unit dose)



Similarly, a faster early insulin action and a reduced late insulin action was observed with Lyumjev in type 2 diabetes patients.

Total and maximum glucose lowering effect of Lyumjev increased with dose within the therapeutic dose range. The early onset and total insulin action were similar when Lyumjev was administered in the abdomen, upper arm, or thigh.

Postprandial Glucose (PPG) Lowering

Lyumjev reduced the PPG during a standardized test meal over the complete 5 hour test meal period (change from premeal area under the curve (AUC) (0 – 5 h)) compared to Humalog.

- In patients with type 1 diabetes, Lyumjev reduced the PPG during the 5 hour test meal period by 32% when given at the start of the meal and 18% when given 20 minutes after the start of the meal compared to Humalog.
- In patients with type 2 diabetes, Lyumjev reduced the PPG during the 5 hour test meal period by 26% when given at the start of the meal and 24% when given 20 minutes after the start of the meal compared to Humalog.

Clinical efficacy and safety

The efficacy of Lyumjev was evaluated in 4 randomised, active controlled trials in adults and 1 randomised, active controlled trial in paediatric patients with type 1 diabetes.

Type 1 Diabetes – Adults

PRONTO-T1D was a 26 week, treat-to-target, trial that evaluated the efficacy of Lyumjev in 1222 patients on multiple daily injection therapy. Patients were randomised to either blinded mealtime Lyumjev, blinded mealtime Humalog, or open-label postmeal Lyumjev, 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.

Efficacy results are provided in Table 2 and Figure 2.

37.4% of patients treated with mealtime Lyumjev, 33.6% of patients treated with mealtime Humalog and 25.6% of patients treated with postmeal Lyumjev reached a target HbA1c of < 7%.

Basal, bolus and total insulin doses were similar among study arms at 26 weeks.

Following the 26 week period, the two blinded treatment arms continued to 52 weeks. HbA1c was not statistically significantly different between treatments at the 52 week endpoint.

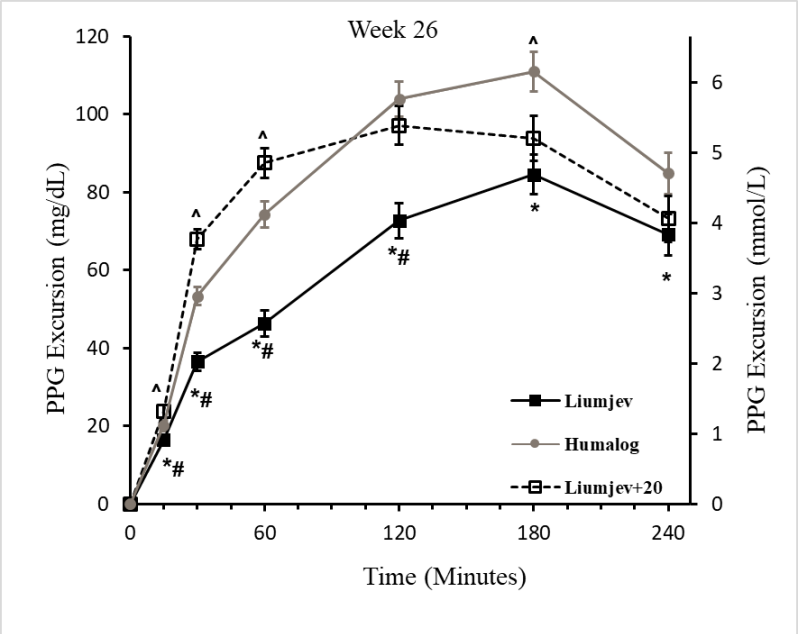
Table 2 Results from 26 week basal-bolus clinical trial in patients with type 1 diabetes

