PRODUCT MONOGRAPH

LIPRELOG™

(insulin lispro injection)
Solution for Injection, 100 units/mL, Lilly Standard

THERAPEUTIC CLASSIFICATION
Anti-Diabetic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Parenteral	Solution for Injection, 100 units/mL	**LIPRELOG (100 units/mL)**: Dibasic sodium phosphate, glycerol, hydrochloric acid, *m*-cresol distilled, sodium hydroxide and water for injection, zinc (as ion).

INDICATIONS AND CLINICAL USE

LIPRELOG (insulin lispro injection), is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. LIPRELOG insulin is also indicated for the initial stabilization of diabetes mellitus. LIPRELOG (insulin lispro injection) is a short acting insulin analogue and is for use in conjunction with a longer acting insulin, such as HUMULIN N (insulin isophane (rDNA origin) NPH), except when used in a subcutaneous insulin infusion pump.

CONTRAINDICATIONS

LIPRELOG (insulin lispro) is contraindicated during episodes of hypoglycemia (see SYMPTOMS AND TREATMENT OF OVERDOSAGE) and in patients sensitive to insulin lispro or any of the excipients they contain (for a complete list of excipients, see DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect associated with insulins, including LIPRELOG. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death (see OVERDOSAGE).
- Due to its quick onset of action, LIPRELOG (insulin lispro) should be given within 15 minutes before a meal.
- When necessary, LIPRELOG (insulin lispro injection) may be given shortly after a meal instead (within 20 minutes of the start of the meal).
- When used via a subcutaneous insulin infusion pump, LIPRELOG (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- Consumer Information before use.
- Any change of insulin or human insulin analogue should be made cautiously and only under medical supervision. Changes in purity, strength, brand (manufacturer), type (insulin lispro, regular, NPH, etc.), species (beef, pork, beef-pork, human), and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage (see DOSAGE AND ADMINISTRATION).
- LIPRELOG shall not be used if it is not water clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.

General

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

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulin therapies, including LIPRELOG. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhea).

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.

To avoid transmission of disease, a cartridge or prefilled syringe should not be used by more than one person.

LIPRELOG (insulin lispro injection) had a similar safety profile to HUMULIN R (insulin injection (rDNA origin) Regular) over the course of the clinical studies. LIPRELOG has been

shown to control glycosylated hemoglobin (HbA1c) levels as effectively as human insulin in comparator studies specifically designed to study meal time therapy without optimization of basal insulin regimens. Once a patient is using LIPRELOG, reassessment and adjustment, as necessary, of the basal insulin regimen (dosage and number of injections) has been shown to optimize overall glycemic control.

Any rapid- or short-acting insulin formulation should be used with caution in patients with gastroparesis. However, some patients with gastroparesis may benefit from postprandial administration of LIPRELOG, which has been shown to provide postprandial glycemic control similar to that provided by human insulin injected 30 minutes pre-prandially. Using the postprandial dosing approach, the insulin dose can be adjusted according to the actual caloric intake and/or the observed rise in blood glucose following a meal.

Insulin plus Thiazolidinediones (TZDs):

TZDs, alone or in combination with other antidiabetic 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 Warnings and Precautions information when the use of these drugs in combination with any insulin, including LIPRELOG, is contemplated.

Transferring Patients from Other Insulins:

Patients taking LIPRELOG may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may change or become less pronounced than those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g., regular, NPH, or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first few weeks or months and under medical supervision (see WARNINGS AND PRECAUTIONS).

Patients whose blood glucose is greatly improved, e.g., by intensified insulin therapy, may lose some or all of the warning symptoms of hyperglycemia and should be advised accordingly. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.

Carcinogenesis and Mutagenesis

Like human insulin, in one year animal studies insulin lispro did not produce proliferative effects or tumors in organs and tissues when given at very high subcutaneous doses in chronic toxicity tests. In animal studies, there is no evidence of insulin lispro induced fertility impairment.

Endocrine and Metabolism

Hypoglycemia:

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapy including LIPRELOG. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death (see ADVERSE REACTIONS).

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see OVERDOSAGE).

Hypoglycemic reactions following treatment with insulin products including LIPRELOG are mostly mild and easily managed.

Changes in insulin therapy or changes in life style (i.e. diet, exercise/physical activity) may require a change in dosage to avoid hypoglycemia. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Glucose monitoring is recommended for all patients with diabetes mellitus who are also taking LIPRELOG (see Monitoring and Laboratory Tests).

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) especially in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

Diabetic patients should be instructed to carry a few lumps of sugar, candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur (see Part III, CONSUMER INFORMATION).

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions or loss of consciousness. In extreme circumstances, even death can occur without recognizable symptoms. Some people may not recognize when their blood sugar drops low.

In certain cases (e.g., long duration of diabetes mellitus, diabetic nerve disease, intensified diabetes mellitus control, patients with psychiatric illness, elderly patients or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycemia (pallor, sweating, anxiety, headache, tachycardia, hunger) may change or be less pronounced.

Hyperglycemia:

Inadequate dosing or discontinuation of LIPRELOG, especially in type 1 diabetes mellitus, may lead to hyperglycemia and when untreated, hyperglycemic events may eventually lead to diabetic ketoacidosis or coma which are potentially fatal (see ADVERSE REACTIONS). Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include polydipsia; polyuria; nausea; abdominal pain, vomiting; drowsiness; blurred vision, flushed dry

skin; loss of appetite, weight loss as well as acetone odour of breath (see ADVERSE REACTIONS).

Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. This may constitute a risk in situations where these abilities are of special importance such as driving a car or operating machinery.

Hepatic/Biliary/Pancreatic

Although impaired hepatic function does not affect the absorption or disposition of LIPRELOG, careful glucose monitoring and dose adjustments of insulin, including LIPRELOG, may be necessary.

Immune

Local Allergic Reactions:

With insulin therapies including LIPRELOG, patients may experience redness, swelling, pain, inflammation, or itching at the site of injection (see ADVERSE REACTIONS).

Most of these minor reactions usually resolve in a few days to a few weeks. 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 CONTRAINDICATIONS).

Rarely, subcutaneous administration of insulin products, including LIPRELOG can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions.

Systemic Allergic Reactions:

Systemic allergic reactions have rarely occurred with insulin treatments, including LIPRELOG (see 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 ADVERSE REACTIONS).

Severe cases of generalized allergy including anaphylactic reaction may be life threatening (see CONTRAINDICATION).

Antibody Production:

Immune responses can occur with insulin products, including production of auto antibodies (IgG). In general, glycemic control is not affected by the presence of auto antibodies. Very rarely, auto antibodies may cause hyperglycemia (insulin resistance) or hypoglycemia (inappropriate release). Insulin antibodies are frequently cross-reactive. Patients who have demonstrated an allergic reaction to other insulin products may demonstrate an allergic reaction to LIPRELOG.

Renal

The requirements for insulin may be reduced in patients with renal impairment.

Reproduction Studies

There are no adequate and well-controlled studies with LIPRELOG during pregnancy and lactation (see TOXICOLOGY).

Information for Patients

Patients should be informed about potential advantages and disadvantages of LIPRELOG therapy, including possible side effects. Patients should also be offered continued education and advice on insulin therapies, delivery device options, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, and instruction for use of injection devices, storage of insulin, travelling and others (see PART III: CONSUMER INFORMATION).

Female patients with diabetes mellitus should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health is essential in pregnant patients with diabetes (see Special Populations and PART III: CONSUMER INFORMATION).

Special Populations

Pregnant Women

LIPRELOG can be used in pregnancy if clinically indicated. Data on a large number of exposed pregnancies do not indicate any adverse effect of LIPRELOG 100 units/mL on pregnancy or on the health of the foetus/newborn. It is essential to maintain good glucose control in both gestational diabetes and throughout pregnancy in type 1 and type 2 patients. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health is essential in pregnant patients with diabetes. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Women

The use of LIPRELOG in nursing mothers has not been studied. Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

Pediatrics (3 to 18 years of age)

Clinical trials have been performed in children (61 patients aged 3 to 11) and children and adolescents (481 patients aged 9 to 18 years), comparing LIPRELOG 100 units/mL to regular human insulin. LIPRELOG 100 units/mL showed better postprandial blood glucose control while maintaining a similar safety profile.

As in adults, LIPRELOG 100 units/mL should be given within 15 minutes before a meal. When necessary, LIPRELOG 100 units/mL may be given shortly after a meal instead (within 20 minutes of the start of the meal).

Geriatrics (> 65 years of age)

LIPRELOG may be used in elderly patients, if clinically indicated.

Information on the effect of age and gender on the pharmacokinetics of LIPRELOG is unavailable. However, in large clinical trials, sub-group analysis based on age and gender did not indicate any difference in postprandial glucose parameters between LIPRELOG 100 units/mL and regular human insulin.

In clinical studies of LIPRELOG 100 units/mL, glycosylated hemoglobin (HbA_{1c}) values and hypoglycemia rates in patients ≥ 65 years of age did not differ from younger 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.

