PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

LYUMJEV™
LYUMJEV™ KwikPen®
LYUMJEV™ Junior KwikPen®
LYUMJEV™ Tempo Pen™
insulin lispro injection
Solution, 100 units/mL, subcutaneous or intravenous use

LYUMJEV™ KwikPen®
insulin lispro injection
Solution, 200 units/mL, subcutaneous use

Lilly Standard

Antidiabetic Agent
ATC Code: A10AB04
fast-acting

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Lyumjev (insulin lispro injection) is indicated for treatment of adult patients with diabetes mellitus who require insulin for the control of glucose homeostasis (see 15 CLINICAL TRIALS).

Lyumjev should generally be used in a regimen with intermediate- or long-acting insulin to maintain adequate glucose control (see 8 WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Lyumjev vials may also be used for continuous subcutaneous insulin infusion (CSII) in pump systems that are licensed in Canada for insulin infusion. Refer to the insulin infusion pump manufacturer's user manual to see if Lyumjev can be used.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience with insulin lispro suggests that use in the geriatric population is not associated with differences in safety or effectiveness (see 8 WARNINGS AND PRECAUTIONS, Special Population).

2 CONTRAINDICATIONS

Lyumjev is contraindicated in patients:

- during episodes of hypoglycemia (see 8 WARNINGS AND PRECAUTIONS).
- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products, the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with diabetes mellitus treated with insulins. (See 8 & 5 HYPOGLYCEMIA, HYPERGLYCEMIA AND OVERDOSAGE).
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (See 8 ENDOCRINE AND METABOLISM – HYPOGLYCEMIA).
- Any conversion of insulin products should be made cautiously and only under medical supervision. (See 4 DOSING AND ADMINSTRATION).
- Due to its rapid onset of action and shorter duration of action, Lyumjev should be administered 0 to 2 minutes before the start of the meal. When necessary, Lyumjev may be administered up to 20 minutes after starting a meal (see 15 CLINICAL TRIALS and 4 DOSAGE AND ADMINISTRATION).
- Lyumjev should not be used if it is not water clear and colourless.
- Lyumjev 200 units/mL should not be administered via a subcutaneous infusion pump or mixed with any other insulin (including Lyumjev 100 units/mL).
- DO NOT transfer insulin lispro solution in the Lyumjev 200 units/mL KwikPen to other devices, such as a syringe. The markings on the insulin syringe will not measure the dose correctly. Overdose can result causing severe hypoglycemia.
- DO NOT dilute or mix Lyumjev with any other insulin products or solutions, except I.V. infusion fluids under medical supervision.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The potency of insulin analogues, including Lyumjev, is expressed in units. One (1) unit of Lyumjev corresponds to 1 international unit of human insulin or 1 unit of other fast-acting insulin analogues.
- Always check insulin label before administration (see 8 WARNINGS AND PRECAUTIONS).
- Inspect Lyumjev visually before use and discard for particulate matter or discolouration. Only use Lyumjev if the solution appears clear and colourless.
- The dose counter of Lyumjev prefilled pens (100 units/mL and 200 units/mL) shows the number of units of Lyumjev to be injected. No dose conversion is required if transferring a patient between the 100 units/mL and 200 units/mL strengths.
- Lyumjev should not be used by patients with visual impairment without help of a trained person.
- Lyumjev in a vial is to be used with insulin syringes with the corresponding unit scale (U-100 or 100 Units/mL) or in Continuous Subcutaneous Insulin Infusion (CSII) therapy.
- DO NOT dilute or mix Lyumjev with any other insulin products except I.V. infusion fluids under medical supervision.
- Train patients on proper use and injection technique before initiating Lyumjev. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Rotate injection sites within the same region from one injection to the next so that the same site is not used more than approximately once a month to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis (see 8 WARNINGS AND PRECAUTIONS).

- Before travelling between different time zones, the patient should seek the health professional's advice since this means the patient has to take insulin and meals at different times.
- Lyumjev 200 units/mL should not be administered via a subcutaneous infusion pump or mixed with any other insulin (including Lyumjev 100 units/mL).
- DO NOT transfer insulin lispro solution in the Lyumjev 200 units/mL KwikPen to other devices, such as a syringe. The markings on the insulin syringe will not measure the dose correctly. Overdose can result causing severe hypoglycemia.
- When used via a subcutaneous insulin infusion pump, Lyumjev (insulin lispro injection) 100 units/mL should not be diluted or mixed with any other insulin. Patients should carefully read and follow the insulin infusion pump manufacturer's instructions and Part III - Patient Medication Information before use.

4.2 Recommended Dose and Dosage Adjustment

The dosage of Lyumjev must be individualized. Individualize and adjust the dosage of Lyumjev based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.

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 or timing of food intake), changes in renal or hepatic function, or during acute illness to minimize the risk of hypoglycemia or hyperglycemia.

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS).

Starting Dose in Insulin-Naïve Patients:
Type 1 Diabetes Mellitus: Lyumjev is to be used as mealtime insulin and requires subsequent individual dosage adjustments. The recommended starting dose of Lyumjev in insulin naïve adult patients with type 1 diabetes is approximately 50% of the total daily insulin dose and should be divided between each daily meal. The remainder of the total daily insulin dose should be administered as intermediate- or long-acting insulin. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus: The suggested initial dose for adult patients is 4 units at one or more meals. The number of injections and subsequent titration will depend on individual glycemic targets.

Converting to Lyumjev from Other Insulins
Close glucose monitoring is recommended when converting from other mealtime insulins and in the initial weeks thereafter.

If converting from another mealtime insulin to Lyumjev, the change can be done on a unit-to-unit basis. Due to the faster onset of insulin action, Lyumjev should be injected at the start of a meal. When necessary, Lyumjev may be administered up to 20 minutes after starting the meal (see 15 CLINICAL TRIALS).

Converting a patient from another type, brand or manufacturer of insulin must be done under medical supervision and may result in the need for a change in dosage.

Doses and timing of concurrent intermediate- or long-acting insulin or other concomitant antidiabetic treatment may need to be adjusted.

4.3 Administration

Subcutaneous

- Inject Lyumjev 0 to 2 minutes before the start of a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks.
- Lyumjev can be administered within 20 minutes after starting a meal.
- Lyumjev given by subcutaneous injection should generally be used in regimens with intermediate- or long-acting insulin.

Continuous Subcutaneous Insulin Infusion (Insulin Pump): Lyumjev 100 units/mL ONLY

- Do not administer Lyumjev 200 units/mL using a continuous subcutaneous insulin infusion pump.
- Lyumjev 100 units/mL can be used for CSII in pumps suitable for CSII and will cover both the bolus insulin requirement (approximately 50%) and the basal insulin requirement. Use Lyumjev 100 units/mL in accordance with the insulin infusion pumps' instructions for use.
- Train patients using CSII pump therapy to administer insulin by injection and have alternate insulin therapy available in case of pump failure.
- Administer Lyumjev 100 units/mL by continuous subcutaneous infusion into the subcutaneous tissue of the abdominal wall. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized subcutaneous amyloidosis (see 8 WARNINGS AND PRECAUTIONS).
- Change the infusion set and the infusion set insertion site according to the insulin infusion pump manufacturers' user manual.
- Change Lyumjev 100 units/mL in the pump reservoir at least every 9 days or according to the pump user manual, whichever is shorter.
- Do NOT dilute or mix Lyumjev 100 units/mL when administering by continuous subcutaneous infusion.
- Do NOT expose Lyumjev 100 units/mL in the pump reservoir to temperatures greater than 37°C (98.6°F).

Intravenous Administration for Lyumjev 100 units/mL Only

- Do not administer Lyumjev 200 units/mL intravenously.
- Dilute Lyumjev 100 units/mL to concentrations from 0.1 unit/mL to 1.0 unit/mL using 0.9% sodium chloride or 5% dextrose.
- Intravenous administration of Lyumjev 100 units/mL must be performed under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.
- Store diluted Lyumjev for up to 14 days in a refrigerator at 2°C to 8°C until time of use. The same solution may be stored for up to 20 hours at room temperature at 20°C to 25°C.
- Care should be taken to ensure that the insulin is injected into the IV infusion bag and not simply the entry port.

4.4 Missed Dose

Instruct patients who forget a mealtime dose to monitor their blood glucose level to decide if an

insulin dose is needed, and to resume their usual dosing schedule at the next meal.

5 OVERDOSAGE

Overdose causes hypoglycemia, which may be severe and life-threatening, with accompanying symptoms that include listlessness, confusion, palpitations, sweating, vomiting, and headache. Insulin overdose, particularly when given intravenously, may also cause hypokalemia, which may be severe and life-threatening. Hypokalemia must be corrected appropriately.

Hypoglycemia may occur as a result of an excess of insulin lispro relative to food intake, energy expenditure, or both. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection or Intravenous	Solution for injection, 100 U/mL • 1 mL of the solution contains 100 Units of insulin lispro (equivalent to 3.5 mg).	Glycerol, magnesium chloride hexahydrate, metacresol, sodium citrate dihydrate, treprostinil sodium, zinc oxide, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.
Subcutaneous injection	Solution for injection, 200 U/mL • 1 mL of the solution contains 200 Units of insulin lispro (equivalent to 6.9 mg).	

Lyumjev is available as a sterile, aqueous, clear, and colourless solution for subcutaneous or intravenous administration in 10 mL vials and 3 mL cartridges and disposable pens in the following package sizes:

- Pack size for vial (U-100) is 1 x 10 mL
- Pack size for 3 mL cartridge (U-100) is 5 x 3 mL
- Pack size for 3 mL KwikPen (U-100 pre-filled pen) is 5 x 3 mL

- Pack size for 3 mL Junior KwikPen (U-100 pre-filled pen) is 5 x 3 mL
- Pack size for 3 mL Tempo Pen (U-100 pre-filled pen) is 5 x 3 mL
- Pack sizes for 3 mL KwikPen (U-200 pre-filled pen) are 2 x 3 mL and 5 x 3 mL

Not all pack sizes and presentations may be marketed.

7 DESCRIPTION

Lyumjev (insulin lispro injection) is a fast-acting formulation of a human insulin analog used to lower glucose. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro 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.

Lyumjev is a sterile, aqueous, clear, and colourless solution for subcutaneous or intravenous administration.

8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General
As with all insulins, the duration of action of Lyumjev may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose.

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph, (see 8 WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin, including Lyumjev, is contemplated.

Lyumjev pens and cartridges should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Changes in insulin, insulin strength, manufacture, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments in concomitant oral anti-diabetic treatment may be needed.

Hypokalemia
All insulin products, including Lyumjev, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia [e.g., patients using potassium-lowering medications, patients taking medications

sensitive to serum potassium concentrations, patients receiving intravenously administered insulin, or patients losing potassium through other means (e.g., diarrhea)] (see 5 OVERDOSAGE).

Endocrine and Metabolism

Hypoglycemia

As with other insulins, hypoglycemia is the most common adverse reaction of insulin therapy, including Lyumjev (see 9 ADVERSE REACTIONS). Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see 9 ADVERSE REACTIONS, Hypoglycemia and 5 OVERDOSAGE).

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behavior, hunger, convulsions, loss of consciousness, temporary or permanent impairment of brain function, or, in extreme circumstances, even death which can occur without recognizable symptoms.

Some people may not recognize when their blood sugar drops low.

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 insulin preparations, 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. Factors which may increase the risk of hypoglycemia include changes in meal pattern, changes in level of physical activity, or changes to co-administered medication. Patients with renal or hepatic impairment may be at high risk of hypoglycemia.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Hyperglycemia

The use of inadequate doses or discontinuation of treatment, especially in patients requiring insulin, may lead to hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction

Pump or infusion set malfunctions can lead to 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 4 DOSAGE AND ADMINISTRATION, and 12 STORAGE, STABILITY, AND DISPOSAL).

Hepatic and Renal Impairment
Patients with hepatic or renal impairment may be at increased risk of hypoglycemia and may require more frequent Lyumjev dose adjustment and more frequent glucose monitoring.

Immune
Injection site and local allergic reaction
With insulin therapies including Lyumjev, patients may experience rash, redness, bruising, swelling, pain, inflammation, or itching at the site of injection (see 9 ADVERSE REACTIONS).

Most of these minor reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of LYUMJEV. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients (see 2 CONTRAINDICATIONS). Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions.

Systemic Allergic Reaction
Systemic allergic reactions have rarely occurred with insulin treatments, including Lyumjev (see 9 ADVERSE REACTIONS). These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop in blood pressure (see 9 ADVERSE REACTIONS).

Severe cases of generalized allergy including anaphylactic reaction may be life threatening (see 2 CONTRAINDICATION). If hypersensitivity reactions occur, discontinue Lyumjev; treat per standard of care and monitor until symptoms and signs resolve.

Antibody production
As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The presence of such antibodies may necessitate adjustment of the insulin dose to correct for tendencies toward hyper- or hypoglycemia.

In a 26-week study in type 1 diabetes patients (N=777), 49% were anti-drug (insulin lispro) antibody (ADA)-positive at baseline, 91% of which were cross-reactive with native insulin. A total of 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 which were cross-reactive with native insulin.

In a 26-week study in type 2 diabetes patients (N=335), 35% were ADA-positive at baseline, 81% of which were cross-reactive with native insulin. A total of 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 which were cross-reactive with native insulin.

Avoidance of accidental mix-ups/medication errors
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Lyumjev and other insulin products.

Do NOT transfer insulin from the Lyumjev KwikPen 200 units/mL to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia.

Patients must visually verify the units of the dose prior to administering Lyumjev. Therefore, the requirement for patients to self-administer is that they can read the dose scale. Patients, who are blind or have poor vision, must be instructed to always get assistance from another person who has good vision and is trained in administration of insulins.