	Mealtime Lyumjev + basal insulin	**Mealtime Humalog + basal insulin**	**Postmeal Lyumjev + basal insulin**
Number of randomized subjects (N)	451	442	329
HbA_{1c} (%)			
Baseline → week 26	7.34 → 7.21	7.33→7.29	7.36→7.42
Change from baseline	-0.13	-0.05	0.08
Treatment difference	-0.08 [-0.16, -0.00][C]		0.13 [0.04, 0.22][D]
HbA_{1c} (mmol/mol)			
Baseline → week 26	56.7→55.3	56.7→56.1	56.9→57.6
Change from baseline	-1.4	-0.6	0.8
Treatment difference	-0.8 [-1.7, 0.00][C]		1.4 [0.5, 2.4][D]
1 hour postprandial glucose excursion (mg/dL) [A]			
Baseline → week 26	77.3 →46.4	71.5 →74.3	76.3→87.5
Change from baseline	-28.6	-0.7	12.5
Treatment difference	-27.9 [-35.3, -20.6][C,E]		13.2 [5.0, 21.4][D]
1 hour postprandial glucose excursion (mmol/L) [A]			
Baseline → week 26	4.29→2.57	3.97 →4.13	4.24→4.86
Change from baseline	-1.59	-0.04	0.70
Treatment difference	-1.55[-1.96, -1.14][C,E]		0.73 [0.28,1.19][D]
2 hour postprandial glucose excursion (mg/dL) [A]			
Baseline → week 26	112.7→72.7	101.6 →103.9	108.0 →97.2
Change from baseline	-34.7	-3.5	-10.2
Treatment difference	-31.2 [-41.1, -21.2][C,E]		-6.7 [-17.6, 4.3] [D].
2 hour postprandial glucose excursion (mmol/L) [A]			
Baseline → week 26	6.26→4.04	5.64→5.77	5.99→5.40
Change from baseline	-1.93	-0.20	-0.56
Treatment difference	-1.73 [-2.28, -1.18][C,E]		-0.37 [-0.98, -0.24][D]
Body weight (Kg)			
Baseline → week 26	77.3→77.9	77.3→78.2	77.6→78.1
Change from baseline	0.6	0.8	0.7
Treatment difference	-0.2 [-0.6, 0.1][A]		-0.1[-0.5, 0.3][D]
Severe hypoglycaemia [B] **(% of patients)**	5.5%	5.7%	4.6%

Week 26 and change from baseline values are based on the least-squares means (adjusted means).
The 95% confidence interval is stated in '*[ ]*'.
[A] Meal test.
[B] Severe hypoglycaemia is defined as episode requiring assistance of another person due to patient's neurological impairment.

[C] The difference is for mealtime Lyumjev – mealtime Humalog.
[D] The difference is for postmeal Lyumjev – mealtime Humalog.
[E] Statistically significant in favour of mealtime Lyumjev.

Figure 2. Time course of blood glucose excursion during mixed-meal tolerance test at week 26 in patients with type 1 diabetes



PPG = Postprandial glucose
Lyumjev and Humalog administered at mealtime
Lyumjev +20 = Lyumjev was injected 20 minutes after the start of the meal
*p < 0.05 for pairwise comparison on Lyumjev versus Humalog
^p < 0.05 for pairwise comparison on Lyumjev +20 versus Humalog
#p < 0.05 for pairwise comparison on Lyumjev +20 versus Lyumjev

Continuous glucose monitoring (CGM) in Type 1 Diabetes – Adults

A subset of patients (N = 269) participated in an evaluation of the 24 hour ambulatory glucose profiles captured with blinded CGM. At the 26 week assessment, patients treated with mealtime Lyumjev demonstrated statistically significant improvement in PPG control during CGM assessment of glucose excursions or incremental AUC 0 - 2 hours, 0 - 3 hours, and 0 - 4 hours after meals compared to patients treated with Humalog. Patients treated with mealtime Lyumjev reported statistically significantly longer time in range (6 am to midnight) with 603 minutes in range, (3.9 to 10 mmol/L, 71 – 180 mg/dL), and 396 minutes in range (3.9 to 7.8 mmol/L, 71 to 140 mg/dL), 44 and 41 minutes longer than Humalog patients respectively.

Type 2 Diabetes – Adults

PRONTO-T2D was a 26 week, treat-to-target trial that evaluated the efficacy of Lyumjev in 673 patients were randomised to either blinded mealtime Lyumjev or to blinded mealtime Humalog, both in combination with a basal insulin (insulin glargine or insulin degludec) in a basal-bolus regimen. Mealtime Lyumjev or mealtime Humalog was injected 0 - 2 minutes before the meal. Efficacy results are provided in Table 3 and Figure 3.