Other Disease States

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

Monitoring and Laboratory Tests

Self-Monitoring of Blood Glucose

With insulin therapy, including LIPRELOG, the need for regular blood glucose self-monitoring should be considered to obtain optimal glycemic control (see PART III: CONSUMER INFORMATION). HbA_{1C} should be measured every 3 to 4 months in all patients taking insulin products.

ADVERSE REACTIONS

Body as a Whole – Allergic Reaction(s)

Local allergy in patients may occur as redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy to insulin is less common but potentially more serious. Generalized allergy to insulin may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse or sweating. Severe cases of generalized allergic reaction may be life-threatening.

Skin and Appendages – injection site reaction, lipodystrophy, pruritis, rash.

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions. A change in injection technique may help alleviate the problem.

Metabolic – Hypoglycemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycemia may lead to loss of consciousness and, in extreme cases, death.

Continuous Subcutaneous Insulin Infusion – LIPRELOG 100 units/mL

In a 39-week, randomized open-label, three way crossover, controlled multicenter study in patients with type 1 diabetes, the perceived catheter set occlusion rates were similar across rapid-acting insulin analog, including LIPRELOG, insulin aspart and insulin glulisine (Figure 1).

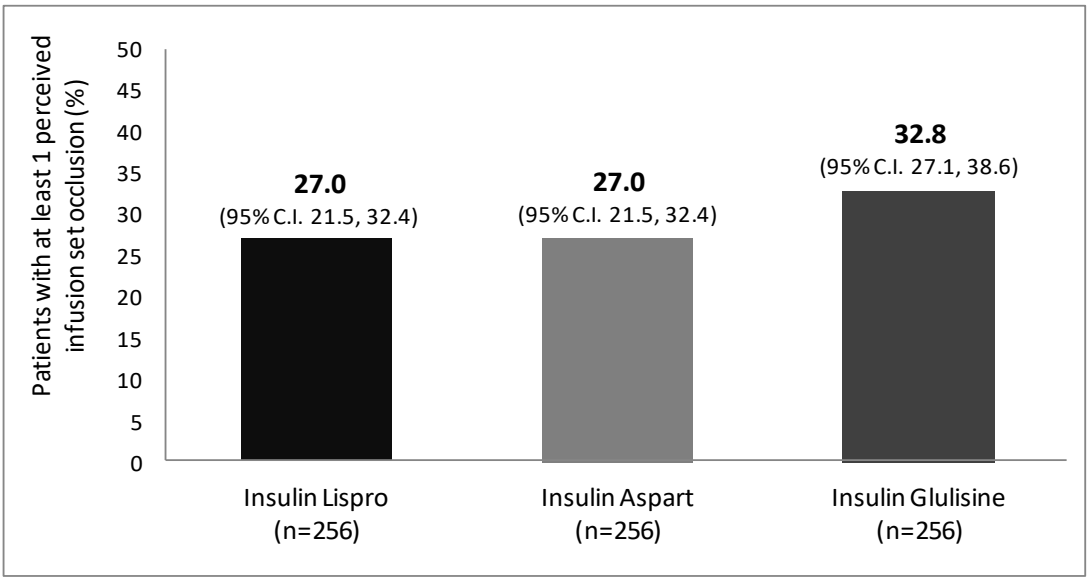


Figure 1. Patients (%) with at least 1 perceived set occlusion over 13 weeks.

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for LIPRELOG 100 units/mL and regular human insulin treated patients (Table 1).

Table 1. Rates of Catheter Occlusions and Infusion Site Reactions

	LIPRELOG 100 units/mL (n=38)	**Regular Human Insulin 100 units/mL** (n=39)
Number of catheter occlusion/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

Post-Market Adverse Drug Reactions

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

DRUG INTERACTIONS

Drug-Drug Interactions

Drug interactions with insulin formulations including LIPRELOG may include the following:

Insulin requirements may be decreased in the presence of agents such as oral hypoglycemic agents, octreotide, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), non-selective beta-adrenergic blockers, alcohol, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers and anabolic steroids.

Drugs that may increase insulin requirements such as oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics, and danazol. The hypoglycemic action of insulin may also be antagonized by diphenylhydantoin.

Hormones that tend to counteract the hypoglycemic effects of insulin include growth hormone, corticotropin, glucocorticoids, thyroid hormone, and glucagon. Epinephrine not only inhibits the secretion of insulin, but also stimulates glycogen breakdown to glucose. Thus, the presence of such diseases as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma complicate the control of diabetes.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see WARNINGS AND PRECAUTIONS).

The physician should be consulted when using other medications in addition to LIPRELOG.

Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia (see WARNINGS AND PRECAUTIONS, and OVERDOSAGE).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of LIPRELOG is determined by a physician in accordance with the requirements of the patient.

Although LIPRELOG has a quicker onset of action and shorter duration of activity, dosing is comparable to regular human insulin. The dosage of LIPRELOG, like all other insulin formulations, is dependent upon the individual patient requirements. The dose and number of insulin injections should be adjusted to maintain blood glucose concentrations as close to normal as possible.

Additional adjustment of dosage may be required in diabetes patients with renal impairment, during intercurrent illness and/or emotional disturbances.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet.

Recommended Dose and Dosage Adjustment

New Patients:

Patients receiving insulin for the first time can be started on LIPRELOG in the same manner as they would be on animal-source or human insulin.

Patients should be monitored closely during the adjustment period.

Transfer Patients:

When transferring patients to LIPRELOG, use the same dose and dosage schedule. However, some patients transferring to LIPRELOG may require a change in dosage from that used with their previous insulin. Analysis of a database of type 1 diabetic patients indicated that basal insulin requirements increased by 0.04 U/Kg, while LIPRELOG requirements decreased by 0.03 U/Kg, after one year of treatment. For type 2 diabetic patients, both short acting and basal insulin requirements increased slightly after one year of treatment with both LIPRELOG and HUMULIN R.

Optimizing Glycemic Control:

In order to achieve optimal glycemic control, changes in total daily dosage, the number of injections per day, and/or timing of injections may be necessary when using LIPRELOG.

Once a patient is using LIPRELOG, reassessment and adjustment as necessary of the basal insulin regimen (dosage and number of injections) has been shown to optimize overall glycemic control.

Administration

LIPRELOG is a clear, colourless solution. It is important to always examine the appearance of the vial or cartridge of LIPRELOG prior to administration. It should not be used if it is cloudy, unusually viscous or gelled, precipitated, or even slightly coloured; if there are clumps floating in the liquid, or if particles appear to be sticking to the sides or bottom of the vial or cartridge.

LIPRELOG 100 units/mL should be given by subcutaneous injection or by continuous subcutaneous insulin infusion pump and may, although not recommended, also be given by intramuscular injection. When administered by continuous subcutaneous infusion by an external insulin pump, the LIPRELOG in the reservoir should be changed at least every 14 days. Infusion sets should be changed according to pump manufacturer's instructions (typically 3 days is recommended) or as directed by healthcare professionals. It may also be administered intravenously under conditions where regular human insulin is given intravenously. When used as a meal-time insulin, LIPRELOG should be given within 15 minutes before a meal, or when necessary shortly after a meal instead (within 20 minutes of the start of the meal).

Subcutaneous administration, preferably by the patient, should be in the upper arms, thighs, buttocks or abdomen. When compared to HUMULIN R, LIPRELOG retains its more rapid onset and shorter duration of action irrespective of the subcutaneous injection site used. Therefore, injection sites can be rotated so that the same site is not used more than approximately once a month.

Care should be taken to ensure that a blood vessel has not been entered. The injection site should not be massaged.

Instructions for Use/Handling

To prevent the possible transmission of disease, never share a LIPRELOG pen or cartridge between patients, even if the needle on the delivery device is changed.

Mixing of Insulins:

Mixing LIPRELOG 100 units/mL with HUMULIN N does not decrease the absorption rate or the total bioavailability of LIPRELOG. Given alone or mixed with HUMULIN N, LIPRELOG results in a more rapid absorption and glucose-lowering effect compared with human regular insulin.

If LIPRELOG 100 units/mL is mixed with a longer-acting insulin, LIPRELOG 100 units/mL should be drawn into the syringe first to prevent clouding of the LIPRELOG 100 units/mL by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously. LIPRELOG 100 units/mL should not be diluted or mixed with any other insulin when used in a subcutaneous insulin infusion pump.

The effects of mixing LIPRELOG with either animal-source insulins or human insulin preparations produced by other manufacturers have not been studied. This practice is not recommended.

OVERDOSAGE

With the rapid onset of activity of LIPRELOG, it is important that the insulin analogue be given close to mealtime (within 15 minutes before a meal). When necessary, LIPRELOG may be given shortly after a meal instead (within 20 minutes of the start of the meal). A significant deviation could put the patient at risk of hypoglycemia.

Insulins have no specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycemia may occur as a result of an excess of insulin or LIPRELOG relative to food intake and energy expenditure or in patients who have an infection or become ill (especially with diarrhea or vomiting).

Hypoglycemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycemic episodes will respond to oral administration of glucose or sugar-containing foods.

Correction of moderately severe hypoglycemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Insulin lispro, the active pharmaceutical ingredient in LIPRELOG is created by inverting the natural Pro-Lys sequence in human insulin at positions 28 and 29 in the C terminal portion of the B-chain. This change in amino acid sequence slightly modifies the physicochemical properties of the molecule relative to native human insulin in such a manner that insulin lispro self-associates less avidly and dissociates into its monomeric form more rapidly than regular insulin. As a result, insulin lispro is absorbed more rapidly than regular soluble insulin from subcutaneous sites of injection and also has a shorter duration of action.

The reversed sequence of lysine and proline in insulin lispro, is identical to that on the B-chain of human IGF-1. The incidence of self-association with IGF-1 is known to be lower than observed with human insulin. Incorporating this IGF-1-like feature into the human insulin molecule markedly changes the physico-chemical behaviour of the resulting insulin lispro but does not

significantly alter its pharmacodynamic action because the terminal part of the B-chain does not participate in insulin's interaction with the insulin receptor. In vitro experiments showed that insulin lispro interacts with the insulin receptor much like regular human insulin does. Although binding to the IGF-1 receptor is higher than for regular human insulin (1.5 times more) it is significantly less than that of IGF-1 itself (more than a thousand times less) and does not promote cell growth in biological assays to any greater extent than human insulin.

The primary activity of insulins, including LIPRELOG, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis and promotes the conversion of excess glucose into fat.

Pharmacodynamics and Pharmacokinetics

LIPRELOG

LIPRELOG is absorbed more rapidly than regular soluble insulin from subcutaneous sites of injection and also has a shorter duration of action. Due to its quick onset of action, LIPRELOG should be given within 15 minutes before a meal. When necessary, LIPRELOG may be given shortly after a meal instead (within 20 minutes of the start of the meal).

Subcutaneously injected regular insulin typically results in serum insulin concentrations that peak later and remain elevated for a longer time than those following normal pancreatic insulin secretion in non-diabetics. When regular insulin is used to control postprandial blood glucose, adequate control is often not achieved because the amount of regular insulin needed to normalize postprandial glucose excursion often leads to late hypoglycemia. By producing more rapid and higher serum insulin concentrations with a shorter duration of activity (2-5 hours), LIPRELOG decreases glucose excursion during and after meals with less chance for hypoglycemia.

A glucose clamp study was performed, in healthy volunteers, in which a 10 Unit dose of LIPRELOG 100 units/mL was compared to HUMULIN R. Doses were given subcutaneously; an additional 10 Unit dose of intravenous regular insulin was given as an absolute reference.

LIPRELOG 100 units/mL showed statistically higher peak concentrations (C_{max}) which occurred earlier than observed with HUMULIN R (t_{max}). Total absorption was comparable, with area under the curve (AUC) values of serum concentration vs. time which were not statistically different (Tables 2, 3).

Table 2. Pharmacodynamics of LIPRELOG 100 units/mL Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Mean	LIPRELOG 100 units/mL	HUMULIN R 100 units/mL
Duration of action (hr)*	3.5-4.75 hr	5.0-7.5 hr
Onset of Action (hr)*	0.5-0.75 hr	0.5-1.0 hr
Time of Maximum Effect (hr)*	0.75-2.5 hr	0.75-4.5 hr

*Results predicted from a pharmacokinetic-pharmacodynamic link model

Table 3. Pharmacokinetics of LIPRELOG 100 units/mL Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Mean	LIPRELOG 100 units/mL	HUMULIN R 100 units/mL
t_{max} (min)	53 ± 30	101 ± 40
C_{max} (ng/mL)	3.20 ± 1.33	1.79 ± 0.77
AUC (ng•min/mL)	380 ± 52.2	423 ± 71.8

Subsequent pharmacokinetic studies in type 1 patients confirmed that a significantly faster increase in serum insulin levels and a shorter plasma half life resulted from an injection of LIPRELOG (insulin lispro injection) 100 units/mL when compared to HUMULIN R (Figure 2).

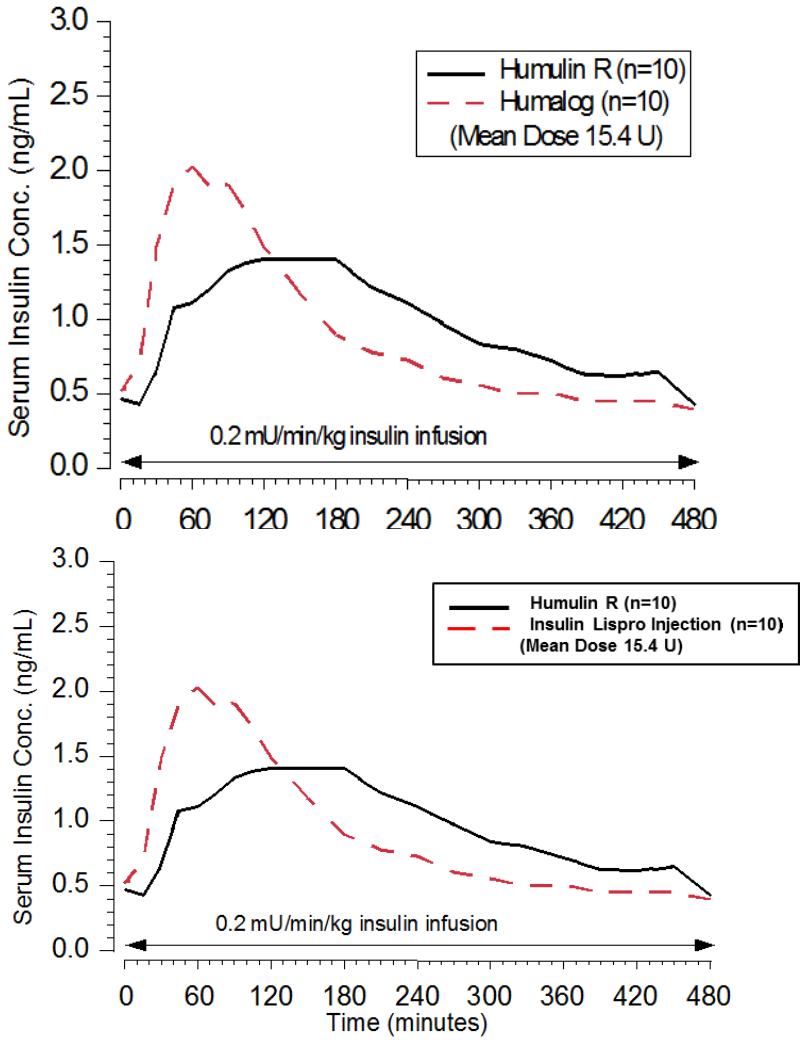


Figure 2. **Mean Serum Insulin Concentrations in type 1 Patients Following Injection of HUMULIN R and Insulin Lispro Injection 100 units/mL (Basal 0.2mU/min/kg insulin infusion).**

Postprandial and overall glycemic control: In clinical studies after one year, the decrease in glucose excursion during and after meals with LIPRELOG 100 units/mL was consistent, although not always significant, when compared to HUMULIN R. However, there was no significant difference in HbA_{1c} levels between the two treatment groups. These studies were specifically designed to study meal time therapy without optimization of basal insulin regimens.

Subsequent clinical studies have demonstrated that in an intensive insulin treatment regimen with basal insulin optimization, LIPRELOG 100 units/mL controls postprandial glucose and

contributes to lower HbA_{1c} levels to a greater degree than regular human insulin, without increasing the risk of hypoglycemia.

Hypoglycemia: The frequency of hypoglycemia was not statistically significant in one year parallel studies (LIPRELOG 100 units/mL, n=543; HUMULIN R, n=561), but was significantly less with LIPRELOG therapy in a six month crossover study in type 1 patients (n=1008) which also demonstrated a significant reduction in nocturnal hypoglycemia with LIPRELOG.

Use in Pumps:

When used in subcutaneous insulin infusion pumps, treatment with LIPRELOG 100 units/mL has been shown to result in lower HbA_{1c} levels compared to regular human insulin without increasing the risk of hypoglycemia. In clinical trials that compared LIPRELOG 100 units/mL with regular human insulin, LIPRELOG 100 units/mL consistently showed significant HbA_{1c} improvement in the range of 0.33% to 0.65%.

Hepatic Insufficiency:

Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. In a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of LIPRELOG when compared to patients with no history of hepatic dysfunction. In that study, LIPRELOG maintained its more rapid absorption and elimination when compared to human regular insulin. Careful glucose monitoring and dose adjustments of insulin, including LIPRELOG, may be necessary in patients with hepatic dysfunction.

Renal Insufficiency:

Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and varying degrees of renal function (from normal to severe impairment, including endstage renal failure), the pharmacokinetic differences between LIPRELOG and human regular insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose adjustments of insulin, including LIPRELOG, may be necessary in patients with renal dysfunction.