Monitoring and Laboratory Tests
With insulin therapy, including Lyumjev, the need for regular blood glucose self-monitoring should be considered to obtain optimal glycemic control. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. If a patient is pregnant, careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Mixing of Insulins
DO NOT dilute or mix Lyumjev with any other insulin products or solutions, except I.V. infusion fluids under medical supervision.

Lipodystrophy and Cutaneous Amyloidosis
Subcutaneous administration of insulin products can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (enlargement or thickening of adipose tissue) or cutaneous amyloidosis (lumps in the skin) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions.

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. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Other
Control of diabetes mellitus may be further complicated by diseases such as acromegaly, Cushing's syndrome, hyperthyroidism and pheochromocytoma.

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, acute painful peripheral neuropathy, and peripheral oedema. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

8.1 Special Populations

8.1.1 Pregnant Women

There are no adequate and well-controlled studies with Lyumjev in pregnant women. The extent

of exposure in pregnancy during clinical trials is very limited. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Lyumjev should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Intensified blood glucose control and monitoring of pregnant women with diabetes or a history of gestational diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values. Careful monitoring of glucose control is essential in these patients.

Animal data from a combined fertility and embryo-fetal development study on insulin lispro in rats demonstrated fetal growth retardation (decrease in fetal weight and an increased incidence of fetal runts/litter) at a dose of 20 units/kg body weight/day (1.6-fold the human dose on a body surface area basis) (see 16 NON-CLINICAL TOXICOLOGY).

Animal data from an embryo-fetal development study on the excipient, treprostinil, conducted in rabbits demonstrated an increase in post-implantation loss and a decrease in the number of live fetuses per litter, due to increases in early and late resorptions at a high dose of 0.4 mg/kg body weight/day (exposure of 3866-fold the human exposure) (see 16 NON-CLINICAL TOXICOLOGY).

8.1.2 Breast-feeding

There are no data on the presence of Lyumjev in human milk, the effects on the breastfed infant, or the effect on milk production. For this reason, caution should be exercised when Lyumjev is administered to a nursing mother. 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. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

8.1.3 Pediatrics

Pediatrics (**<18 years of age)**: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.1.4 Geriatrics

Geriatrics (≥65 years of age): In clinical studies, 187 of 1116 (16.8%) Lyumjev-treated patients with type 1 or type 2 diabetes were ≥65 years of age and 18 of 1116 (1.6%) were ≥75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger adult patients.

As with all insulins, caution should be exercised when Lyumjev is administered to geriatric patients. In general, dose selection for an elderly patient should take into consideration the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population. In geriatric patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia (see 8 WARNINGS AND PRECAUTIONS)
- Allergic reactions (see 8 WARNINGS AND PRECAUTIONS)

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data in Table 2 reflect the exposure of 780 patients with type 1 diabetes (PRONTO-T1D) to Lyumjev with a mean exposure duration of 26 weeks. 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 3 reflect the exposure of 336 patients with type 2 diabetes (PRONTO-T2D) to Lyumjev with a mean exposure duration of 26 weeks. 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%.

Table 2 Adverse Reactions in Adult Patients with Type 1 Diabetes (Incidence ≥1%) Through Week 26

	Mealtime Lyumjev + basal insulin N=451 (%)	Postmeal Lyumjev + basal insulin N=329 (%)	Mealtime Humalog + basal insulin N=442 (%)
Hypoglycemia[a]	398 (88.3)	298 (90.6)	400 (90.5)
Severe hypoglycemia[b]	25 (5.5)	15 (4.6)	25 (5.7)
Nasopharyngitis	64 (14.2)	48 (14.6)	63 (14.3)
Injection site reaction	13 (2.9)	8 (2.4)	1 (0.2)
Allergic reactions	13 (2.9)	9 (2.7)	8 (1.8)

[a] All documented hypoglycemia less than 3.0 mmol/L

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

Table 3 Adverse Reactions in Adult Patients with Type 2 Diabetes (Incidence ≥1%) Through Week 26

	Mealtime Lyumjev + basal insulin	Mealtime Humalog + basal insulin

	N=336 (%)	N=337 (%)
Hypoglycemia[a]	251 (74.7)	264 (78.3)
Severe hypoglycemia[b]	3 (0.9)	6 (1.8)
Nasopharyngitis	42 (12.5)	36 (10.7)
Upper respiratory tract infection	25 (7.4)	20 (5.9)
Injection site reaction	9 (2.7)	0
Allergic reactions	6 (1.8)	8 (2.4)

[a] All documented hypoglycemia less than 3.0 mmol/L

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

The data in Table 4 reflect the exposure of 215 patients with type 1 diabetes (PRONTO-Pump-2) to Lyumjev in a continuous subcutaneous insulin infusion (CSII) study with a mean exposure duration of 16 weeks. 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%.

Table 4 Adverse Reactions in Adult Patients with Type 1 Diabetes Using CSII (Incidence ≥1%) Through Week 16

	Lyumjev N=215 (%)	Humalog N=217 (%)
Hypoglycemia[a]	181 (84.6)	186 (85.7)
Severe hypoglycemia[b]	3 (1.4)	2 (0.9)
Infusion site reaction	41 (19.1)	16 (7.4)
Infusion site pain	34 (15.8)	6 (2.8)
Nasopharyngitis	13 (6.0)	12 (5.5)
Allergic reactions	3 (1.4)	5 (2.3)

[a] All documented hypoglycemia less than 3.0 mmol/L

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

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including Lyumjev (see 8 WARNINGS AND PRECAUTIONS).

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

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including Lyumjev (see 8 WARNINGS AND PRECAUTIONS). Allergic reactions were reported in patients treated with Lyumjev including eczema (0.4%), rash (0.4%), dermatitis (0.3%), hypersensitivity (0.2%), and pruritus (0.2%).

Injection/Infusion Site-Related Reactions
As with other insulin therapies, patients may experience pain, rash, redness, inflammation, bruising, or itching at the site of Lyumjev injection or infusion.

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

In Study PRONTO-Pump-2, infusion site-related reactions were reported in 37.7% of patients treated with Lyumjev (mild in 27.9%, moderate in 7.9%, and severe in 1.9%). Of the 215 patients treated with Lyumjev, 7 discontinued treatment due to infusion site-related reactions (3.3%).

Lipodystrophy
Administration of insulin, including Lyumjev, may result in lipodystrophy [lipohypertrophy (enlargement or thickening of tissue) or lipoatrophy (depression in the skin)]. Lipodystrophy was reported in 0.2% of patients treated with Lyumjev.

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. In the clinical trials, after 26 weeks of treatment 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 1.4 kg.

Edema
Cases of edema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy. Peripheral edema occurred in 0.2% of patients treated with Lyumjev.

9.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were reported in the clinical program in patients with type 1 or type 2 diabetes. Causality of these events has not been established.

- **Cardiac disorders:** tachycardia, sinus tachycardia, palpitations, and acute myocardial infarction
- **Ear and labyrinth disorders:** vertigo
- **Eye disorders:** diabetic retinopathy, macular edema, and retinopathy
- **Gastrointestinal disorders:** nausea
- **General disorders and administration site conditions:** injection site pain, injection site bruising, injection site erythema, infusion site induration, infusion site pruritus, asthenia, fatigue, pyrexia, edema, and edema peripheral.
- **Immune system disorders**: hypersensitivity

- **Injury, poisoning and procedural complications:** infusion related reaction
- **Investigations:** weight increased, blood creatine phosphokinase increased
- **Metabolism and nutrition disorders:** diabetic ketoacidosis, obesity, and hyperglycemia
- **Musculoskeletal and connective tissue disorders:** myalgia, joint swelling, and musculoskeletal pain
- **Nervous system disorders:** hypoglycemic unconsciousness, dizziness, and hypoglycemic coma
- **Psychiatric disorders:** depression, insomnia, and anxiety
- **Skin and subcutaneous tissue disorders:** pruritis and rash
- **Vascular disorders:** hypertension

10 DRUG INTERACTIONS

10.1 Overview

A number of medicinal products are known to interact with the glucose metabolism. Therefore an increased frequency of glucose monitoring may be required when Lyumjev is co-administered with these drugs.

10.2 Drug-Drug Interactions

The following substances may reduce insulin requirement:
Antidiabetic agents (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors), ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.

The following substances may increase insulin requirement:
Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, growth hormone, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.

The following substances may reduce or increase insulin requirement:
Alcohol, beta-blockers, clonidine, lithium salts, octreotide/lanreotide, and pentamidine. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The following substances may mask the symptoms of hypoglycemia:
Beta-blockers, clonidine, guanethidine, and reserpine.

Other:
To avoid the risk of developing new or worsening heart failure, the use of thiazolidinediones (TZDs) in combination therapy with insulin is not indicated (See 8 WARNINGS AND PRECAUTIONS)

10.3 Drug-Food Interactions

Please refer to DOSAGE AND ADMINISTRATION for timing of food consumption.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

The primary activity of Lyumjev is the regulation of glucose metabolism. Insulins, including insulin lispro, the active ingredient 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.

11.2 Pharmacodynamics

Early and Late Insulin Action
A glucose clamp study was conducted in 40 patients with type 1 diabetes given Lyumjev and Humalog subcutaneously as a single 15 unit dose. 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 53% lower with Lyumjev than observed with Humalog.
- The duration of action of Lyumjev was 43 minutes shorter than Humalog.
- The total glucose infused during the clamp was comparable between Lyumjev and Humalog.

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

Total and maximum glucose lowering effect of Lyumjev increased with dose within the dose range of 7 to 30 units. The duration of action for Lyumjev is between 3 and 5 hours. The early onset and total insulin action were similar when Lyumjev was administered in the abdomen, deltoid, or thigh.

Postprandial Glucose Lowering
Lyumjev reduced the postprandial glucose excursion during a standardized test meal over the complete 5-hour test meal period (change from premeal AUC[0-5h]) compared to Humalog.

- In patients with type 1 diabetes, Lyumjev reduced the postprandial glucose by approximately 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 postprandial glucose 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.

11.3 Pharmacokinetics

Absorption: Insulin lispro absorption was accelerated and had a shorter duration of exposure in healthy subjects and patients with diabetes following injection of Lyumjev compared to Humalog (Figure 4).

- 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, eight times more insulin lispro was available during the first 15 minutes compared to Humalog; three times more insulin lispro was available during the first 30 minutes compared to Humalog.
- Time to maximum insulin lispro concentration was achieved 57 minutes after administration of Lyumjev.
- Lyumjev had 43% less insulin lispro in the circulation after 3 hours following injection compared to Humalog.
- The duration of exposure for Lyumjev was 1 hour shorter compared to Humalog.
- The total insulin lispro exposure and maximum concentration were comparable between Lyumjev and Humalog.

In type 1 patients, the day-to-day variability [CV%] of Lyumjev was 13% for total insulin lispro exposure (AUC, 0-10h) and 23% for maximum insulin lispro concentration (C_{max}).

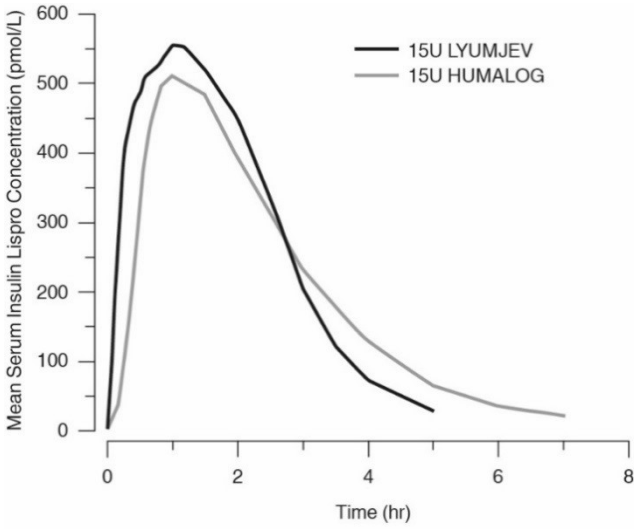


Figure 4 Serum Insulin Lispro After Subcutaneous Injection of Lyumjev or Humalog (15 unit dose)

The absolute bioavailability of insulin lispro after subcutaneous administration of Lyumjev in the abdomen, deltoid and thigh was 64-65%. The accelerated absorption of insulin lispro and early insulin lispro exposure is maintained regardless of injection site (abdomen, upper arm, and

thigh). 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. No exposure data are available following injection in the buttocks.

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

Continuous subcutaneous insulin infusion (CSII)
The absorption of insulin lispro was accelerated when Lyumjev was administered in patients with type 1 diabetes by CSII.

- 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.

Insulin absorption after Lyumjev 200 units/mL
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 serum insulin lispro concentration-time curve from time zero to the last quantifiable concentration and maximum insulin lispro concentration. The accelerated insulin lispro absorption after administration of Lyumjev 200 units/mL was similar to that observed with Lyumjev 100 units/mL.

Distribution: The geometric mean (% coefficient of variation [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.

Metabolism: As a human insulin analog produced by recombinant DNA technology, the expected consequence of metabolism of insulin lispro is the degradation to small peptides and individual amino acids.

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 and Conditions

Age, Gender, Race, and BMI: Based on the population PK analyses, Lyumjev age (18 to 77), gender, and race did not affect the pharmacokinetics of Lyumjev.

Although body weight was identified as a significant covariate on the clearance and volume of distribution, dose adjustment for Lyumjev based on body weight is not recommended. As with all other insulin products, dosing should be individualized based on clinical response.

Geriatrics: The pharmacokinetic and glucodynamic properties of Lyumjev and Humalog were investigated in a single dose study in 80 patients (41 young adults, 22-45 years; and 39 elderly adults, 65-77 years) with type 1 diabetes. In geriatric patients with type 1 diabetes, Lyumjev showed an accelerated insulin absorption, and a shorter duration of exposure while maintaining a similar total exposure and maximum concentration, compared to Humalog.