58.2% of patients treated with mealtime Lyumjev and 52.5% of patients treated with mealtime Humalog reached a target HbA1c of < 7%.

Basal, bolus and total insulin doses were similar among study arms at the end of the trial.

Table 3 Results from 26 week basal-bolus clinical trial in patients with type 2 diabetes

	Mealtime Lyumjev + basal insulin	**Mealtime Humalog + basal insulin**
Number of randomised subjects (N)	336	337
HbA_{1c} (%)		
Baseline → week 26	7.28→6.92	7.31→6.86
Change from baseline	-0.38	-0.43
Treatment difference	0.06 [-0.05, 0.16]	
HbA_{1c} (mmol/mol)		
Baseline → week 26	56.0→52.1	56.4→51.5
Change from baseline	-4.1	-4.7
Treatment difference	0.6 [-0.6, 1.8]	
1 hour postprandial glucose excursion (mg/dL)[A]		
Baseline → week 26	76.6→63.1	77.1→74.9
Change from baseline	-13.8	-2.0
Treatment difference	-11.8 [-18.1, -5.5][C]	
1 hour postprandial glucose excursion (mmol/L)[A]		
Baseline → week 26	4.25→3.50	4.28→4.16
Change from baseline	-0.77	-0.11
Treatment difference	-0.66 [-1.01, -0.30][C]	
2 hour postprandial glucose excursion (mg/dL)[A]		
Baseline → week 26	99.3→80.4	99.6→97.8
Change from baseline	-19.0	-1.6
Treatment difference	-17.4 [-25.3, -9.5][C]	
2 hour postprandial glucose excursion (mmol/L)[A]		
Baseline → week 26	5.51→4.47	5.53→5.43
Change from baseline	-1.06	-0.09
Treatment difference	-0.96 [-1.41, -0.52][C]	
Body weight (Kg)		
Baseline → week 26	89.8→91.3	90.0 →91.6
Change from baseline	1.4	1.7
Treatment difference	-0.2 [-0.7, 0.3]	
Severe hypoglycaemia (% of patients)[B]	0.9%	1.8%

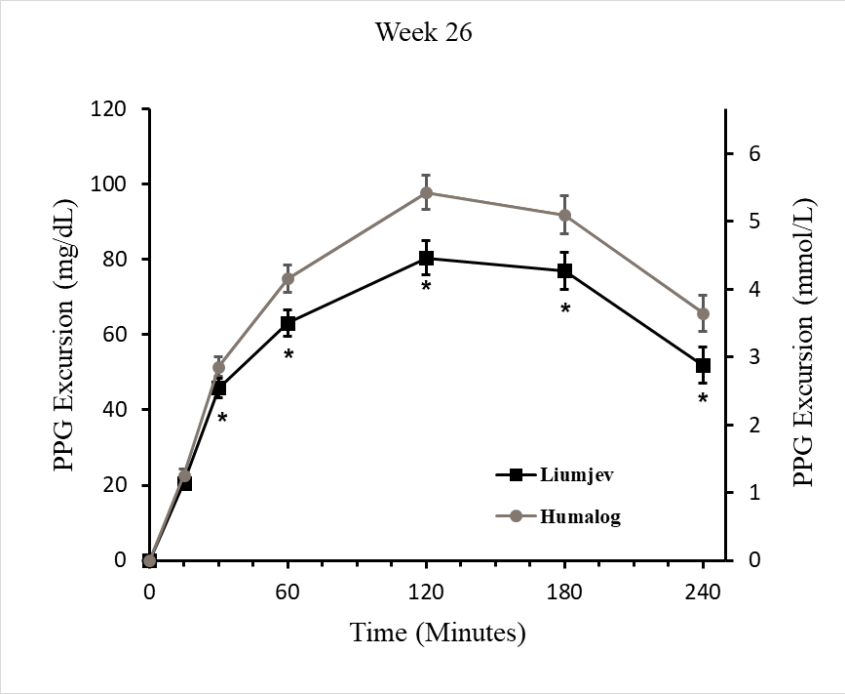
Week 26 and change from baseline values are based on the least-squares means (adjusted means).
The 95% confidence interval is stated in *'[ ]'*. The difference is for mealtime Lyumjev – mealtime Humalog.