STORAGE AND STABILITY

Prior to first use, LIPRELOG must be stored in a refrigerator between 2° and 8°C. They should not be frozen or exposed to excessive heat or sunlight. Cartridges, vials, and prefilled pens that are in current use, should be stored at room temperature (below 30°C and away from direct heat and light) and discarded after 28 days. Do not use after expiry date on label.

When administered by continuous subcutaneous infusion by an external insulin pump, the LIPRELOG 100 units/mL in the reservoir should be changed at least every 14 days. Infusion sets should be changed according to pump manufacturer's instructions (typically 3 days is recommended) or as directed by healthcare professionals.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LIPRELOG (insulin lispro injection) 100 units/mL is available as a clear, colourless, aqueous solution for parenteral administration in vials, cartridges or prefilled insulin delivery devices:

- Vial, 10 mL
- Cartridge, 3 mL, 5 cartridges/box
- KwikPen, 3 mL prefilled pen, 5 pens/box
- Junior KwikPen; 3 mL prefilled pen, 5 pens/box

Not all pack sizes and presentations may be marketed.

Cartridges are designed for use with Lilly injector systems. The cartridge containing LIPRELOG 100 units/mL is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be reused.

Non-medicinal Ingredients:

LIPRELOG 100 units/mL contains glycerol, dibasic sodium phosphate, *m*-cresol, zinc (as ion) and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

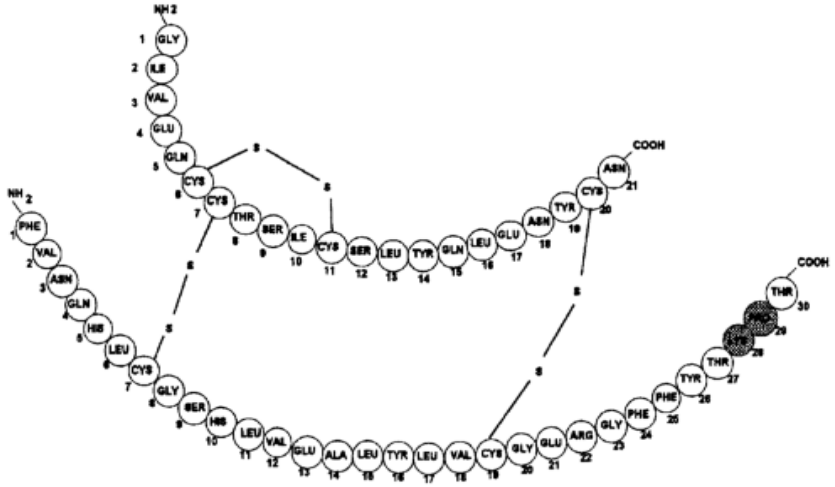
Proper name: Insulin lispro

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

Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_6$

Molecular mass: Molecular Weight: 5808

Structural formula: Insulin lispro is identical in structure to human insulin except for amino acids 28 and 29 of the B-chain; the analogue is Lys(B28) Pro(B29) whereas human insulin is Pro(B28) Lys(B29).



Description: Zinc-insulin lispro crystals appear as a white to off-white solid

Solubility Profile: Soluble in:
0.01 M Hydrochloric acid
0.2 M Sodium sulfate, pH 2.3
0.2 M Sodium phosphate, pH 2.2
0.4 M Ammonium bicarbonate, pH 7.5

pI: Approximately 5.65

DETAILED PHARMACOLOGY

The absorption of insulin is dependent on the disassociation of insulin hexamers, which form when insulin is prepared at concentrations found in commercial insulin preparations. The formation of the hexamers occurs by self-association of insulin molecules at the C-terminal end of the B chain. IGF-1 contains an area which shares some homology with human insulin.

Previous studies demonstrated that IGF-1 does not form hexamers. It was also noted that in the area of IGF-1 which is analogous to the 28 and 29 position of the B chain for human insulin, the amino acid sequence is lysine proline, the reverse of the human insulin sequence. The development of LIPRELOG (insulin lispro) is based on the reversal of these two amino acids in human insulin.

In the absence of excipients, insulin lispro shows little tendency to self-association. Unlike soluble insulin, insulin lispro will not form hexamers, or crystals, except in the presence of zinc or phenol or *m*-cresol. The latter are widely used preservatives in pharmaceutical insulin preparations. Thus, a unique mechanism is provided whereby formulations of insulin lispro are stabilized against physical and chemical degradation, yet dissociate more rapidly than traditional insulin preparations following injection.

Insulin lispro dissociates into monomers almost immediately in dilute solution, due to rapid loss of phenol or *m*-cresol from the insulin-zinc complexes. A similar phenomenon is assumed to occur following subcutaneous injection. It can be noted that addition of zinc and *m*-cresol, to insulin lispro preparations does result in slightly slower absorption, as compared to a solution prepared from pure insulin lispro crystals, although formulated insulin lispro still absorbs faster than soluble regular insulin preparations and retains its glucodynamic advantages.

Preclinical Pharmacology

The minor amino acid sequence inversion in insulin lispro does not significantly affect the biological properties of insulin lispro as described below. *In vivo* studies were conducted with rats, rabbits, dogs and two different pig models. These studies demonstrated that insulin lispro is equivalent to human insulin with respect to hypoglycemic potency. The dog study and one of the pig studies also showed very convincingly that insulin lispro is more rapidly absorbed from subcutaneous injection sites.

In Vitro Studies:

Insulin lispro was compared to human insulin and found to be equipotent in terms of binding to the human placental insulin receptor and in stimulating [^{14}C]glucose uptake into rat adipocytes. Insulin lispro has been shown to have a slightly higher affinity to the human placental and skeletal muscle IGF-1 receptors than human insulin (approximately 1.5 times). However, both insulin lispro and human insulin have affinities that are approximately 0.001 times that of IGF-1 itself.

In one study, insulin lispro was found to be approximately 2 times more potent than human insulin at stimulating [^{3}H]thymidine incorporation into human aortic smooth muscle cells (a measure of cellular proliferation), while in another study insulin lispro and human insulin were

equipotent at stimulating growth of human mammary epithelial cells (ED_{50} insulin, 16.0 ± 3.0 nM; ED_{50} insulin lispro, 18.6 ± 4.0 nM, n=4, p=NS).

In Vivo Studies:

Rat Hypoglycemia Test: Studies with normal male rats indicated that the effective dose needed to give a 50% hypoglycemic response (ED_{50} ± SEM) was 7.2 ± 0.3 µg/kg for insulin lispro and 7.8 ± 0.1 µg/kg for human insulin. In this study the analogue was 108% as active as human insulin, no difference in time of action was found.

Rabbit Hypoglycemia Test: A modified British Prolongation test was conducted using 95 rabbits to compare insulin lispro with U 40 HUMULIN R. Insulin lispro was also formulated at 40 U/mL assuming full potency (i.e., 28.85 U/mg protein). Blood samples were collected at 20, 40, 60, 90, 120, 150, and 210 minutes following subcutaneous injections of each insulin (0.2 U/kg). Resulting blood glucose profiles were virtually identical with the exception of a significantly lower glucose level at 20 minutes for insulin lispro.

Experiments in Dogs: Several dose ranging and time action experiments were conducted in dogs comparing insulin lispro with various human insulin formulations. An optimal experimental design involved the subcutaneous administration of 0.1 U/kg for both the insulin lispro and HUMULIN R (both insulins formulated at 100 U/mL). Blood glucose levels decreased faster and returned to normal sooner in the dogs treated with the insulin lispro. Likewise, the serum levels of the compound rose more rapidly than the human insulin levels.

Studies in Pigs: Crossbred barrows weighing 60 to 85 kg were given subcutaneous injections of either insulin lispro or HUMULIN R, each formulated at 20 U/mL. This animal model was very sensitive to both insulins with 0.1 U/kg causing up to a 75% reduction in blood glucose. A dose of 0.025 U/kg caused a 23% fall in blood glucose for both insulins with evidence for a quicker action with insulin lispro.

The kinetics of insulin lispro was compared to HUMULIN R in 12 pigs with surgically pre-implanted jugular venous and arterial catheters. Twenty hour-fasted animals underwent two studies: (i) an IV injection and (ii) a subcutaneous injection (300 mU/kg) of insulin or analogue. Insulin kinetics over the range of concentrations studied were assumed linear and absorption rates of the insulin and analogues were calculated by deconvolution of their levels after subcutaneous injection with the corresponding IV decay curve. Normoglycemia was maintained by glucose infusion using a glucose controller. The time course of absorption was as follows: % absorbed for HUMULIN R and lispro respectively, at t=15 min were 16 and 17%; t=30 min: 30 and 46%; t=45 min: 42 and 67%; t=60 min: 53 and 78%; t=90 min: 70 and 88%; t=120 min: 82 and 93%. Thus, HUMULIN R peaks rapidly (15 ± 6 min) but at only 1.2 ± 0.03% absorption/min and continues to be absorbed over an extended period (170 min for 93 ± 4% absorption). Insulin lispro peaks at 21 ± 2 min but at 2 ± 0.02% absorption/min and is almost completely (93 ± 3%) absorbed by 2 hours.