Hepatic Insufficiency: Hepatic impairment is not known to impact the pharmacokinetics of insulin lispro.

Renal Insufficiency: Renal impairment is not known to impact the pharmacokinetics of insulin lispro.

12 STORAGE, STABILITY AND DISPOSAL

Not in-use (unopened) Lyumjev vials, pens, and cartridges should be stored in a refrigerator between 2°C to 8°C, but not in a freezer. Do not freeze Lyumjev and do not use Lyumjev if it has been frozen. Lyumjev should not be exposed to direct heat or light.

Always remove the needle after each injection and store Lyumjev pens without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

The storage conditions are summarized in Table 5.

Table 5 Storage Conditions for Vials, Pens, and Cartridges

Lyumjev Presentation	Not In-use (Unopened)		In-use (Opened)	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (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 (including pump in-use time for CSII).

[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.

Use in an External 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 37°C (98.6°F). The infusion set and infusion set insertion site should be changed according to the manufacturer's user manual.

Storage of Lyumjev in infusion fluids

Store diluted Lyumjev for up to 14 days in a refrigerator at 2°C to 8°C until time of use. The same solution may be stored for up to 20 hours at room temperature at 20°C to 25°C (see 4 DOSAGE AND ADMINISTRATION).

13 SPECIAL HANDLING INSTRUCTIONS

Needles and Lyumjev pens and cartridges must not be shared. The cartridge must not be refilled.

Lyumjev should only be used if it appears as an aqueous, clear, and colourless solution.

Lyumjev which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

Lyumjev 200 units/mL should not be administered via a subcutaneous infusion pump or mixed with any other insulin (including Lyumjev 100 units/mL).

DO NOT transfer insulin lispro solution in the Lyumjev 200 units/mL KwikPen to other devices, such as a syringe. The markings on the insulin syringe will not measure the dose correctly. Overdose can result causing severe hypoglycemia.

In case of emergency in current Lyumjev users (hospitalization or insulin pen malfunction), patients should be prepared to inject insulin with an alternative method.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

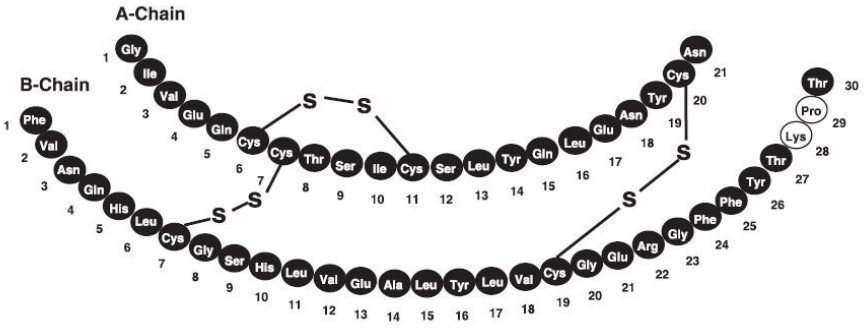
Drug Substance

Proper name: insulin lispro

Chemical name: Lys(B28), Pro(B29) Human Insulin Analogue (recombinant DNA origin)

Molecular formula and molecular mass: $C_{257}H_{383}N_{65}O_{77}S_6$ and 5808 Daltons

Structural formula:



Product Characteristics

Physicochemical properties: Sterile, aqueous, clear, and colourless solution. The solution pH is 7.0 to 7.8.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

The efficacy of Lyumjev administered at mealtime or postmeal in adult patients with type 1 diabetes and used in combination with a once or twice daily administered basal insulin was evaluated in a 26 week randomized, treat-to-target, active-controlled trial (PRONTO-T1D). Prior to randomization, there was an 8 week lead in period during which basal insulin was titrated to a target of 5.6 mmol/L. Patients (n=1222) were then 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 100 units/mL (once or twice daily) or insulin degludec 100 units/mL (once daily). 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.

The efficacy of Lyumjev administered at mealtime in adult patients with type 2 diabetes and used in combination with a once or twice daily administered basal insulin was evaluated in a 26 week randomized, treat-to-target, active-controlled trial (PRONTO-T2D). Patients at study entry

were on up to three oral anti-diabetic medications (OAMs), basal insulin and at least one prandial insulin injection or premixed insulin with at least two injections daily. They were allowed to continue on metformin and/or a SGLT2 inhibitor. Prior to randomization, there was an 8 week lead in period during which basal insulin was titrated to a target of 5.6 mmol/L. Patients were then randomized to either mealtime Lyumjev or to mealtime Humalog, both in combination with insulin glargine 100 units/mL (once or twice daily) or insulin degludec (100 units/mL or 200 units/mL once daily) 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.

The efficacy of Lyumjev administered by continuous subcutaneous insulin infusion (CSII) by external pump in adults with Type 1 diabetes compared to Humalog was evaluated in a 16 week randomized (1:1), active controlled, treat-to-target, multinational trial (PRONTO-Pump-2). Patients (n=432) 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.

Table 6 Summary of Patient Demographics for Clinical Trials in Type 1 and Type 2 Diabetes

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PRONTO-T1D	Multicentre, multinational, randomized (4:4:3), 3-arm, partially double-blind, active controlled, treat-to-target, parallel group comparing meal-time Lyumjev and post-meal Lyumjev to Humalog, in a basal-bolus regimen, all in combination with either insulin glargine 100 units/mL (once or twice daily) or insulin degludec 100 units/mL (once daily) in adult patients with type 1 diabetes.	Treatment arms: • Mealtime bolus treatment with Lyumjev SC (n=451) • Postmeal bolus treatment with Lyumjev SC (n=329) • Mealtime bolus treatment with Humalog SC (n=442) Treatment duration: 26 weeks	1222	44.4 years (18-84)	M: 688 (56%) F: 534 (44%)
PRONTO-T2D	Multicentre, multinational, randomized (1:1), double blind, 2-arm, active controlled, treat-to-target, parallel group comparing mealtime Lyumjev to mealtime Humalog, both in	Treatment arms: (1) Mealtime bolus treatment with Lyumjev SC (n=336)	673	60.6 years (28-84)	M: 359 (53%) F: 314 (47%)

	combination with insulin glargine 100 units/mL (once or twice daily) or insulin degludec (100 units/mL or 200 units/mL once daily) in a basal-bolus regimen, in adult patients with type 2 diabetes who at study entry were on up to three oral anti-diabetic medications (OAMs), basal insulin, and at least one prandial insulin injection or premixed insulin with at least two injections daily.	(2) Mealtime bolus treatment with Lyumjev SC (n=337) Treatment duration: 26 weeks			
PRONTO-Pump-2	Multicentre, multinational, randomized (1:1), double blind, 2-arm, active controlled, treat-to-target, parallel group comparing CSII Lyumjev to CSII Humalog in adult patients with type 1 diabetes.	Treatment arms: • Basal and bolus treatment with Lyumjev CSII (n=216) • Basal and bolus treatment with Humalog CSII (n=216) Treatment duration: 16 weeks	432	46.4 years (17-83)	M: 193 (44.7%) F: 239 (55.3%)

15.2 Study Results

PRONTO-T1D (Study ITRM): Type 1 Diabetes - Adult

At week 26, treatment with mealtime Lyumjev provided a mean reduction in HbA_{1c} that met the pre-specified non-inferiority margin (0.4%) compared to mealtime Humalog. In addition, postmeal Lyumjev met the prespecified non-inferiority margin (0.4%) compared to mealtime Humalog (see Table 7). Insulin doses were similar for all treatment groups at baseline and at 26 weeks.

Table 7 Results at Week 26 from Study PRONTO-T1D

	Mealtime Lyumjev + basal insulin	**Mealtime Humalog + basal insulin**	**Postmeal Lyumjev + basal insulin**
Number of randomized subjects (N)	451	442	329
HbA_{1c} (%) (mean)[a,b]			
Baseline	7.3	7.3	7.4
Adjusted mean change from baseline	-0.18	-0.09	0.05
Estimated treatment difference versus Humalog [95% CI]	-0.08 [-0.16, -0.003][c]		0.14 [0.05, 0.23][c]

[a] Subjects included in the analysis are a subset of the randomized population that had baseline and at least one post-baseline assessment. The primary analysis included 450, 442, and 325 subjects

randomized to and treated with mealtime Lyumjev, mealtime Humalog, and postmeal Lyumjev, respectively. Missing data at Week 26 were imputed by return to baseline , assuming a washout of any potential treatment effect. At Week 26, primary efficacy was missing for 3.6%, 4.8%, and 4% 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.

In the mealtime Lyumjev treated group, the 1- and 2-hour PPG increments (standardized meal test) were 4.29 and 6.22 mmol/L at baseline and 2.59 and 4.07 mmol/L at end of trial, respectively. In the Humalog treated group, the 1- and 2- hour PPG increments were 3.97 and 5.64 mmol/L at baseline and 4.13 and 5.77 mmol/L at end of trial, respectively. At Week 26, the estimated treatment difference in change from baseline in 1- and 2-hour PPG increments between mealtime Lyumjev and Humalog were -1.53 (95% CI [1.94, 1.13]) and -1.69 (95% CI [-2.24, -1.14]) respectively.

PRONTO-T2D (ITRN): Type 2 Diabetes – Adults

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 8). Insulin doses were similar in both treatment groups at baseline and at 26 weeks.

Table 8. Results at Week 26 from Study PRONTO-T2D

	Mealtime Lyumjev + basal insulin	**Mealtime Humalog + basal insulin**
Number of randomized subjects (N)	336	337
HbA_{1c} (%)[a,b]		
Baseline mean	7.3	7.3
Adjusted mean change from baseline	-0.43	-0.46
Estimated treatment difference versus Humalog [95% CI][c]	0.03 [-0.08, 0.13]	

[a] Subjects included in the analysis are a subset of the randomized population that had baseline and at least one post-baseline assessment. The primary analysis included 334 and 336 subjects randomized to and treated with mealtime Lyumjev and mealtime Humalog, respectively. Missing data at Week 26 were imputed by return to baseline, assuming a washout of any potential treatment effect. At Week 26, primary efficacy was missing for 4.2% of subjects for both mealtime Lyumjev and, mealtime Humalog.

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

[c] Tested for non-inferiority.

In the mealtime Lyumjev treated group, the 1- and 2-hour PPG increments (standardized meal test) were 4.26 and 5.52 mmol/L at baseline and 3.48 and 4.46 mmol/L at end of trial, respectively. In the Humalog treated group, the 1- and 2- hour PPG increments were 4.29 and 5.53 mmol/L at baseline and 4.14 and 5.44 mmol/L at end of trial, respectively. At Week 26, the estimated treatment difference in change from baseline in 1- and 2-hour PPG increments between mealtime Lyumjev and Humalog were -0.67 (95% CI [-1.01, -0.32]) and 0.98 (95% CI [-1.41, -0.54]) respectively.

PRONTO-Pump-2 (Study ITRO): Type 1 Diabetes – Adult Continuous Subcutaneous Insulin Infusion (CSII)

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 Humalog (see Table 9). Total daily insulin doses were similar for both treatment groups at baseline and at 16 weeks.

Table 9 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,b]		
Baseline mean	7.6	7.5
Adjusted mean change from baseline	-0.06	-0.09
Estimated treatment difference versus Humalog [95% CI]	0.03 [-0.05, 0.11][c]	

[a] Subjects included in the analysis are a subset of the randomized population that had baseline and at least one post-baseline assessment. The primary analysis included 209 and 214 subjects randomized to and treated with mealtime Lyumjev and mealtime Humalog, respectively. Missing data at Week 16 were imputed by return to baseline approach. At Week 16, HbA1c assessment was missing for 7 subjects (3.3%) and 9 subjects (4.3%) for Humalog and Lyumjev, respectively.

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

[c] Tested for non-inferiority.

In the mealtime Lyumjev treated group, the 1- and 2-hour PPG levels (standardized meal test) were 11.27 and 12.68 mmol/L at baseline and 9.59 and 10.74 mmol/L at end of trial, respectively. In the Humalog treated group, the 1- and 2- hour PPG levels were 10.88 and 12.30 mmol/L at baseline and 10.95 and 12.34 mmol/L at end of trial, respectively. At Week 26, the estimated treatment difference in change from baseline in 1- and 2-hour PPG levels between mealtime Lyumjev and Humalog were -1.37 (95% CI [-2.01, -0.72]) and -1.60 (95% CI [-2.41, -0.79]) respectively.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The effect of insulin lispro given parenterally to laboratory animals in single-dose and repeat-dose toxicology studies was the expected finding of lowered blood glucose. No other clinical signs or effects were observed in the single-dose toxicity studies of insulin lispro that have been conducted in rats and in dogs by the intravenous and subcutaneous routes of administration. Repeat-dose toxicity studies of 1, 6, and 12 months duration in rats and of 1 and 12 -months duration in dogs were conducted by subcutaneous administration. In these studies, lowering of blood glucose was accompanied by changes in serum lipids and body weight gain. No unexpected findings or toxicities were seen in any of these studies. The no-observed-adverse-effect level (NOAEL) in the 12-month studies was the highest dose tested, which was 200 U/kg body weight/day in rats and 2 units/kg body weight/day in dogs (16-fold and 0.5-fold a human subcutaneous dose of 2 units/kg body weight/day, based on units/body surface area, respectively).