[A] Meal test.

[B] Severe hypoglycaemia is defined as episode requiring assistance of another person due to patient's neurological impairment.

[C] Statistically significant in favour of mealtime Lyumjev.

Figure 3. Time course of blood glucose excursion during mixed-meal tolerance test at week 26 in patients with type 2 diabetes



PPG = Postprandial glucose
Lyumjev and Humalog administered at mealtime
Data are LSM (SE), *p < 0.05

Type 1 Diabetes – Adults. CSII

PRONTO-Pump was a 12 week cross over design (2 periods of 6 weeks), double-blind, trial that evaluated the compatibility and safety of Lyumjev and Humalog with an external CSII System in patients who wore a continuous glucose monitor throughout the study. There was no statistically significant treatment difference in the rate or incidence of infusion set failures (n = 49).

In period 1 of the cross over study, Lyumjev had a numerically greater reduction in mean HbA1c than Humalog. Lyumjev reduction was -0.39% [- 4.23 mmol/mol] from a baseline of 6.97% [52.68 mmol/mol] and Humalog reduction was - 0.25% [- 2.78 mmol/mol] from a baseline of 7.17% [54.89 mmol/mol]. Lyumjev had a statistically significantly longer mean duration of time with glucose in target ranges 71 – 140 mg/dL (3.9 to 7.8 mmol/L) within 1 and 2 hours after the start of breakfast compared to Humalog.

PRONTO-Pump-2 was a 16 week randomised (1:1), double-blind, trial that evaluated the efficacy of Lyumjev in 432 patients with type 1 diabetes currently using continuous subcutaneous insulin infusion. Patients were randomised 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.

At week 16, Lyumjev was non-inferior to Humalog in reducing HbA1c. Lyumjev reduction was -0.06% [- 0.7 mmol/mol] from a baseline of 7.56% [59.1 mmol/mol] and Humalog reduction was -0.09% [- 1.0 mmol/mol] from a baseline of 7.54% [58.9 mmol/mol]. The treatment difference was 0.02% [95% CI: - 0.06, 0.11] and 0.3 mmol/mol [95% CI: - 0.6, 1.2], respectively compared to Humalog.

Following a standardized test meal, treatment with Lyumjev demonstrated statistically significantly lower 1 hour and 2 hour postprandial glucose. The treatment difference was - 1.34 mmol/L [95% CI: - 2.00, - 0.68] and -1.54 mmol/L [95% CI: - 2.37, - 0.72], respectively compared to Humalog.

Special populations

Elderly
In the two 26 week clinical studies (PRONTO-T1D and PRONTO-T2D), 187 of 1,116 (17%) Lyumjev treated patients with type 1 diabetes or type 2 diabetes were ≥ 65 years of age and 18 of 1,116 (2%) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Paediatric population
PRONTO-Peds was a 26-week, randomised (2:2:1), treat-to-target, trial that evaluated the efficacy of Lyumjev in 716 patients with type 1 diabetes, aged 3 to < 18 years. Patients were randomised 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.

Insulin doses were similar in all treatment groups at baseline and at 26 weeks.

Table 4. Results from 26 week PRONTO-Peds trial in paediatric patients with type 1 diabetes

	Mealtime Lyumjev + basal insulin	**Mealtime Humalog + basal insulin**	**Postmeal Lyumjev + basal insulin**
Number of randomised subjects (N)	280	298	138
HbA_{1c} (%) (mean)			
Baseline → week 26	7.78 → 7.85	7.81 → 7.88	7.77 → 7.86
Change from baseline	0.06	0.09	0.07
Treatment difference	-0.02 [-0.17, 0.13][A]		-0.02 [-0.20, 0.17][B]
HbA_{1c} (mmol/mol)			
Baseline → week 26	61.6 → 62.4	61.8 → 62.6	61.4 → 62.4
Change from baseline	0.71	0.94	0.77
Treatment difference	-0.23 [-1.84, 1.39][A]		-0.17 [-2.15, 1.81][B]

Week 26 and change from baseline values are based on the least-squares means (adjusted means).
The 95% confidence interval is stated in '*[ ]*'.
[A]The difference is for mealtime Lyumjev – mealtime Humalog.
[B] The difference is for postmeal Lyumjev – mealtime Humalog.