Cardiovascular, Respiratory, and Renal Effects: Insulin lispro was examined for potential cardiovascular and respiratory effects in male beagle dogs anesthetized with a-chloralose. Animals (3/group) received 0.05 mL vehicle/kg (HUMULIN BR Diluent) or 0.1 U/kg insulin lispro intravenous (IV) bolus injection. Cardiovascular, electrocardiographic, and respiratory

parameters were measured prior to dosing, and at 5, 10, 15, 30, 45, and 60 minutes after dosing. No toxicologically important changes in QRS duration (maximum 9% at 10 min) and Q-Tc interval (maximum 10% at 5 min) occurred. The increases in QRS duration and Q-Tc interval were similar to that observed after administration of 0.1 units/kg of regular human insulin.

Female Fischer 344 rats (8/group) were given a single subcutaneous dose of 0, 1, 3, or 6 U/kg insulin lispro to evaluate effects of insulin lispro on renal function and electrolyte excretion. Immediately after administration of insulin lispro, the rats were given an oral dose of 25 mL/kg saline solution for hydration. Urine was collected for 5 hours for the determination of volume, pH sodium, potassium, chloride, creatinine, and osmolality. At the end of the urine collection period, blood samples were obtained for the determination of serum sodium, creatinine, and osmolality. Creatinine clearance, osmolal clearance, and fractional excretion of sodium were calculated.

The results of this study demonstrate that a single subcutaneous dose of <6 U/kg insulin lispro did not result in any serious adverse effects on renal function. However, since changes were observed in one or more parameters at each dose level, a clear no-effect level was not achieved.

Clinical Pharmacology:

Glucose Clamp Studies: Comparison of LIPRELOG 100 units/mL to Regular Insulin

A glucose clamp study was performed, in healthy volunteers, in which a 10 U dose of LIPRELOG 100 units/mL was compared to HUMULIN R. Doses were given subcutaneously; an additional 10 U dose of intravenous HUMULIN R was given as an absolute reference (Table 4).

LIPRELOG 100 units/mL showed statistically higher peak concentrations (C_{max}) which occurred earlier than HUMULIN R (t_{max}). Total absorption was comparable, with serum concentration vs. time area under the curve (AUC) values which were not statistically different.

Table 4. Pharmacokinetics of LIPRELOG 100 units/mL Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Treatment	N	Dose	C_{max} (ng/ml)	t_{max} (min)	AUC (ng•min/mL)
LIPRELOG, SC (A)	10	10 U	3.20 ± 1.33	53 ± 30	380 ± 52.2
HUMULIN R, SC (B)	10	10 U	1.79 ± 0.77	101 ± 40	423 ± 71.8
HUMULIN R, IV (C)	10	10 U	58.0 ± 25.1	2 ± 1	601 ± 163
ANOVA results*			A B C	A B C	AB C
p value			*<.001*	*0.001*	*<.001*

*Treatments with statistically comparable values are underlined together.

Glucodynamic data from the same study showed slightly lower maximum glucose infusion rate (R_{max}) values for HUMULIN R when compared to LIPRELOG 100 units/mL, although this comparison was not statistically different. However, the time required to achieve this maximum infusion rate (TR_{max}) was significantly earlier for LIPRELOG 100 units/mL. The total glucose demand induced by any of the subcutaneous administrations (G_{tot}) were comparable (Table 5).

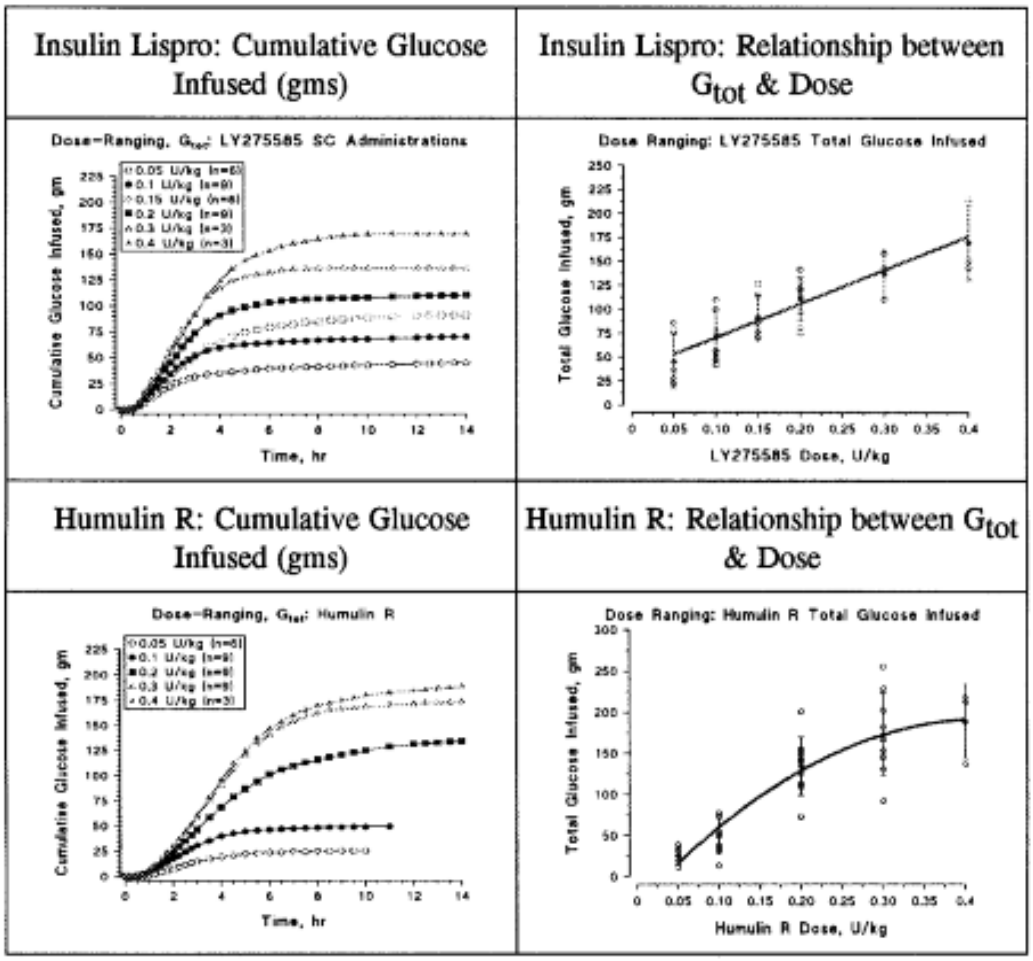
Table 5. Glucodynamics of LIPRELOG 100 units/mL Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Treatment	R_{max} (mg/min)	TR_{max} (min)	G_{tot} (gm)
LIPRELOG, SC (A)	550 ± 203	116 ± 43	85.1 ± 28.2
HUMULIN R, SC (B)	393 ± 180	179 ± 93	81.2 ± 29.9
HUMULIN R, IV (C)	718 ± 247	23 ± 5	50.1 ± 12.9
ANOVA results*	AB C	A B C	AB C
p value	*<0.01*	*<0.01*	*<.001*

*Treatments with statistically comparable values are underlined together.

Dose Ranging Studies:

Six differing doses of insulin were administered subcutaneously to each of 18 healthy volunteers. As previously demonstrated the peak insulin level was achieved later and the duration of the glucodynamic effect of HUMULIN R was prolonged as the dose was increased. This study found that the timing of the insulin peak was affected very little by increasing the dose of LIPRELOG with only a modest effect in prolonging the duration of the glucose infusion required to balance the increasing doses. Also of interest is the observation of a linear relationship between dose and glucose effect with LIPRELOG whereas the relationship was nonlinear for HUMULIN R. This implies that LIPRELOG might have a more predictable effect upon glucose levels across the dosage range (Figure 3).



Total Glucose Infused (G_{tot}) for Insulin Lispro and Humulin R

Figure 3. Dose Ranging Studies in Healthy Volunteers

Comparison of LIPRELOG to Regular Insulin in Patients with type 1 Diabetes

A study was performed comparing the abilities of LIPRELOG 100 units/mL and HUMULIN R to control blood glucose after administration of a high calorie meal to patients with type 1 diabetes. Patients were given a low-dose insulin infusion (0.2 mU/kg/min) for basal requirements, then received a dose of either HUMULIN R or LIPRELOG 100 units/mL subcutaneously just prior to a meal of pizza, Coke®, and tiramisu (1016 total calories, 57% carbohydrates, 31.6% fat). The dose of subcutaneous regular insulin/ LIPRELOG 100 units/mL was selected by the patient based upon previous insulin use, and kept constant between both treatments within any one patient. The mean ± SD subcutaneous HUMULIN R/ LIPRELOG dose was 15.4 ± 3.5 U. Whole blood glucose concentrations were measured on a continuous basis after dosing, and blood samples were collected for determination of insulin and LIPRELOG concentrations.