Repeat-dose subcutaneous toxicity studies were also conducted with the excipient treprostinil in rats and dogs. In rats, doses administered were 0.1 and 0.6 mg/kg body weight/day in a 14-day study and 0.01 to 0.1 mg/kg body weight/day in the 3- and 6-month studies. In dogs, doses administered were 0.07 and 0.28/0.14 mg/kg body weight/day in a 7-day study and 0.004 to

0.07 mg/kg body weight/day in the 3- and 6-month studies. Toxicities were observed at the high doses administered in the 7- and 14-day studies, including myocardial degeneration and necrosis in rats and hypoactivity, increased capillary refill time, and bradycardia in dogs. Adverse injection site reactions were also observed in rats and dogs at the high doses. In the 3- and 6-month studies, treprostinil was well-tolerated in rats and dogs at all doses. Clinical signs were limited to transient, dose-related flushing of the extremities secondary to the vasodilatory pharmacology of treprostinil. In rats, non-adverse reductions in food consumption, body weight, and body weight gain were observed at the high-dose in the 6-month study. In dogs, transient post-dosing findings of decreases in systolic arterial pressure and arterial pulse pressure (both dose levels) and an increase in heart rate and shortened QT interval (high-dose) were observed, but were without adverse effects on the QTc interval. No evidence of subcutaneous injection site reactions to treprostinil occurred either when treprostinil was injected alone in the above studies or when treprostinil was injected in combination with insulin lispro in a 2-week local tolerance study in rats. Furthermore, there was no indication of direct target organ toxicity in either rats or dogs. Based on the results of the 6-month studies, the -NOAEL was 0.1 mg/kg body weight/day in rats and 0.07 mg/kg body weight/day in dogs, the highest doses tested (exposures of 374-fold and 179-fold the human AUC at a treprostinil dose of 2000 ng/day, respectively).

Carcinogenesis
Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin lispro. In the 12-month chronic toxicity studies conducted in rats and dogs, insulin lispro did not produce proliferative effects or tumours in organs and tissues at any dose administered.

Carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of treprostinil.

Genotoxicity
Insulin lispro was non-genotoxic in the bacterial reverse mutation test, the in vitro unscheduled DNA synthesis assay conducted in primary cultures of adult rat hepatocytes, the in vitro mammalian cell gene mutation test conducted in L5178Y TK+/- mouse lymphoma cells, the in vitro mammalian chromosomal aberration test conducted in Chinese hamster ovary (CHO) cells, and the in vivo mammalian erythrocyte (bone marrow) micronucleus test conducted in male and female ICR mice.

Treprostinil was non-genotoxic in the in vitro bacterial reverse mutation test, the in vitro chromosomal aberration test conducted in CHO cells, and the in vivo mammalian erythrocyte (bone marrow) micronucleus test conducted in male and female rats.

Reproductive and Developmental Toxicity
Reproduction and teratology studies have been conducted with insulin lispro using the subcutaneous route of administration. In a combined fertility and embryo-fetal development study, female rats were administered subcutaneous insulin lispro injections of 1, 5 and 20 units/kg body weight/day (0.08-, 0.4-, and 1.6-fold the human subcutaneous dose of 2 units/kg body weight/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day (GD) 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was observed at the 20 units/kg body weight/day dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter. The effects were considered secondary to maternal

hypoglycemia. The NOAEL for the developmental toxicity of insulin lispro in this study was 5 units/kg body weight/day.

A second embryo-fetal development study was conducted in rabbits in which pregnant rabbits were administered subcutaneous insulin lispro injections from GD 7 to 19 at doses of 0.1, 0.25, and 0.75 units/kg body weight/day (0.02-, 0.04-, and 0.1-fold the human subcutaneous dose of 2 units/kg body weight/day, based on units/body surface area, respectively). No maternal toxicity or adverse effects on fetal development were observed. The NOAEL for the maternal and developmental toxicity of insulin lispro in this study was 0.75 units/kg body weight/day, the highest dose tested.

In a male fertility study, no adverse effects on male fertility were observed when male rats administered subcutaneous insulin lispro injections of 5 and 20 units/kg body weight/day (0.4- and 1.6-fold the human subcutaneous dose of 2 units/kg body weight/day, based on units/body surface area) for 6 months were mated with untreated female rats. In addition, in a combined fertility, perinatal, and postnatal study in male and female rats subcutaneously administered 1, 5, and 20 units/kg body weight/day (0.08-, 0.4-, and 1.6-fold the human subcutaneous dose of 2 units/kg body weight/day, based on units/body surface area), mating and fertility were not adversely affected in either gender at any dose.

Reproductive and developmental toxicity studies were also conducted with treprostinil in rats and rabbits using the subcutaneous route of administration. In fertility and early embryonic development studies conducted separately in male and female rats, there were no adverse effects of treprostinil on sperm density and motility, estrus cyclicity, mating, fertility, conception, implantation, and embryonic survival. The NOAEL in both studies was 0.1 mg/kg body weight/day, the highest dose tested (male and female exposures of 316-fold and 224-fold the human AUC at a treprostinil dose of 2000 ng/day, respectively). Embryo-fetal development studies indicated that treprostinil was not teratogenic in rats at doses up to 0.1 mg/kg body weight/day, but in rabbits, resulted in an increase in post-implantation loss and a decrease in the number of live fetuses per litter, due to increases in early and late resorptions at a dose of 0.4 mg/kg/day (exposure of 3866-fold the human AUC). The NOAEL for effects on embryo-fetal development was therefore a maternal dose of 0.1 mg/kg body weight/day in rats, the highest dose tested (exposure of 311-fold the human AUC), and 0.14 mg/kg body weight/day in rabbits (exposure of 1432-fold the human AUC). Maternal toxicity was also observed in the rabbit study at doses of 0.14 and 0.4 mg/kg body weight/day, and therefore, the NOAEL for maternal toxicity in rabbits was 0.05 mg/kg body weight/day (exposure of 614-fold the human AUC). In a prenatal and postnatal development study in rats, there was no evidence of F0 maternal toxicity or adverse effects on F1 offspring growth, behavior, and reproduction at maternal doses up to 0.1 mg/kg (exposure of 195-fold the human AUC).

Juvenile Toxicity

No juvenile animal toxicology studies have been conducted with insulin lispro or treprostinil.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

LYUMJEV™
LYUMJEV™ KwikPen®
LYUMJEV™ Junior KwikPen®
LYUMJEV™ Tempo Pen™
insulin lispro injection
Solution, 100 Units/mL

LYUMJEV™ KwikPen®
insulin lispro injection
Solution, 200 Units/mL

subcutaneous use

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www.lilly.ca

Lilly

Read this carefully before you start taking **Lyumjev** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Lyumjev**.

Serious Warnings and Precautions

- Low blood sugar is the most common adverse effect of insulin products, including Lyumjev.
- Blood sugar levels should be monitored for all patients with diabetes.
- If low blood sugar or high blood sugar reactions are not treated, they can cause loss of consciousness, coma or even death.
- Any change in insulin products should be made carefully and with medical supervision.
- Lyumjev should be injected up to 2 minutes before the start of the meal. When necessary, Lyumjev may be administered up to 20 minutes after starting the meal. (See *'How to take Lyumjev?')*
- DO NOT use Lyumjev 200 units/mL in an insulin infusion pump. Do not mix Lyumjev 200 units/mL with any other insulin.
- DO NOT transfer Lyumjev 200 units/mL to a syringe or other device. The markings on the insulin syringe will not measure the dose correctly. Overdose can result and lead to severe hypoglycemia.
- Accidental mix-up between Lyumjev and other insulin products is possible. Always carefully check the insulin label before each injection to avoid mix-ups between insulin products.
- DO NOT dilute or mix Lyumjev with any other insulin products or solutions, except when given into your vein under medical supervision.
- Only use Lyumjev if the solution looks water-clear and colourless.

What is Lyumjev used for?

- The treatment of adults with diabetes mellitus who require insulin for the control of high blood sugar.
- The treatment of people with type 2 diabetes, generally used in combination with an intermediate- or long-acting insulin for the control of high blood sugar.

How does Lyumjev work?
Lyumjev is a fast-acting insulin lispro formulation used to treat diabetes. Lyumjev will start to lower your blood sugar within 20 minutes after starting a meal. Due to this short action Lyumjev should normally be taken in combination with intermediate- or long-acting insulin preparation.

What are the ingredients in Lyumjev?
Medicinal ingredients: insulin lispro.
Non-medicinal ingredients: glycerol, magnesium chloride hexahydrate, metacresol, sodium citrate dihydrate, treprostinil sodium, Water for Injection and zinc oxide. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Lyumjev comes in the following dosage forms:
Solution for injection, 100 units/mL (each mL contains 100 units of insulin lispro):
- Vial; pack size: 1 vial of 10 mL
- Cartridge; pack size: 5 cartridges of 3 mL
- KwikPen® (pre-filled pen); pack size: 5 pre-filled pens of 3 mL
- Junior KwikPen® (pre-filled pen); pack size: 5 pre-filled pens of 3 mL
- Tempo Pen™ (pre-filled pen); pack size: 5 pre-filled pens of 3 mL

Solution for injection, 200 units/mL (each mL contains 200 units of insulin lispro):
- KwikPen® (pre-filled pen); pack sizes: 2 pre-filled pens of 3 mL and 5 pre-filled pens of 3 mL

Not all pack sizes and presentations may be available.

Lyumjev is a water-clear, colourless and aqueous solution for injection.

Lyumjev 10 mL vial can be used with a syringe or for filling a pump reservoir in a continuous infusion pump system.

Lyumjev cartridges are designed for use with Lilly's reusable insulin pens. Patients need to check their device manual to determine if the Lyumjev cartridge is compatible for use in other devices.

Do not use Lyumjev if:
- Your blood sugar is too low (hypoglycemia).
- You are allergic to anything in Lyumjev. (See *What are the ingredients in Lyumjev?*)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Lyumjev. Talk about any health conditions or problems you may have, including if you:
- Are experiencing stress, are ill, or have infections. These may affect your insulin needs.
- Take a class of oral antidiabetic drugs called thiazolidinediones (TZDs). Taking TZDs with insulin may increase risk of swelling and heart failure.
- Have trouble with your adrenal, pituitary or thyroid glands. Your healthcare provider may

decide to alter your insulin dose.
- Suffer from diarrhea, vomiting or eat less then usual. You may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Have kidney or liver problems. You may need to check your blood sugar level more often and talk to your healthcare provider about changes in your dose.
- Are pregnant or planning a pregnancy or are breastfeeding.
- Are planning to travel over time zones. Travelling over time zones may affect your insulin needs and the timing of your injections.

Other warnings you should know about:
Do not share your Lyumjev with other people, even if the needle is changed. You may give other people a serious infection or get a serious infection from them.

Know the type and strength of insulin you take. Do not change the type or amount of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

Swelling around your joints – When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

Low blood sugar (hypoglycemia) may occur earlier after an injection/infusion of Lyumjev compared to other mealtime insulins due to the earlier onset of action of Lyumjev.

Eye disorder - Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder.

Never drive or use machinery if you feel a low blood sugar (hypoglycemic) reaction coming on. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery).

High Blood Sugar (Hyperglycemia) and Ketoacidosis
You have hyperglycemia if your blood sugar gets too high.
This might happen:
- If you forget to take or stop taking insulin.
- If you keep taking less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.
- If you drink alcohol.
- If you get an infection or fever.

The warning signs appear gradually. They include: increased urination, feeling thirsty, losing your appetite, feeling sick (nausea or vomiting), feeling drowsy or tired, flushed dry skin, a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis (a condition with too much acid in the blood). If you don't treat it, this could lead to diabetic coma and death.

What to do if you get any of these signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice right away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Lyumjev:

Insulin requirements may be reduced if you take any of the medicines below:

- Other medicines for the treatment of diabetes
- Medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide
- Fibrates (medicine used for lowering high levels of blood fats)
- Monoamine oxidase inhibitors (MAOI) (medicines used to treat depression)
- Medicines used to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates
- Sulfonamide antibiotics (medicines used to treat infections)
- Somatostatin analogs, such as octreotide
- Fluoxetine

Insulin requirements may be increased if you take any of the medicines below:

- Atypical antipsychotics (e.g. olanzapine and clozapine)
- Hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), growth hormone, thyroid hormones, glucagon
- Corticosteroids (used to treat inflammation)
- Danazol (medicine acting on ovulation)
- Protease inhibitors (used to treat HIV infection)
- Diuretics (also called water pills), used to treat high blood pressure or fluid retention
- Isoniazid (used to treat tuberculosis)
- Some medicines used to treat asthma, such as albuterol, epinephrine, terbutaline
- Niacin and phenothiazines

Insulin requirements may increase or decrease if you take any of the medicines below:

- High blood pressure medicines, such as: beta-blockers or clonidine
- Some medicines used to treat mental health problems, such as: lithium salts
- Alcohol (including wine and beer)
- A medicine used to treat some parasitic infections, called pentamidine. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Some medicines may make it harder to recognize the warning signs of your blood sugar being too low (hypoglycemia). Such medicines include: beta-blockers medicines, clonidine, guanethidine, or reserpine.

How to take Lyumjev:

Check your insulin label each time you give your injection to make sure you are using the correct insulin.

Inspect Lyumjev visually before use. Only use Lyumjev if the solution appears clear and colourless. **Do not** use Lyumjev if it is thick, cloudy, or coloured, or if you see lumps or particles in it.

Do not use Lyumjev past the expiration date printed on the label or 28 days after you first start using a new vial, cartridge or KwikPen.

Lyumjev 100 units/mL and Lyumjev 200 units/mL can be injected under the skin (subcutaneous) of your stomach area, buttock, upper legs, or upper arms.

Lyumjev 100 units/mL is also for use in continuous infusion pumps.

Lyumjev 100 units/mL may also be given in your vein (intravenously) by your healthcare provider.

Change (rotate) your injection sites within the area you choose with each dose to reduce your risk of getting pits in your skin or thickened skin (lipodystrophy) and skin with lumps (localized cutaneous amyloidosis) at the injection sites.