5.2 Pharmacokinetic properties

Absorption

Absorption of insulin lispro was accelerated and the duration of exposure was shorter in healthy subjects and patients with diabetes following injection of Lyumjev compared to Humalog. In patients with type 1 diabetes:

- Insulin lispro appeared in circulation approximately 1 minute after injection of Lyumjev, which was five minutes faster than Humalog.
- Time to 50% maximum concentration was 14 minutes shorter with Lyumjev compared to Humalog.

- Following injection of Lyumjev, there was seven times more insulin lispro in circulation during the first 15 minutes compared to Humalog and three times more insulin lispro during the first 30 minutes compared to Humalog.
- After administration of Lyumjev the time to maximum insulin lispro concentration was achieved at 57 minutes.
- Following injection of Lyumjev there was 41% less insulin lispro in circulation after 3 hours following injection compared to Humalog.
- The duration of insulin lispro exposure for Lyumjev was 60 minutes shorter compared to Humalog.
- The total insulin lispro exposure (ratio and 95% CI of 1.03 (0.973, 1.09)) and maximum concentration (ratio and 95% CI of 1.06 (0.97, 1.16)) were comparable between Lyumjev and Humalog.

In type 1 patients, the day-to-day variability (coefficient of variation [CV%]) of Lyumjev was 13% for total insulin lispro exposure (AUC, 0 - 10h) and 23% for maximum insulin lispro concentration (C_{max}). The absolute bioavailability of insulin lispro after subcutaneous administration of Lyumjev in the abdomen, upper arm and thigh was approximately 65%. The accelerated absorption of insulin lispro is maintained regardless of injection site (abdomen, upper arm and thigh). No exposure data are available following injection in the buttocks.

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 lower for the thigh.

Total insulin lispro exposure and maximum insulin lispro concentration increased proportionally with increasing subcutaneous doses of Lyumjev within the dose range from 7 units to 30 units.

CSII

The absorption of insulin lispro was accelerated when Lyumjev was administered by CSII in patients with type 1 diabetes.

- Time to reach 50% maximum concentration was 14 minutes, 9 minutes shorter than for Humalog.
- Following administration of Lyumjev, 1.5 times more insulin lispro was available during the first 30 minutes compared to Humalog.

Distribution

The geometric mean (CV%) volume of distribution of insulin lispro (Vd) was 34 L (30%) after intravenous administration of Lyumjev as a bolus injection of a 15 unit dose in healthy subjects.

Elimination

The geometric mean (CV%) clearance of insulin lispro was 32 L/hour (22%) and the median half-life of insulin lispro was 44 minutes after intravenous administration of Lyumjev as a bolus injection of a 15 unit dose in healthy subjects.

Special populations

Age, gender, and race did not affect the pharmacokinetics and pharmacodynamics of Lyumjev.

Paediatric population

Children (8 - 11 years) and adolescents (12 - 17 years) with type 1 diabetes on multiple daily injection (MDI) and CSII therapy were studied in a cross-over design to assess the insulin lispro pharmacokinetics and pharmacodynamics following a 0.2 units/kg dose of Lyumjev and Humalog.

The pharmacokinetic differences between Lyumjev and Humalog were, overall, similar in children and adolescents as observed in adults. Following a subcutaneous injection, Lyumjev showed an accelerated absorption with a higher early insulin lispro exposure in children (8 – 11 years) and adolescents (12 – 17 years) whilst maintaining a similar total exposure, maximum concentration and time to maximum concentration compared to Humalog. Following a subcutaneous bolus infusion with CSII therapy, there was a trend towards an accelerated absorption in children and adolescents whilst total exposure, maximum concentration and time to maximum concentration were similar compared to Humalog.