The serum drug concentrations confirmed the glucose clamp trial performed in healthy volunteers (Figure 4, Table 6), and shows a more rapid absorption, with LIPRELOG (insulin

lispro injection) 100 units/mL peaking higher and earlier than HUMULIN R. Total absorption was comparable.

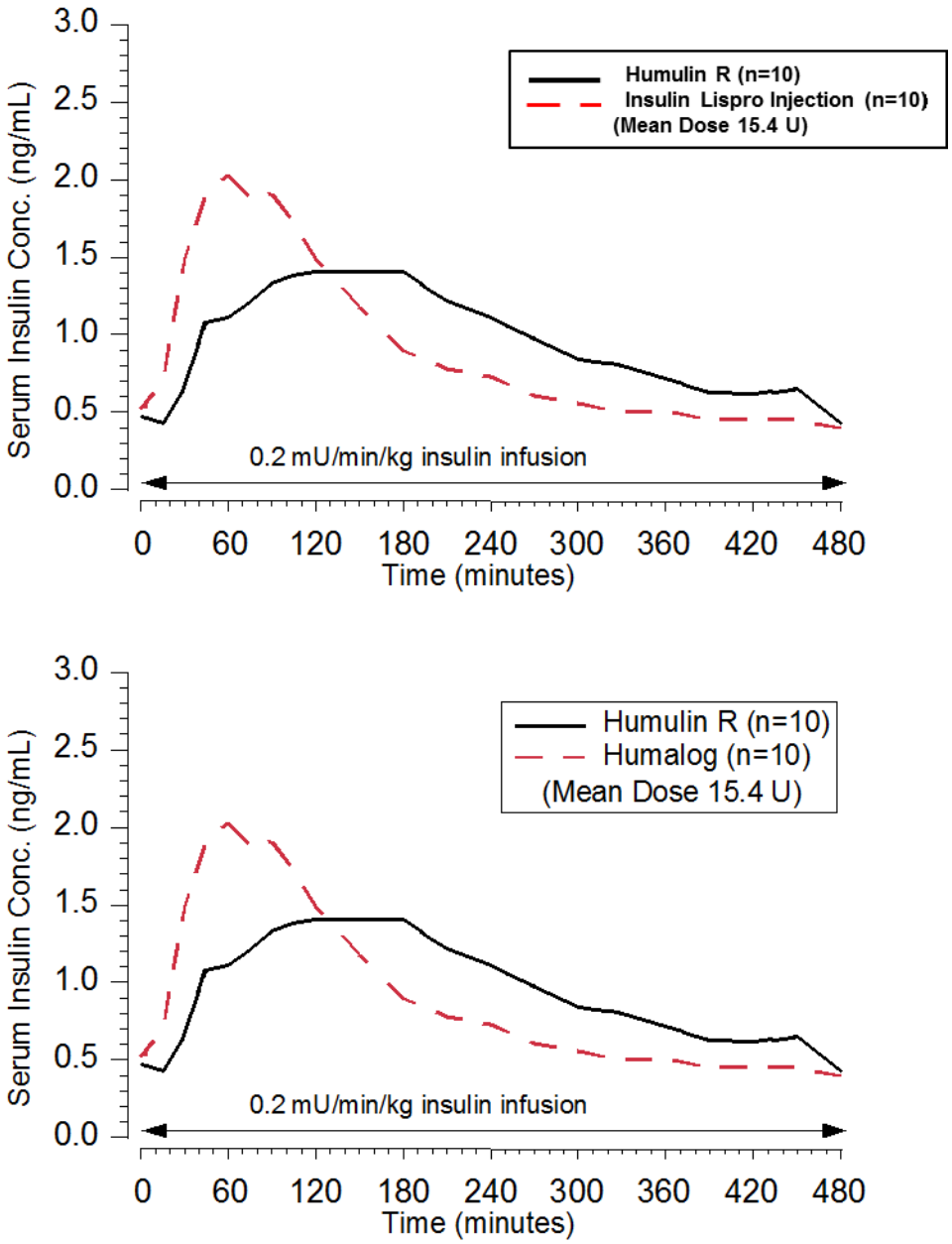


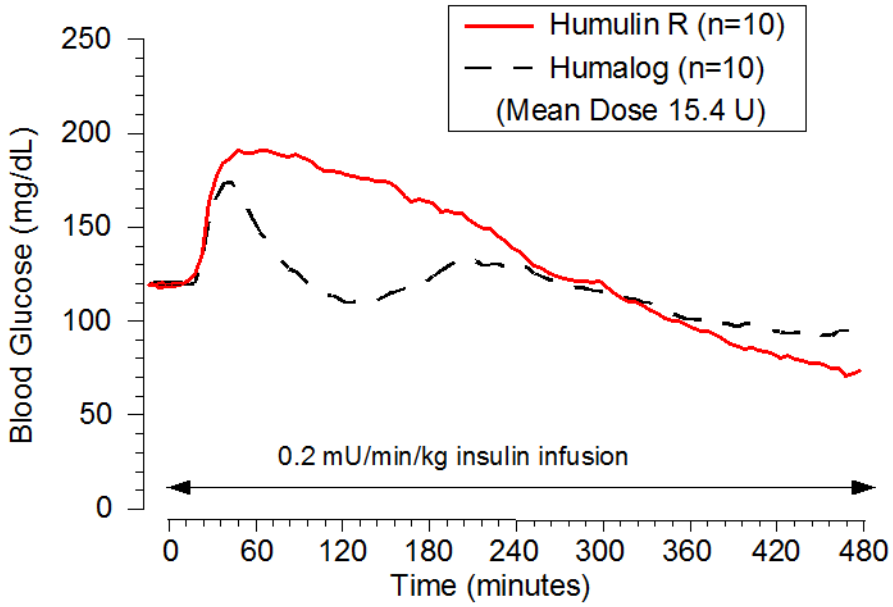
Figure 4. **Mean Serum Insulin Concentrations in type 1 Patients Following Injection of HUMULIN R and Insulin Lispro Injection 100 units/mL (Basal 0.2mU/min/kg insulin infusion).**

Table 6. Mean (+/-SD) Pharmacokinetic Parameters, LIPRELOG 100 units/mL and HUMULIN R, Adjusted for Insulin Infusion.

Treatment	Dose, U	C_{max}, ng/mL	t_{max}, hr	AUC_{0-4}, ng•hr/mL
LIPRELOG	15.4 ± 3.5	1.66 ± 0.42	1.13 ± 0.29	3.64 ± 0.88
HUMULIN R	15.4 ± 3.5	1.07 ± 0.30	1.90 ± 0.46	4.05 ± 0.75
p†	--	*<0.001*	*<0.001*	0.205

Normalized for dose
† Statistical comparisons. P<0.05 considered statistically significant

Glucose concentrations showed that LIPRELOG (insulin lispro injection) 100 units/mL controlled the glucose excursions after this meal more completely than did regular insulin (Figure 5). Baseline blood glucose values were attained within 2 hours after meal consumption with LIPRELOG 100 units/mL. In comparison, baseline blood glucose was not attained for 4-5 hours after dosing regular insulin. Additionally, a trend was apparent showing a greater potential for regular insulin to induce latent hypoglycemia. However, it should be noted that both insulins were given just prior to the meal, HUMULIN R was not given as recommended in the product label.



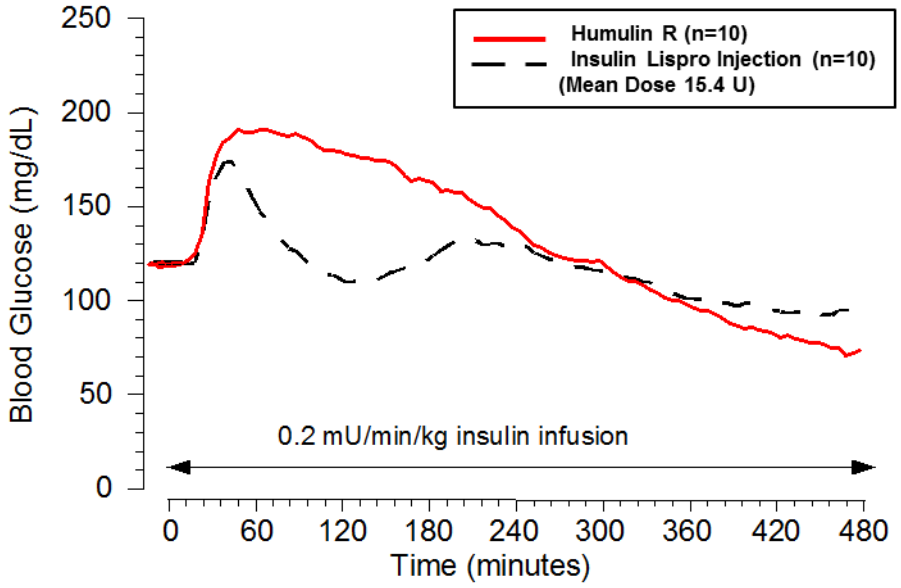


Figure 5. **Mean Blood Glucose Concentrations in type 1 Patients Following Injection of HUMULIN R and Insulin Lispro Injection 100 units/mL Immediately Prior to a Meal.**