- **Do not** use the exact same spot for each injection.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar level.

Lyumjev starts acting fast. Inject Lyumjev at the beginning of a meal or within 20 minutes after you start eating a meal. A maximum effect occurs between 1 and 3 hours after injection. The duration of action of Lyumjev is between 3 and 5 hours.

How to inject Lyumjev 100 units/mL using a vial

- Use a syringe marked for U100 insulin.
- Wash your hands with soap and water.
- Check the Lyumjev label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- Always use a new syringe and needle for each injection to prevent infections and blocked needles.
- If you are using a new vial, pull off the plastic protective cap, but do not remove the rubber stopper.
- Wipe the rubber stopper with an alcohol swab.
- Remove the cover from the needle. Draw air into the syringe equal to the amount of your insulin dose.
- Put the needle through the rubber stopper of the Lyumjev vial and inject the air into the vial.
- Turn the vial and syringe upside down and slowly pull the plunger down until the plunger tip is a few units past the line for your dose.
- If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top.
- Slowly push the plunger up until the plunger tip reaches the line for your prescribed dose.

Check the syringe to make sure that you have the right dose.
- Pull the syringe out of the rubber stopper of the vial.
- Inject the insulin under the skin. Use the injection technique advised by healthcare provider. Push the plunger in as far as it will go.
- Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not** rub the area.
- Discard needle and disposable plastic syringe after each injection, in a closable, puncture resistant sharps container.

How to use Lyumjev 100 units/mL in an insulin infusion pump system
Follow the instructions from the pump manufacturer and recommendations from your healthcare provider regarding the use of Lyumjev in a pump. Before using Lyumjev in the pump system, you must have received a comprehensive instruction in the use and information about any actions to be taken in case of illness, too high or too low blood sugar or failure of the pump system. Your healthcare provider should provide recommendations for appropriate pump basal rates and bolus settings.

Filling the pump using a Lyumjev vial:
- Lyumjev should never be diluted or mixed with any other insulin.
- Before inserting the needle, use soap and water to clean your hands and the skin where the needle is inserted to avoid any infection at the infusion site.
- When you fill a new reservoir, do not leave large air bubbles in either the syringe or the tubing.
- Changing of the infusion set (tubing and needle) must be done according to the instructions in the product information supplied with the infusion set.

To get the benefit of insulin infusion, and to detect possible malfunction of the insulin infusion pump, it is recommended that you measure your blood sugar level regularly.

What to do if the pump system fails
You should always have an alternative delivery method for your insulin available for injection under the skin (for example, needles and syringes) in case the pump system fails.

How to use a Lyumjev 100 units/mL cartridge
Lyumjev cartridges are for use in reusable insulin pen injectors. Follow the Instructions for Use that comes with the pen injector. **Do not** use Lyumjev cartridges if they are cracked or broken.

How to use a prefilled Lyumjev KwikPen or a prefilled Lyumjev Tempo Pen
Lyumjev KwikPens (100 units/mL or 200 unit/mL) and Lyumjev Tempo Pen (100 units/mL) are prefilled with insulin. Follow the Instructions for Use that comes with the KwikPen or Tempo Pen.

Usual dose:
Your healthcare provider will tell you how much Lyumjev to take and when to take it. Take Lyumjev exactly as your healthcare provider tells you to.

Overdose:
Excess insulin may cause low blood sugar (hypoglycemia)
You get hypoglycemia if your blood sugar gets too low. This might happen if you:
- Take too much insulin.

- Eat too little or miss a meal.
- Exercise more than usual.

The warning signs of hypoglycemia may come on suddenly and can include: cold sweat, cool pale skin, headache, slurred speech, fast heartbeat, feeling sick, feeling very hungry, temporary changes in vision, drowsiness, unusual tiredness and weakness, nervousness or tremor, feeling anxious, feeling confused, and difficulty concentrating.

If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.

If you have hypoglycemia that makes you pass out, or if you frequently get hypoglycemia, talk to your healthcare provider. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

Treating hypoglycemia
Mild to moderate hypoglycemia may be treated by eating foods or drinking beverages that contain sugar. Adjustments in drug dosage, meal patterns, or exercise may be needed.

What others need to do in case you pass out:
Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away and give you glucagon if available. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness by taking glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Call for medical help right away after being given glucagon. You need to find the reason for your severe hypoglycemia in order to avoid another episode.

If you think you have taken too much Lyumjev, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Causes of low potassium (hypokalemia)
If you take too much insulin, particularly when given intravenously, it might cause hypokalemia (low potassium). Hypokalemia must be corrected appropriately.

Missed dose:
If you miss a dose of Lyumjev, monitor your blood sugar levels to decide if an insulin dose is needed. Continue with your regular dosing schedule at the next meal.

What are possible side effects from using Lyumjev?
These are not all the possible side effects you may experience when taking Lyumjev. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects may be observed while taking Lyumjev:
Very common (more than 1 out of 10 patients)

Low Blood Sugar [See section '*Excess insulin may cause low blood sugar (hypoglycemia)*']

Common (less than 1 out of 10 patients)

Reaction at administration site

Allergic reactions

Uncommon

Changes under the skin where you give injections (lipodystrophy)

Rash

Itchy skin

Reaction at the administration site

Local reactions at the place you inject/infuse Lyumjev may occur. The signs may include: pain, rash, redness, inflammation, bruising and itching. The reactions usually disappear after a few days.

Allergic reactions

If you have a serious allergic reaction to the insulin or any of the ingredients in Lyumjev, stop using Lyumjev and see a doctor right away. The signs of a serious allergic reaction may include:

- A rash over your whole body
- Trouble breathing
- A fast heartbeat
- Swelling of your face, tongue, or throat
- Sweating
- Feeling faint

Changes under the skin where you give injections (lipodystrophy)

Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your healthcare provider. If you keep injecting in the same place, these changes can become more severe and affect the amount of medicine your body gets. Tell your healthcare provider if you notice any skin changes at the injection site. Tell your healthcare provider if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare provider may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Skin reactions:

Signs of skin allergy such as rash and itching may occur.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Hypoglycemia	✓		
COMMON Allergic reaction			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Refrigerate unopened Lyumjev vials, pens, and cartridges between 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 30°C after 28 days.

Do not use Lyumjev after the expiry date which is stated on the label and carton.

Keep out of reach and sight of children.

When used in an insulin infusion pump system:
Lyumjev 100 units/mL inside of the pump reservoir should be replaced:
- At least every 9 days, or according to the pump user manual, whichever is shorter, or
- After being exposed to temperatures above 37°C

If you use Lyumjev in an insulin pump, change the infusion set and the infusion set insertion site according to the pump manufacturer's user manual.

If you want more information about Lyumjev:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.
- Instructions for Use can be found on www.lilly.ca.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

Lyumjev, KwikPen and Tempo Pen are trademarks owned by or licensed to Eli Lilly and Company, its subsidiaries or affiliates.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

This leaflet was prepared by Eli Lilly Canada Inc.

Last Revised September 14, 2021

A4-LUM-0000-CA-PMI-YYYYMMDD

Instructions for Use

LYUMJEV™ KwikPen® (LOOM-jehv)

insulin lispro injection

for subcutaneous use

3 mL pen

100 units/mL

www.lilly.ca

Read the Instructions for Use before you start taking Lyumjev and each time you get another Lyumjev KwikPen (Pen). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

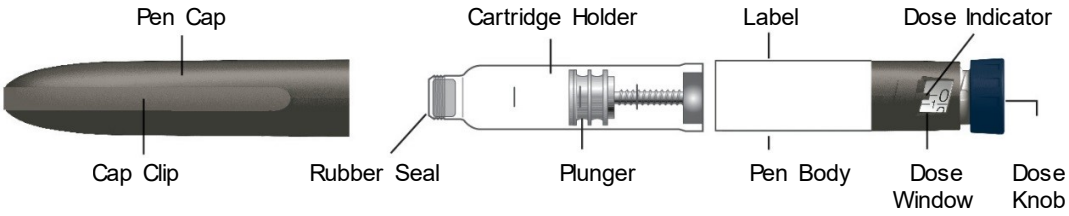
The Pen is for single patient use only. Do not share your Lyumjev KwikPen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.

Lyumjev KwikPen is a disposable prefilled pen containing 300 units of Lyumjev.

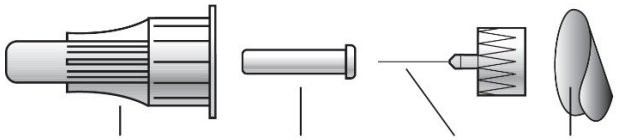
- Your healthcare provider will tell you how many units to give as your dose and how to inject your prescribed dose of insulin.
- You can give yourself more than 1 dose from the Pen.
- Each turn of the dose knob dials 1 unit of insulin. You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give yourself more than 1 injection. Always check the number in the dose window to make sure you dialed the correct dose.
- The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 300 units in the Pen.

People who are blind or have vision problems should not use the Pen without help from a person trained to use the Pen.

Lyumjev KwikPen Parts



Pen Needle Parts
(Needles Not Included)



Dose Knob

How to recognize your Lyumjev KwikPen

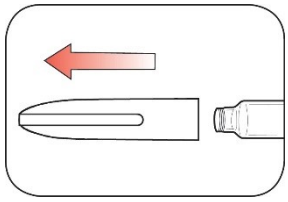
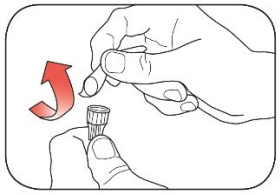
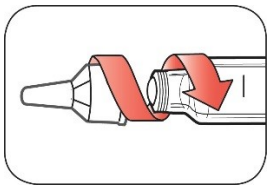
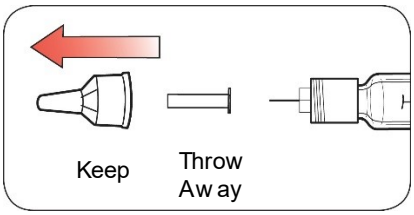
- Pen colour: Taupe
- Dose Knob: Blue, with raised ridges on side
- Label: Blue and white

Supplies needed to give your injection

- Lyumjev KwikPen, [100 units/mL]
- KwikPen compatible needle (BD [Becton, Dickinson and Company] Pen needles recommended)
- Alcohol swab
- Gauze (optional)

Preparing your Pen

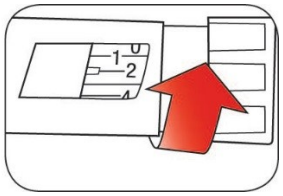
- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the label or for more than 28 days after you first start using the Pen.
- Always use a **new needle** for each injection to help prevent infections and blocked needles.

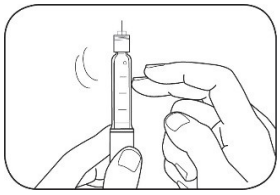
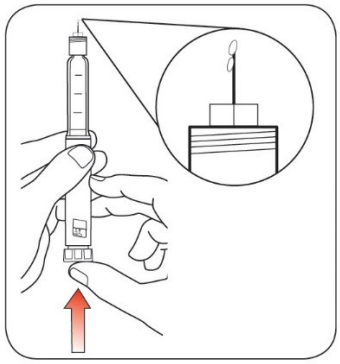
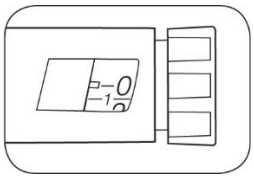
Step 1: • Pull the Pen cap straight off. – **Do not** remove the Pen label. • Wipe the rubber seal with an alcohol swab.	
Step 2: • Check the liquid in the Pen. • Lyumjev should look clear and colourless. **Do not** use if it is cloudy, coloured, or has particles or clumps in it.	
Step 3: • Select a new needle. • Pull off the paper tab from the outer needle shield.	
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight.	
Step 5: • Pull off the outer needle shield. **Do not** throw it away. • Pull off the inner needle shield and throw it away.	

Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the needle and cartridge that may collect during normal use and ensures that your Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6: • To prime your Pen, turn the dose knob to select 2 units.	

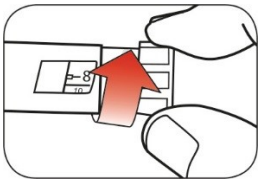
Step 7: • Hold your Pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top.	
Step 8: • Continue holding your Pen with the needle pointing up. Push the dose knob in until it stops and "**0**" is seen in the dose window. Hold the dose knob in and **count to 5 slowly**. You should see insulin at the tip of the needle. – If you **do not** see insulin, repeat priming steps 6 to 8, but not more than 4 times. – If you **still do not** see insulin, change the needle and repeat priming steps 6 to 8. Small air bubbles are normal and will not affect your dose.	 

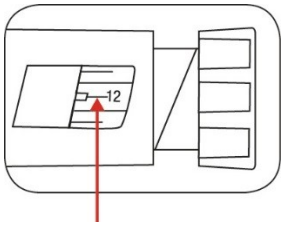
Selecting your dose

- You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give more than 1 injection.
  - If you need help with dividing up your dose the right way, ask your healthcare provider.
  - Use a new needle for each injection and repeat the priming steps.