Patients with renal and hepatic impairment

Renal and hepatic impairment is not known to impact the pharmacokinetics of insulin lispro.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development after exposure to insulin lispro.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Sodium citrate dihydrate
Metacresol
Magnesium chloride hexahydrate
Zinc oxide
Treprostinil sodium
Hydrochloric acid and sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with any other insulin or any other medicinal product except those mentioned in section 6.6.

6.3 Shelf life

Before use

The expiry date of the products is indicated on the package materials.

After first use

28 days

Lyumjev 100 units/mL solution for injection in vial

When the vial is diluted for intravenous use
Chemical, physical in-use stability has been demonstrated for 14 days at 2 – 8 °C and 20 hours at 20 - 25 °C when protected from light. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use

are the responsibility of the user and would not normally be longer than 24 hours at 2 - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions (see section 6.6).

6.4 Special precautions for storage

Before use

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

After first use

Do not store above 30 °C.
Do not freeze.

Lyumjev 100 units/mL solution for injection in vial

Store in the original package in order to protect from light.

Lyumjev 100 units/mL solution for injection in cartridge

Do not refrigerate.
Keep the cap on the pen once cartridge inserted, in order to protect from light.

Lyumjev 100 units/mL KwikPen solution for injection in pre-filled pen
Lyumjev 100 units/mL Junior KwikPen solution for injection in pre-filled pen

Do not refrigerate.
Keep the cap on the pen in order to protect from light.

6.5 Nature and contents of container

Lyumjev 100 units/mL solution for injection in vial

Type I clear glass vials, sealed with halobutyl stoppers and secured with aluminium seals.

10 mL vial: Packs of 1 vial.

Lyumjev 100 units/mL solution for injection in cartridge

Type I clear glass cartridges, sealed with disc seals secured with aluminium seals and halobutyl plungers.

3 mL cartridge: Packs of 2, 5 or 10 cartridges.

Lyumjev 100 units/mL KwikPen solution for injection in pre-filled pen

Type I clear glass cartridges, sealed with disc seals secured with aluminium seals and halobutyl plungers.

The 3 mL cartridges are sealed in a disposable pen injector KwikPen.

The medicinal product is packed in a white carton with dark blue bands and an image of the pen. The KwikPen is taupe, the dose knob is blue with raised ridges on side.

3 mL KwikPen: Packs of 1 pre-filled pen, 2 pre-filled pens or 5 pre-filled pens.

Lyumjev 100 units/mL Junior KwikPen solution for injection in pre-filled pen

Type I clear glass cartridges, sealed with disc seals secured with aluminium seals and halobutyl plungers.

The 3 mL cartridges are sealed in a disposable pen injector Junior KwikPen.

The medicinal product is packed in a white carton with stripes of peach, light blue and dark blue bands and an image of the pen. The Junior KwikPen is taupe, the dose knob is peach with raised ridges on end and side.

3 mL Junior KwikPen: Packs of 1 pre-filled pen, 2 pre-filled pens or 5 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Lyumjev must look clear and colourless. It should not be used if it is cloudy, coloured, or has particles or clumps in it.

Lyumjev must not be used if it has been frozen.

A new needle must always be attached before each use. Needles must not be re-used. Needles are not included.

Lyumjev 100 units/mL solution for injection in vial

Intravenous use

Lyumjev 100 units/mL vial can be diluted to concentrations of 0.1 to 1.0 unit/mL in 5% glucose solution for injection or sodium chloride 9 mg/mL (0.9%) solution for injection for intravenous use. Compatibility has been demonstrated in ethylene-propylene copolymer and polyolefin with polyvinyl chloride bags.

It is recommended that the system is primed before starting the infusion to the patient.

CSII

Lyumjev 100 units/mL vial can be used to fill a continuous insulin infusion pump for a maximum of 9 days. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

Eli Lilly Israel Ltd., 4 HaSheizaf st., POB 4246, Ra'anana 4366411, Israel.

8. MANUFACTURER

Eli Lilly and Company,

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Lilly Corporate Center, Indianapolis, Indiana (IN) 46285, USA.

9. LICENSE NUMBER

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 169-13-36423-00

Revised in February 2025.

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