TOXICOLOGY

Acute Toxicity

Table 7. **Results of Acute Toxicity Studies with Insulin Lispro**

Species, Strain	No./ Sex/ Group; Age	Dose (U/kg)	Route of Administration	Duration of Observations	Parameters Evaluated	Observations
Rat, Fischer 344	5; 8-9 weeks	0, 10	Intravenous	2 weeks	Mortality; clin. obs.; body wt.; pathology	No effects MLD[a] >10 Units/kg
Rat, Fischer 344	5; 8-9 weeks	0, 10	Subcutaneous	2 weeks	Mortality; clin. obs.; body wt.; pathology	No effects MLD[a] >10 Units/kg
Rat, Fischer 344	5; 8-9 weeks	0, 10[b]	Subcutaneous	2 weeks	Mortality; clin. obs.; body wt.; pathology	No effects MLD[a] >10 Units/kg

Dog, beagle	2; 17-21 months	0, 0.1	Intravenous	2 weeks	Mortality; clin. obs.; body wt.; food consumption; hematology; clin. chemistry	↓ blood glucose MLD[a] > 0.1 Units/kg
Dog, beagle	2; 11-29 months	0, 2	Subcutaneous	2 weeks	Mortality; clin. obs.; body wt.; food consumption; hematology; clin. chemistry	↓blood glucose MLD[a] > 2 Units/kg

a MLD = median lethal dose
b New formulation with increased *m*-cresol preservative.

Long-Term Toxicity

Table 8. Results of Subchronic/Chronic Toxicity Studies with Insulin Lispro

Species, Strain	No./Sex/ Group; Age	Doses (U/kg/ day)	Route of Administration	Duration of Treatment	Parameters Evaluated	Observations
Rat, Fischer 344	10; 4-5 weeks	0, 3	Subcutaneous	1 month	Survival; clin. obs.; ophthalmic exam.; body wt.; food consumption; hematology; clin. chemistry; urinalysis; organ wts.; pathology	No effects.
Dog, beagle	4; 10 months	0, 2	Subcutaneous	1 month	Survival; clin. obs.; ophthalmic & physical exams.; electrocardiograms ; body wt.; food consumption; hematology; clin. chemistry; urinalysis; organ wts.; pathology	↓ blood glucose. ↑ heart rate (M, Day 30).

Species, Strain	No./Sex/ Group; Age	Doses (U/kg/ day)	Route of Administration	Duration of Treatment	Parameters Evaluated	Observations
Rat, Fischer 344	15; 7 weeks	0, 5, 20	Subcutaneous	6 months	Survival; clin. obs.; ophthalmic exam.; body wt.; food consumption; hematology; clin. chemistry; urinalysis; organ wts.; pathology	↑ body wt. gain (M & F: 5 & 20 U/kg). ↑ food consumption (F: 20 U/kg). ↑ EFU (M & F: 5 & 20 U/kg). ↓ triglyceride & cholesterol (M & F: 5 & 20 U/kg).
Dog, beagle	4; 7-8 months	0, 1, 2	Subcutaneous	1 year	Survival; clin. obs.; ophthalmic & physical exams.; electrocardiograms ; body wt.; food consumption; hematology; clin. chemistry; urinalysis; organ wts.; pathology	↓ blood glucose (M & F: 2 U/kg). ↑ triglyceride & cholesterol. ↑ heart rate & T wave alteration.
Rat, Fischer 344	30; 7 8 weeks	0, 20, 200	Subcutaneous	1 year	Survival; clin. obs.; ophthalmic exam.; body wt.; food consumption; hematology; clin. chemistry; urinalysis; immunotoxicity; organ wts.; pathology	↑ body wt., body wt. gain; food consumption; EFU (M & F: 200 U/kg) ↑ EFU (F: 20 U/kg) ↑ glucose (M & F: 200 U/kg) ↓ triglycerides (F: 20 & 200 U/kg) ↓ cholesterol (M & F: 20 & 200 U/kg)

Genetic Toxicity

Insulin lispro injection demonstrated no mutagenic potential in five genotoxicity tests. These tests were the induction of reverse mutations in Salmonella typhimurium and Escherichia coli, induction of unscheduled DNA synthesis in primary cultures of adult rat hepatocytes, induction of mammalian cell mutation in the L5178Y $TK^{+/-}$ mouse lymphoma cell assay, *in vivo* induction of micronuclei in bone marrow of male and female ICR mice, and induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells.

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PART III: CONSUMER INFORMATION

LIPRELOG™ VIALS
(insulin lispro injection)
Solution for Injection, 100 units/mL, Lilly Standard

This leaflet is part III of a three-part "Product Monograph" published when LIPRELOG™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LIPRELOG™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood glucose at a near-normal level.

What it does:

Insulin lispro is a recombinant DNA sourced human insulin analogue. LIPRELOG consists of zinc-insulin lispro crystals dissolved in a clear fluid. LIPRELOG is used to control high blood sugar (glucose) in people with diabetes. LIPRELOG takes effect more rapidly and has a shorter duration of activity as compared to regular insulin.

The rapid onset of activity requires LIPRELOG to be given within 15 minutes before a meal. When necessary, LIPRELOG may be given shortly after a meal instead (within 20 minutes of the start of the meal). The time course of action of any insulin may vary to some extent in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of LIPRELOG is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Proper control is important. Uncontrolled diabetes (hyperglycemia) over a long period of time can result in a number of serious problems such as blindness, kidney failure, poor circulation/heart attacks, strokes and/or nerve damage. These problems can be prevented or reduced by good diabetes management. This will require close and constant cooperation with your diabetes healthcare team including: yourself, your doctor and your diabetes educators (nurses, dietitians, social workers, pharmacists and other healthcare professionals). Thus, you can lead an active, healthy and productive life by eating a balanced daily diet, exercising regularly, and taking your insulin injections as prescribed.

You have been instructed to test your blood and/or your urine regularly for glucose. If your blood tests consistently show above- or below-normal glucose levels or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your doctor know.

When it should not be used:

- When your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of LIPRELOG.
- If you are allergic to anything in LIPRELOG. A complete list of ingredients in LIPRELOG is provided below.

What the medicinal ingredient is:

LIPRELOG contains 100 units/mL of Human Insulin Analogue.

LIPRELOG contains insulin lispro injection.

What the non-medicinal ingredients are:

LIPRELOG contains glycerol, dibasic sodium phosphate, m-cresol, zinc (as ion) and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

What dosage forms it comes in:

LIPRELOG is a sterile solution containing insulin lispro injection. It is available in:
- Vial, 10 mL

LIPRELOG is also available in:
- Cartridge, 3 mL
- KwikPen, 3 mL prefilled pen
- Junior KwikPen, 3 mL prefilled pen

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

Always keep an extra supply of LIPRELOG as well as a spare syringe and needle or injection device on hand. Always wear identification to indicate that you have diabetes so that appropriate treatment can be given if complications occur away from home.

When you receive your insulin from the pharmacy, always check to see that:
1. The name LIPRELOG appears on the carton and bottle (vial) label.
2. The carton and bottle (vial) label is correct for your type of insulin.
3. The insulin strength is U-100.
4. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hypoglycemia or low blood sugar is the most common adverse effect experienced by insulin users. Blood glucose monitoring is recommended for all patients with diabetes. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. Information on how to recognize these symptoms is provided below.
- This Lilly human insulin analogue differs from other insulins because it has a unique structure, a very quick onset of action and a short duration of activity. LIPRELOG should be given within 15 minutes before a meal or when necessary shortly after a meal instead (within 20 minutes of the start of the meal). The short duration of action of LIPRELOG means that if you have Type 1 diabetes you also need to use a longer acting insulin, such as HUMULIN N to give the best glucose control (except when using an insulin infusion pump).
- LIPRELOG should not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial.
- Any change of insulin should be made cautiously and only under medical supervision. Changes in purity, strength, brand (manufacturer), type (regular, NPH, etc), species (beef, pork, beef-pork, human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.
- Mixing of LIPRELOG with either animal insulins or insulin preparations produced by other manufacturers is not recommended.
- Patients taking LIPRELOG may require a change in dosage from that used with other insulins. If an adjustment is needed, it may occur with the first dose or over a period of several weeks.
- Insulin infusion pump: when used in an insulin infusion pump, LIPRELOG should not be diluted or mixed with any other insulin. Carefully read and follow the insulin infusion pump manufacturer's instructions and this insert before using LIPRELOG.