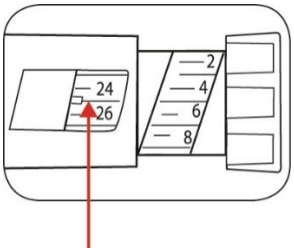
Step 9:

- Turn the dose knob to select the number of units you need to inject. The dose indicator should line up with your dose.
  - The Pen dials 1 unit at a time.
  - The dose knob clicks as you turn it.
  - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to getting too much insulin or not enough insulin.
  - The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the dose indicator.
  - The **even** numbers are printed on the dial. The example to the right shows 12 units.
  - The **odd** numbers, after the number 1, are shown as full lines between the numbers. The example to the right shows 25 units.
- **Always check the number in the dose window to make sure you have dialed the correct dose.**





Example: 12 units shown in the dose window



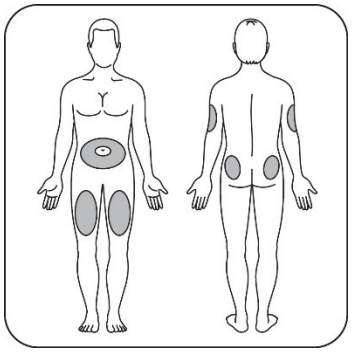
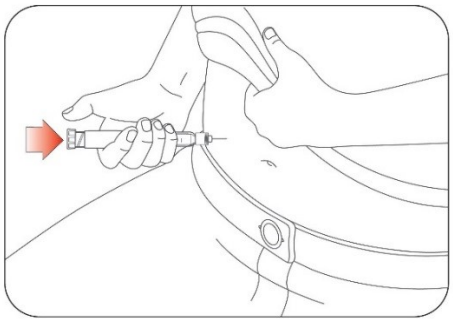
Example: 25 units shown in the dose window

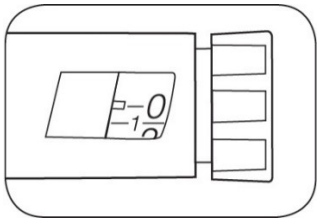
- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

  or
  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you cannot inject.

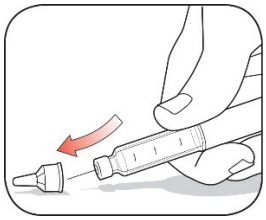
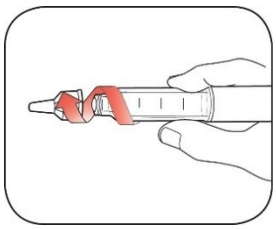
Giving your injection

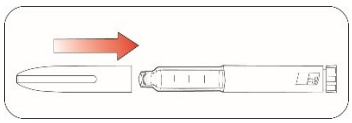
- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 10: • Choose your injection site. Lyumjev is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. • Prepare the injection site as directed by your healthcare professional.	
Step 11: • Insert the needle into your skin. • Push the dose knob all the way in. • Continue to hold the dose knob in and **slowly count to 5** before removing the needle.  **Do not** try to inject your insulin by turning the dose knob. You will **not** receive your insulin by turning the dose knob.	

Step 12: • Pull the needle out of your skin. – A drop of insulin at the needle tip is normal. It will not affect your dose. • Check the number in the dose window. – If you see “0” in the dose window, you have received the full amount you dialed. – If you do not see “0” in the dose window, you did not receive your full dose. **Do not** redial. Insert the needle into your skin and finish your injection. – If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat that injection**. Monitor your blood glucose as instructed by your healthcare provider. – If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 13: • Carefully replace the outer needle shield.	
Step 14: • Unscrew the capped needle and dispose of it as described below (see **Disposing of Pens and needles** section). • **Do not** store the Pen with the needle attached to prevent leaking, blocking the needle, and air from entering the Pen.	

Step 15: • Replace the Pen cap by lining up the cap clip with the dose indicator and pushing straight on.	

Disposing of Pens and needles

- Put used needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw needles directly into your household trash.
- Dispose of the used Pen as instructed by your healthcare professional after you have removed the needle.
- **Do not** recycle the filled sharps container.
- Ask your healthcare provider about options to dispose of the sharps container properly. You can also check the Diabetes Canada website at www.diabetes.ca for information on sharps disposal.
- The directions regarding needle handling are not intended to replace local, healthcare provider or institutional policies.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze Lyumjev. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature up to 30°C. Keep away from heat and light.
- Throw away the Lyumjev KwikPen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob more slowly will make it easier to inject.
  - your needle may be blocked. Put on a new needle and prime the Pen.
  - you may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your Lyumjev KwikPen, contact Lilly at 1-888-545-5972 or call your healthcare provider for help. For more information on Lyumjev KwikPen and insulin, go to www.lilly.ca.

Distributed by:
Eli Lilly Canada Inc.
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Manufactured by:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

LYUMJEV KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1.

The information in this document is current as of the revision date shown below. For the most current information please visit our website at www.lilly.ca or contact us directly at 1-888-545-5972.

Document Revision Date: September 14, 2021

A1-LUMKP-CA-IFU-0000-YYYYMMDD

Instructions for Use

LYUMJEV™ Junior KwikPen® (LOOM-jehv)

insulin lispro injection

for subcutaneous use

3 mL pen

100 units/mL

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www.lilly.ca

Read the Instructions for Use before you start taking Lyumjev and each time you get another Lyumjev Junior KwikPen (Pen). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

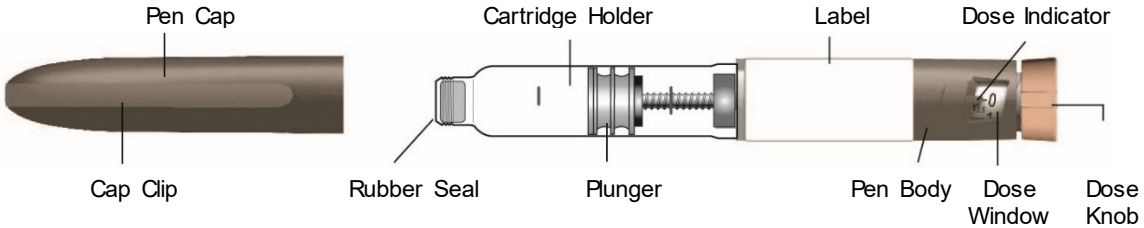
The Pen is for single patient use only. Do not share your Lyumjev Junior KwikPen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.

Lyumjev Junior KwikPen is a disposable prefilled pen containing 300 units of Lyumjev.

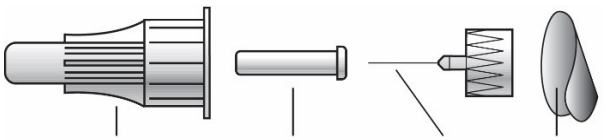
- Your healthcare provider will tell you how many units to give as your dose and how to inject your prescribed dose of insulin.
- You can give yourself more than 1 dose from the Pen.
- Each turn of the dose knob dials 0.5 (½) unit of insulin. You can give from 0.5 (½) unit to 30 units in a single injection.
- If your dose is more than 30 units, you will need to give yourself more than 1 injection. Always check the number in the dose window to make sure you dialed the correct dose.
- The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 300 units in the Pen.

People who are blind or have vision problems should not use the Pen without help from a person trained to use the Pen.

Lyumjev Junior KwikPen Parts



Pen Needle Parts
(Needles Not Included)



Outer Needle Shield | Inner Needle Shield | Needle | Paper Tab

Dose Knob

How to recognize your Lyumjev Junior KwikPen

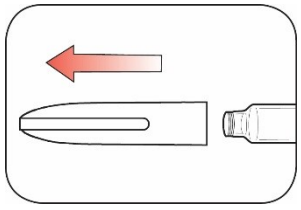
- Pen colour: Taupe
- Dose knob: Peach, with raised ridges on end and side
- Label: White with a peach colour bar, and peach, light blue and dark blue colour band

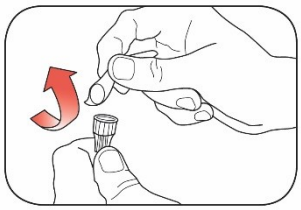
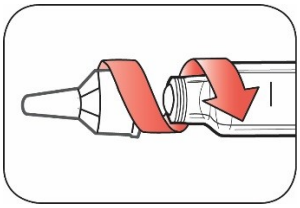
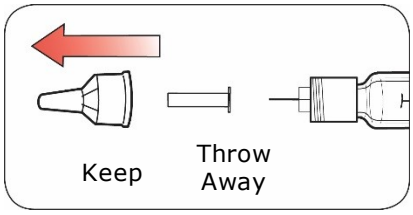
Supplies needed to give your injection

- Lyumjev Junior KwikPen, [100 units/mL]
- KwikPen compatible needle (BD [Becton, Dickinson and Company] Pen needles recommended)
- Alcohol swab
- Gauze (optional)

Preparing your Pen

- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the label or for more than 28 days after you first start using the Pen.
- Always use a **new needle** for each injection to help prevent infections and blocked needles.

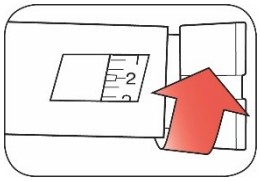
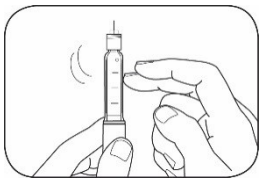
Step 1: • Pull the Pen cap straight off. – **Do not** remove the Pen label. • Wipe the rubber seal with an alcohol swab.	
Step 2: • Check the liquid in the Pen. • Lyumjev should look clear and colourless. **Do not** use if it is cloudy, coloured, or has particles or clumps in it.	

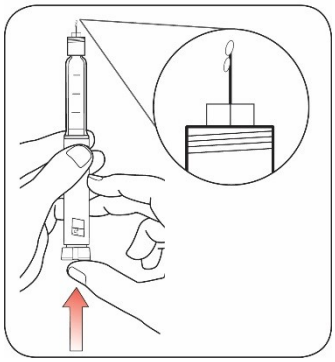
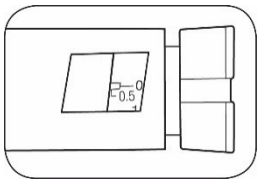
Step 3: • Select a new needle. • Pull off the paper tab from the outer needle shield.	
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight.	
Step 5: • Pull off the outer needle shield. **Do not** throw it away. • Pull off the inner needle shield and throw it away.	

Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the needle and cartridge that may collect during normal use and ensures that your Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6: • To prime your Pen, turn the dose knob to select 2 units.	
Step 7: • Hold your Pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top.	

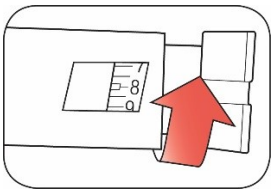
Step 8: • Continue holding your Pen with the needle pointing up. Push the dose knob in until it stops and "**0**" is seen in the dose window. Hold the dose knob in and **count to 5 slowly**. You should see insulin at the tip of the needle. – If you **do not** see insulin, repeat priming steps 6 to 8, but not more than 4 times. – If you **still do not** see insulin, change the needle and repeat priming steps 6 to 8. Small air bubbles are normal and will not affect your dose.	 

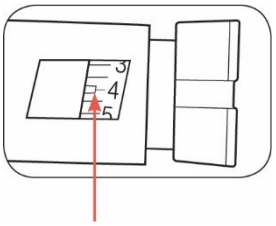
Selecting your dose

- You can give from 0.5 (½) to 30 units in a single injection.
- If your dose is more than 30 units, you will need to give more than 1 injection.
  - If you need help with dividing up your dose the right way, ask your healthcare provider.
  - Use a new needle for each injection and repeat the priming steps.
  - If you usually need more than 30 units, ask your healthcare provider if a different Lyumjev KwikPen would be better for you.

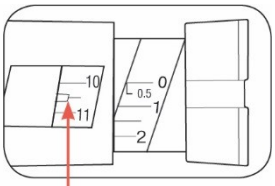
Step 9:

- Turn the dose knob to select the number of units you need to inject. The dose indicator should line up with your dose.
  - The Pen dials 0.5 (½) unit at a time.
  - The dose knob clicks as you turn it.
  - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to getting too much insulin or not enough insulin.
  - The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the dose indicator.
  - The **whole unit** numbers are printed on the dial. The example to the right shows 4 units.
  - The **half units** are shown as lines between the whole unit numbers. The example to the right shows 10.5 units.
- **Always check the number in the dose window to make sure you have dialed the correct dose.**





Example: 4 units shown in the dose window



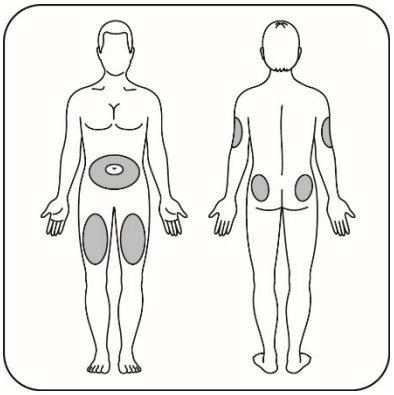
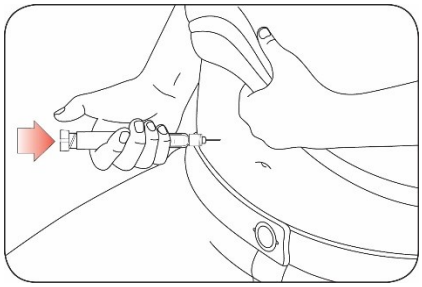
Example: 10 ½ (10.5) units shown in the dose window

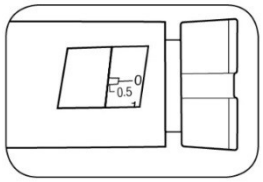
- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

  or
  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you cannot inject.

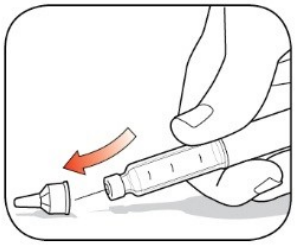
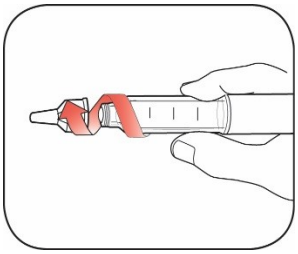
Giving your injection

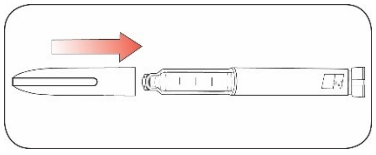
- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 10: • Choose your injection site. Lyumjev is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. • Prepare the injection site as directed by your healthcare professional.	
Step 11: • Insert the needle into your skin. • Push the dose knob all the way in. • Continue to hold the dose knob in and **slowly count to 5** before removing the needle.  **Do not** try to inject your insulin by turning the dose knob. You will **not** receive your insulin by turning the dose knob.	

Step 12: • Pull the needle out of your skin. – A drop of insulin at the needle tip is normal. It will not affect your dose. • Check the number in the dose window. – If you see “0” in the dose window, you have received the full amount you dialed. – If you do not see “0” in the dose window, you did not receive your full dose. **Do not** redial. Insert the needle into your skin and finish your injection. – If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat that injection**. Monitor your blood glucose as instructed by your healthcare provider. – If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 13: • Carefully replace the outer needle shield.	
Step 14: • Unscrew the capped needle and dispose of it as described below (see **Disposing of Pens and needles** section). • **Do not** store the Pen with the needle attached to prevent leaking, blocking the needle, and air from entering the Pen.	

Step 15: • Replace the Pen cap by lining up the cap clip with the dose indicator and pushing straight on.	

Disposing of Pens and needles

- Put used needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw needles directly into your household trash.
- Dispose of the used Pen as instructed by your healthcare professional after you have removed the needle.
- **Do not** recycle the filled sharps container.
- Ask your healthcare provider about options to dispose of the sharps container properly. You can also check the Diabetes Canada website at www.diabetes.ca for information on sharps disposal.
- The directions regarding needle handling are not intended to replace local, healthcare provider or institutional policies.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze Lyumjev. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature up to 30°C. Keep away from heat and light.
- Throw away the Lyumjev Junior KwikPen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob more slowly will make it easier to inject.
  - your needle may be blocked. Put on a new needle and prime the Pen.
  - you may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your Lyumjev Junior KwikPen, contact Lilly at 1-888-545-5972 or call your healthcare provider for help. For more information on Lyumjev Junior KwikPen and insulin, go to www.lilly.ca.

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Manufactured by:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

LYUMJEV Junior KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1.

The information in this document is current as of the revision date shown below. For the most current information please visit our website at www.lilly.ca or contact us directly at 1-888-545-5972.

Document Revision Date: September 14, 2021

A1-LUMKPJR-CA-IFU-0000-YYYYMMDD

Instructions for Use

LYUMJEV™ Tempo Pen™ (LOOM-jehv)

insulin lispro injection

for subcutaneous use

3 mL pen

100 units/mL

www.lilly.ca

Read the Instructions for Use before you start taking Lyumjev and each time you get another Lyumjev Tempo Pen (Pen). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

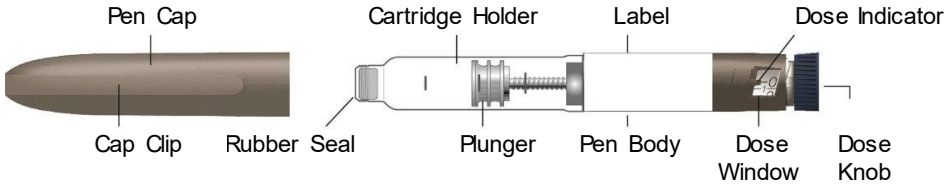
The Pen is for single patient use only. Do not share your Lyumjev Tempo Pen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.

Lyumjev Tempo Pen is a disposable prefilled pen containing 300 units of Lyumjev.

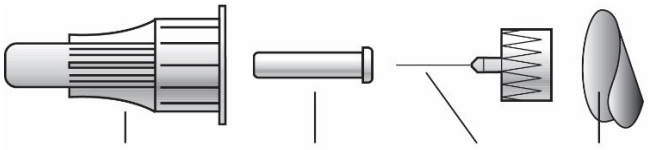
- Your healthcare provider will tell you how many units to give as your dose and how to inject your prescribed dose of insulin.
- You can give yourself more than 1 dose from the Pen.
- Each turn of the dose knob dials 1 unit of insulin. You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give yourself more than 1 injection. Always check the number in the dose window to make sure you dialed the correct dose.
- The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 300 units in the Pen.
- This Tempo Pen contains a magnet that may interfere with the function of an implantable electronic medical device, such as a pacemaker, if placed in close proximity to the implanted medical device. For more information, consult your healthcare provider, refer to your implantable electronic medical device manufacturer or contact Lilly at 1-888-545-5972.

People who are blind or have vision problems should not use the Pen without help from a person trained to use the Pen.

Lyumjev Tempo Pen Parts



Pen Needle Parts
(Needles Not Included)



Dose Knob

How to recognize your Lyumjev Tempo Pen

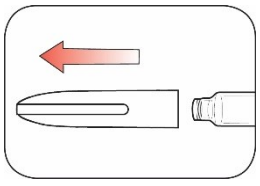
- Pen colour: Taupe
- Dose Knob: Blue, with raised ridges around the entire side
- Label: Blue and white

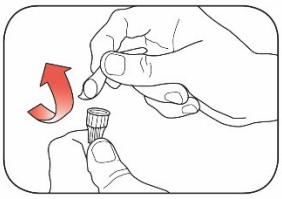
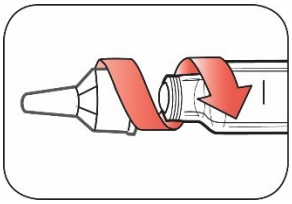
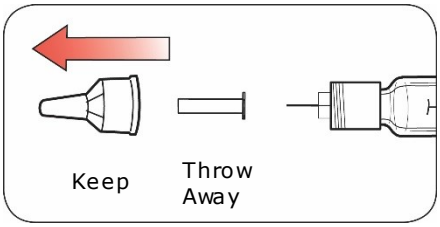
Supplies needed to give your injection

- Lyumjev Tempo Pen, [100 units/mL]
- Tempo Pen compatible needle (BD [Becton, Dickinson and Company] Pen needles recommended)
- Alcohol swab
- Gauze (optional)

Preparing your Pen

- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the label or for more than 28 days after you first start using the Pen.
- Always use a **new needle** for each injection to help prevent infections and blocked needles.

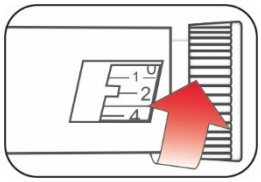
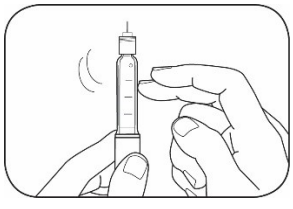
Step 1: • Pull the Pen cap straight off. – **Do not** remove the Pen label. • Wipe the rubber seal with an alcohol swab.	

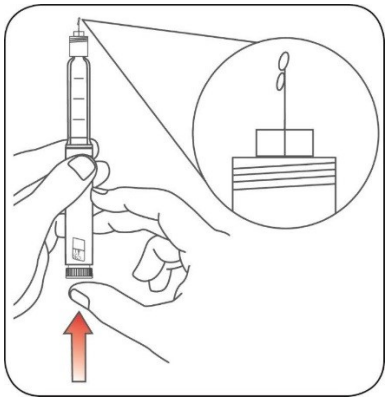
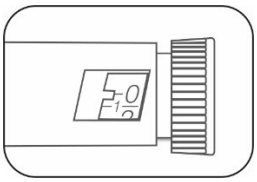
Step 2: • Check the liquid in the Pen. • Lyumjev should look clear and colourless. **Do not** use if it is cloudy, coloured, or has particles or clumps in it.	
Step 3: • Select a new needle. • Pull off the paper tab from the outer needle shield.	
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight.	
Step 5: • Pull off the outer needle shield. **Do not** throw it away. • Pull off the inner needle shield and throw it away.	

Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the needle and cartridge that may collect during normal use and ensures that your Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6: • To prime your Pen, turn the dose knob to select 2 units.	
Step 7: • Hold your Pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top.	

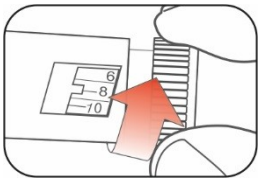
Step 8: • Continue holding your Pen with the needle pointing up. Push the dose knob in until it stops and "**0**" is seen in the dose window. Hold the dose knob in and **count to 5 slowly**. You should see insulin at the tip of the needle. – If you **do not** see insulin, repeat priming steps 6 to 8, but not more than 4 times. – If you **still do not** see insulin, change the needle and repeat priming steps 6 to 8. Small air bubbles are normal and will not affect your dose.	 

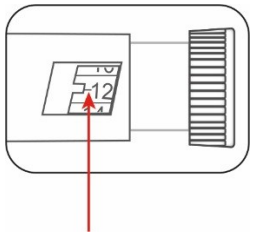
Selecting your dose

- You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give more than 1 injection.
  - If you need help with dividing up your dose the right way, ask your healthcare provider.
  - Use a new needle for each injection and repeat the priming steps.

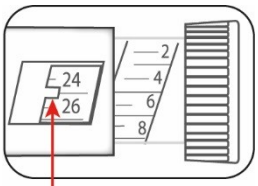
Step 9:

- Turn the dose knob to select the number of units you need to inject. The dose indicator should line up with your dose.
  - The Pen dials 1 unit at a time.
  - The dose knob clicks as you turn it.
  - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to getting too much insulin or not enough insulin.
  - The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the dose indicator.
  - The **even** numbers are printed on the dial. The example to the right shows 12 units.
  - The **odd** numbers, after the number 1, are shown as full lines between the numbers. The example to the right shows 25 units.
- **Always check the number in the dose window to make sure you have dialed the correct dose.**





Example: 12 units shown in the dose window



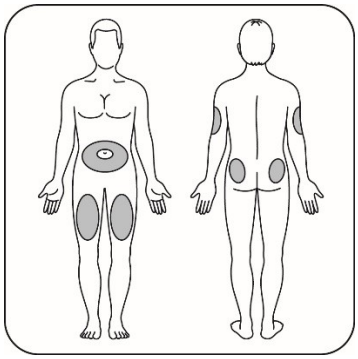
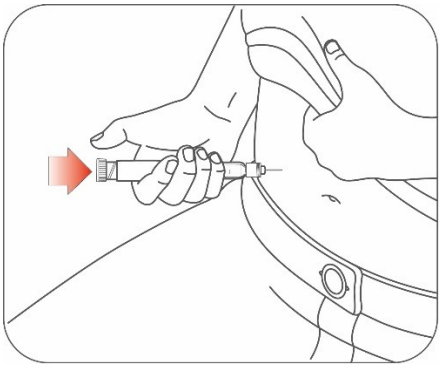
Example: 25 units shown in the dose window

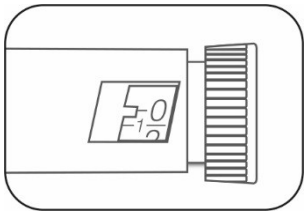
- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

  or
  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you cannot inject.

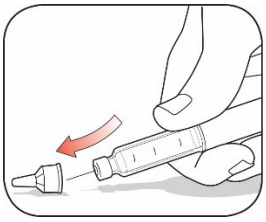
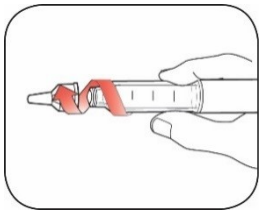
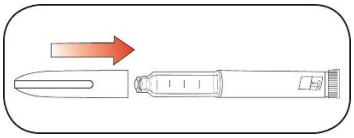
Giving your injection

- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 10: • Choose your injection site. Lyumjev is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. • Prepare the injection site as directed by your healthcare professional.	
Step 11: • Insert the needle into your skin. • Push the dose knob all the way in. • Continue to hold the dose knob in and **slowly count to 5** before removing the needle.  **Do not** try to inject your insulin by turning the dose knob. You will **not** receive your insulin by turning the dose knob.	

Step 12: • Pull the needle out of your skin. – A drop of insulin at the needle tip is normal. It will not affect your dose. • Check the number in the dose window. – If you see “0” in the dose window, you have received the full amount you dialed. – If you do not see “0” in the dose window, you did not receive your full dose. **Do not** redial. Insert the needle into your skin and finish your injection. – If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat that injection**. Monitor your blood glucose as instructed by your healthcare provider. – If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 13: • Carefully replace the outer needle shield.	
Step 14: • Unscrew the capped needle and dispose of it as described below (see **Disposing of Pens and needles** section). • **Do not** store the Pen with the needle attached to prevent leaking, blocking the needle, and air from entering the Pen.	
Step 15: • Replace the Pen cap by lining up the cap clip with the dose indicator and pushing straight on.	

Disposing of Pens and needles

- Put used needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw needles directly into your household trash.
- Dispose of the used Pen as instructed by your healthcare professional after you have removed the needle.
- **Do not** recycle the filled sharps container.
- Ask your healthcare provider about options to dispose of the sharps container properly. You can also check the Diabetes Canada website at www.diabetes.ca for information on sharps disposal.
- The directions regarding needle handling are not intended to replace local, healthcare provider or institutional policies.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze Lyumjev. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature up to 30°C. Keep away from heat and light.
- Throw away the Lyumjev Tempo Pen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob more slowly will make it easier to inject.
  - your needle may be blocked. Put on a new needle and prime the Pen.
  - you may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your Lyumjev Tempo Pen, contact Lilly at 1-888-545-5972 or call your healthcare provider for help. For more information on Lyumjev Tempo Pen and insulin, go to www.lilly.ca.

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LYUMJEV Tempo Pen meets the current dose accuracy and functional requirements of ISO 11608-1.

The information in this document is current as of the revision date shown below. For the most current information please visit our website at www.lilly.ca or contact us directly at 1-888-545-5972.

Document Revision Date: September 14, 2021

A1-LUMTP-CA-IFU-0000-YYYYMMDD

Instructions for Use

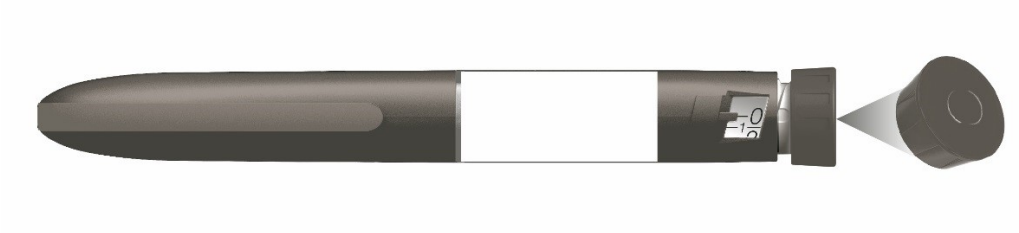
LYUMJEV™ KwikPen® (LOOM-jehv)

insulin lispro injection

for subcutaneous use

3 mL pen

200 units/mL



www.lilly.ca

Read the Instructions for Use before you start taking Lyumjev and each time you get another Lyumjev KwikPen (Pen). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The Pen is for single patient use only. Do not share your Lyumjev KwikPen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.

Lyumjev KwikPen is a disposable prefilled pen containing 600 units of Lyumjev.

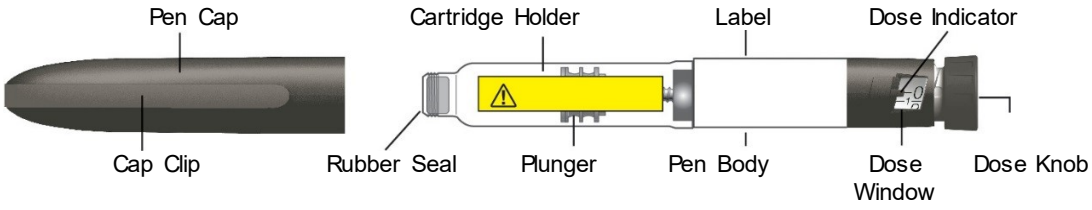
- Your healthcare provider will tell you how many units to give as your dose and how to inject your prescribed dose of insulin.
- You can give yourself more than 1 dose from the Pen.
- Each turn of the dose knob dials 1 unit of insulin. You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give yourself more than 1 injection. Always check the number in the dose window to make sure you dialed the correct dose.
- The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 600 units in the Pen.

This Pen is designed to allow you to give more doses than other pens you may have used in the past. Dial your usual dose as instructed by your healthcare provider.

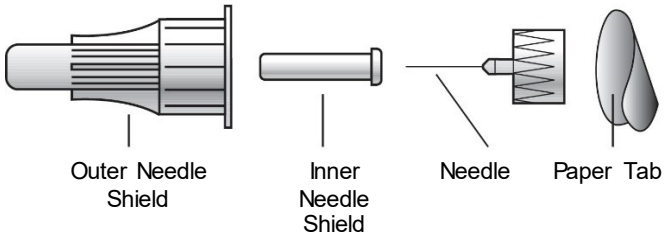
Lyumjev KwikPen is available in two strengths, 100 units/mL and 200 units/mL. Inject Lyumjev 200 units/mL only with your Pen. Do not transfer insulin from your Pen to a syringe. Syringes will not measure 200 units/mL of insulin correctly. A severe overdose can result, causing very low blood sugar which may put your life in danger.

People who are blind or have vision problems should not use the Pen without help from a person trained to use the Pen.

Lyumjev KwikPen Parts



Pen Needle Parts
(Needles Not Included)



Dose Knob

How to recognize your Lyumjev KwikPen

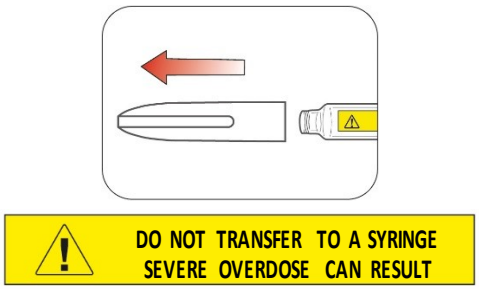
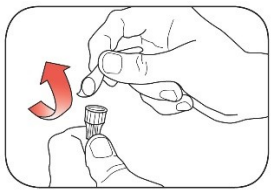
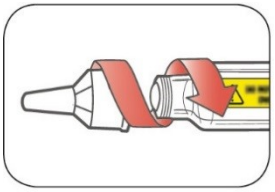
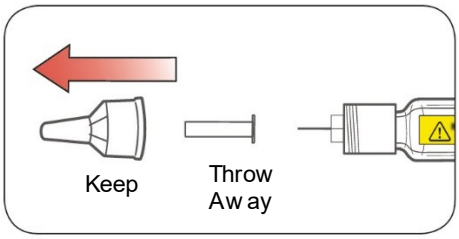
- Pen colour: Taupe
- Dose Knob: Taupe, with raised ridges on side
- Label: White with a blue colour bar and checkerboard design. Yellow warning on cartridge holder.

Supplies needed to give your injection

- Lyumjev KwikPen, [200 units/mL]
- KwikPen compatible needle (BD [Becton, Dickinson and Company] Pen needles recommended)
- Alcohol swab
- Gauze (optional)

Preparing your Pen

- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the label or for more than 28 days after you first start using the Pen.
- Always use a **new needle** for each injection to help prevent infections and blocked needles.

Step 1: • Pull the Pen cap straight off. – **Do not** remove the Pen label. • Wipe the rubber seal with an alcohol swab.	
Step 2: • Check the liquid in the Pen. • Lyumjev should look clear and colourless. **Do not** use if it is cloudy, coloured, or has particles or clumps in it.	
Step 3: • Select a new needle. • Pull off the paper tab from the outer needle shield.	
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight.	
Step 5: • Pull off the outer needle shield. **Do not** throw it away. • Pull off the inner needle shield and throw it away.	

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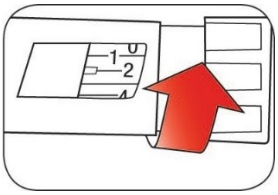
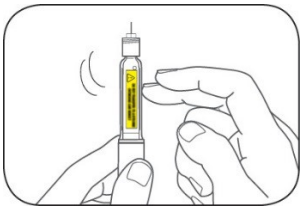
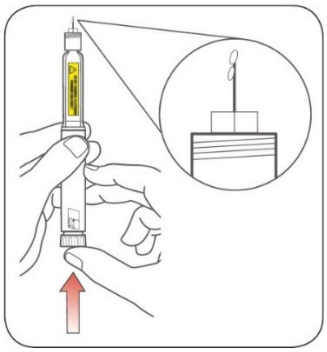
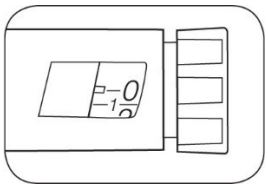
Prime before each injection.

- Priming your Pen means removing the air from the needle and cartridge that may collect during normal use and ensures that your Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 6: • To prime your Pen, turn the dose knob to select 2 units.	

Step 7: • Hold your Pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top.	
Step 8: • Continue holding your Pen with the needle pointing up. Push the dose knob in until it stops and "**0**" is seen in the dose window. Hold the dose knob in and **count to 5 slowly**. You should see insulin at the tip of the needle. – If you **do not** see insulin, repeat priming steps 6 to 8, but not more than 8 times. – If you **still do not** see insulin, change the needle and repeat priming steps 6 to 8. Small air bubbles are normal and will not affect your dose.	 

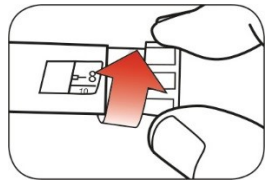
Selecting your dose

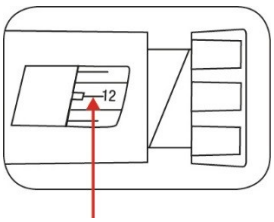
This Pen has been designed to deliver the dose that is shown in the dose window. Dial your usual dose as instructed by your healthcare provider.

- You can give from 1 to 60 units in a single injection.
- If your dose is more than 60 units, you will need to give more than 1 injection.
  - If you need help dividing up your dose the right way, ask your healthcare provider.
  - Use a new needle for each injection and repeat the priming steps.

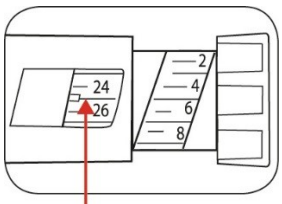
Step 9:

- Turn the dose knob to select the number of units you need to inject. The dose indicator should line up with your dose.
  - The Pen dials 1 unit at a time.
  - The dose knob clicks as you turn it.
  - **Do not** dial your dose by counting the clicks. You may dial the wrong dose. This may lead to getting too much insulin or not enough insulin.
  - The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the dose indicator.
  - The **even** numbers are printed on the dial. The example to the right shows 12 units.
  - The **odd** numbers, after the number 1, are shown as full lines between the numbers. The example to the right shows 25 units.
- **Always check the number in the dose window to make sure you have dialed the correct dose.**





Example: 12 units shown in the dose window



Example: 25 units shown in the dose window

- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

  or

  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you cannot inject. **Do not transfer this to a syringe. Severe overdose can result.**

Giving your injection

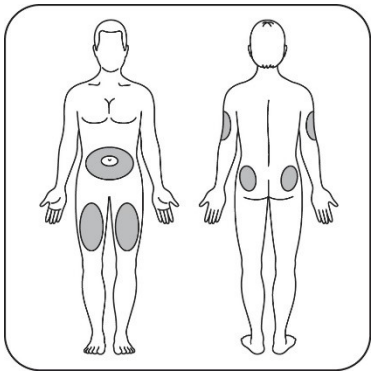
- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 10:

- Choose your injection site.

  Lyumjev is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.

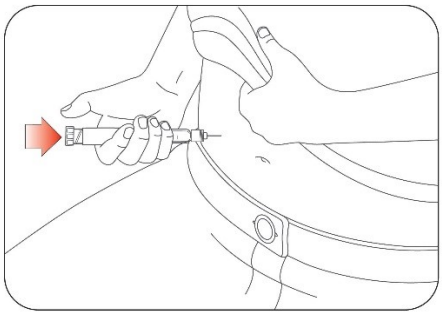
- Prepare the injection site as directed by your healthcare professional.

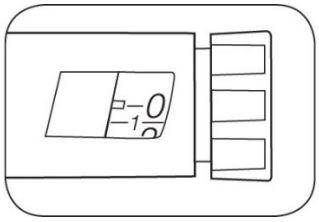


Step 11:

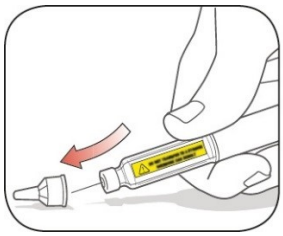
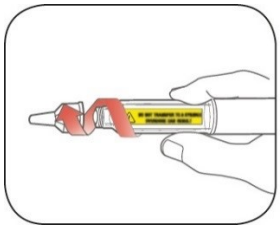
- Insert the needle into your skin.
- Push the dose knob all the way in.
- Continue to hold the dose knob in and **slowly count to 5** before removing the needle.

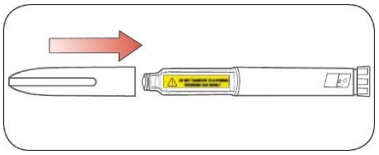
Do not try to inject your insulin by turning the dose knob. You will **not** receive your insulin by turning the dose knob.



Step 12: • Pull the needle out of your skin. – A drop of insulin at the needle tip is normal. It will not affect your dose. • Check the number in the dose window. – If you see “0” in the dose window, you have received the full amount you dialed. – If you do not see “0” in the dose window, you did not receive your full dose. **Do not** redial. Insert the needle into your skin and finish your injection. – If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat that injection**. Monitor your blood glucose as instructed by your healthcare provider. – If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 13: • Carefully replace the outer needle shield.	
Step 14: • Unscrew the capped needle and dispose of it as described below (see **Disposing of Pens and needles** section). • **Do not** store the Pen with the needle attached to prevent leaking, blocking the needle, and air from entering the Pen.	

Step 15: • Replace the Pen cap by lining up the cap clip with the dose indicator and pushing straight on.	

Disposing of Pens and needles

- Put used needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw needles directly into your household trash.
- Dispose of the used Pen as instructed by your healthcare professional after you have removed the needle.
- **Do not** recycle the filled sharps container.
- Ask your healthcare provider about options to dispose of the sharps container properly. You can also check the Diabetes Canada website at www.diabetes.ca for information on sharps disposal.
- The directions regarding needle handling are not intended to replace local, healthcare provider or institutional policies.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze Lyumjev. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature up to 30°C. Keep away from heat and light.
- Throw away the Lyumjev KwikPen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your Pen

- **Keep your Pen and needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob more slowly will make it easier to inject.
  - your needle may be blocked. Put on a new needle and prime the Pen.
  - you may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your Lyumjev KwikPen, contact Lilly at 1-888-545-5972 or call your healthcare provider for help. For more information on Lyumjev KwikPen and insulin, go to www.lilly.ca.

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LYUMJEV KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1.

The information in this document is current as of the revision date shown below. For the most current information please visit our website at www.lilly.ca or contact us directly at 1-888-545-5972.

Document Revision Date: September 14, 2021

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