BEFORE you use LIPRELOG talk to your doctor or pharmacist if:

- You have trouble with your kidneys or liver, your doctor may decide to alter your insulin dose.
- You drink alcohol (including wine and beer): watch for signs of hypoglycemia and never drink alcohol on an empty stomach.
- You exercise more than usual or if you want to change your usual diet. Exercise may lower your body's need for insulin during and for some time after the activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site.
- You are ill. Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently.
- You are travelling across more than 2 time zones. You should consult your doctor concerning adjustments in your insulin schedule.
- You are pregnant. LIPRELOG can be used in pregnancy if clinically indicated. Data on a large number of exposed pregnancies do not indicate any adverse effect of LIPRELOG on pregnancy or on the health of the foetus/newborn. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor.
- When you use other medicines. Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

INTERACTIONS WITH THIS MEDICATION

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), corticosteroids, or thyroid replacement therapy. Insulin requirements may be decreased in the presence of agents such as oral antidiabetic agents, salicylates (aspirin), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers. Always discuss any medications you are taking with your doctor.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

PROPER USE OF THIS MEDICATION

LIPRELOG is a sterile solution. LIPRELOG should be given by subcutaneous injection, or by continuous subcutaneous insulin infusion pump. The concentration of LIPRELOG in 10 mL vials is 100 units/mL (U-100).

When used as a meal-time insulin, LIPRELOG should be given within 15 minutes before a meal, or when necessary shortly after a meal instead (within 20 minutes of the start of the meal).

LIPRELOG is a clear and colourless liquid with a water-like appearance and consistency. Do not use if it appears cloudy,

thickened, or slightly coloured or if solid particles are visible. Always check the appearance of your vial of LIPRELOG before using, and if you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

Injection Procedure

Correct Syringe:

Doses of insulin are measured in units. LIPRELOG is available in 100 units/mL (U-100). It is important that you understand the markings on your syringe, because the volume of LIPRELOG you inject depends on the strength, that is, the number of units/mL. For this reason, you should always use a syringe marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use:

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable plastic syringes and needles should be used only once and then discarded in a closable, puncture-resistant sharps container (like a biohazard container) or as directed by your healthcare professional. NEEDLES AND SYRINGES MUST NOT BE SHARED, as this may risk transmission of infectious agents.

Reusable glass syringes and needles must be sterilized before each injection. **Follow the package directions supplied with your syringe.**

Preparing the Dose:

1. Wash your hands.
2. Inspect the LIPRELOG in the vial. It should look clear and colourless. Do not use LIPRELOG if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.
3. Flip off the plastic protective cap but do not remove the stopper if using a new vial.
4. Wipe the top of the vial with an alcohol swab.
5. If you are mixing insulins, refer to the instructions for mixing below.
6. Remove the cover from the needle. Draw air into the syringe equal to your LIPRELOG dose. Put the needle through the rubber top of the LIPRELOG vial and inject the air into the vial.
7. Turn the vial and syringe upside down. Hold the vial and syringe firmly in one hand.
8. Making sure the tip of the needle is in the LIPRELOG, withdraw the correct dose into the syringe.
9. Before removing the needle from the vial, check your syringe for air bubbles, which reduce the amount of LIPRELOG. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
10. Remove the needle from the vial and lay the syringe down so that the needle does not touch anything.

Mixing LIPRELOG With Longer-Acting Insulin Formulations

MIXING LIPRELOG WITH EITHER ANIMAL INSULINS OR INSULIN PREPARATIONS PRODUCED BY OTHER MANUFACTURERS IS NOT RECOMMENDED.

1. LIPRELOG should be mixed with longer-acting insulins (HUMULIN N) only on the advice of your doctor.
2. Draw air into your syringe equal to the amount of longer-acting HUMULIN insulin you are taking. Insert the needle into the longer-acting insulin vial and inject the air, taking care not to come in contact with the insulin in the vial. Withdraw the needle.
3. Now inject air into your LIPRELOG vial in the same manner, but do not withdraw the needle.
4. Turn the vial and syringe upside down.
5. Making sure the tip of the needle is in the LIPRELOG, withdraw the correct dose of LIPRELOG into the syringe.
6. Before removing the needle from the vial of LIPRELOG, check your syringe for air bubbles, which reduce the amount of LIPRELOG in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose. Gently roll or shake the long acting HUMULIN vial until the insulin is mixed.
7. Remove the needle from the vial of LIPRELOG and insert it into the vial of the longer-acting HUMULIN insulin. Turn the vial and syringe upside down. Making sure the tip of the needle is in the insulin, withdraw your dose of longer-acting HUMULIN insulin.
8. Remove the needle and lay the syringe down so that the needle does not touch anything.

Follow your doctor's instructions on mixing your insulin just before giving your injection. LIPRELOG should be injected immediately after mixing. It is important to be consistent in your method.

Syringes from different manufacturers may vary in the amount of space between the bottom line and the needle. Because of this, do not change the sequence of mixing, or the model and brand of syringe or needle that the doctor has prescribed.

Injection:

Prepare the injection site as directed by your healthcare professional. Insert the needle as instructed by your doctor. 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. To avoid tissue damage, give the next injection at a site at least 1 cm (0.5 inches) from the previous injection site.

Use of LIPRELOG in an Insulin Infusion Pump:

1. Health Canada approved insulin infusion pumps may be used to infuse LIPRELOG U-100. Read and follow the instructions that accompany the infusion pump.
2. Be sure to use the correct reservoir and catheter for the pump.
3. Change the LIPRELOG in the reservoir at least every 14 days. Change the infusion set as recommended in pump manufacturers' instructions (typically every 3 days is recommended) or as directed by your healthcare professional. Use aseptic technique when inserting the infusion set.
4. In the event of a hypoglycemic episode, the infusion should be stopped until the episode is resolved. If repeated or severe low blood glucose levels occur, notify your health care professional and consider the need to reduce or temporarily stop your insulin infusion.
5. A pump malfunction or obstruction of the infusion set can result in a rapid rise in glucose levels. If an interruption to insulin flow is suspected, follow the instructions in the product literature and if appropriate, notify your health care professional.
6. When used with an insulin infusion pump, LIPRELOG should not be mixed with any other insulin.

Usual dose

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual LIPRELOG dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your LIPRELOG dose are illness, pregnancy, medication, exercise and travel.

Overdose

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates, sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia:

One of the most frequent adverse events experienced by insulin users is hypoglycemia (see PROPER USE OF THIS MEDICATION).

Diabetic Acidosis and Coma:

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Lipoatrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy to Insulin:

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

This is not a complete list of side effects. For any unexpected effects while taking LIPRELOG, contact your doctor or pharmacist.

HOW TO STORE IT

Prior to first use, LIPRELOG insulin vials should be stored in a refrigerator between 2° and 8°C. Do not freeze. Do not expose to excessive heat or sunlight. The vial of LIPRELOG that you are currently using can be kept unrefrigerated, for up to 28 days, as long as it is kept as cool as possible (below 30°C) and away from direct heat and light. Vials in use, or not refrigerated, should be discarded after 28 days even if they still contain LIPRELOG. Do not use LIPRELOG if it has been frozen.

DO NOT USE A VIAL OF LIPRELOG AFTER THE EXPIRATION DATE STAMPED ON THE LABEL.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at 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.

This leaflet was prepared by Eli Lilly Canada Inc.,

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

Last revised: March 22, 2021

A1-LIPVL-0000-CA-PMI-YYYYMMDD

PART III: CONSUMER INFORMATION

LIPRELOG™ CARTRIDGES
(insulin lispro injection)
Solution for Injection, 100 units/mL, Lilly Standard

LIPRELOG™ KWIKPEN®
(insulin lispro injection)
Solution for Injection, 100 units/mL, Lilly Standard

LIPRELOG™ JUNIOR KWIKPEN®
(insulin lispro injection)
Solution for Injection, 100 units/mL, Lilly Standard

This leaflet is part III of a three-part "Product Monograph" published when LIPRELOG™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LIPRELOG™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood glucose at a near-normal level.

What it does:

Insulin lispro is a recombinant DNA sourced human insulin analogue. LIPRELOG consists of zinc-insulin lispro crystals dissolved in a clear fluid. LIPRELOG is used to control high blood sugar (glucose) in people with diabetes. LIPRELOG takes effect more rapidly and has a shorter duration of activity as compared to regular insulin.

The rapid onset of activity requires LIPRELOG to be given within 15 minutes before a meal. When necessary, LIPRELOG may be given shortly after a meal instead (within 20 minutes of the start of the meal). The time course of action of any insulin may vary to some extent in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of LIPRELOG is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Proper control is important. Uncontrolled diabetes (hyperglycemia) over a long period of time can result in a number of serious problems such as blindness, kidney failure, poor circulation/heart attacks, strokes and/or nerve damage. These problems can be prevented or reduced by good diabetes management. This will require close and constant cooperation with your diabetes healthcare team including: yourself, your doctor and your diabetes educators (nurses, dietitians, social workers, pharmacists and other healthcare professionals). Thus, you can lead an active, healthy and productive life by eating a balanced daily diet, exercising regularly, and taking your insulin injections as prescribed.

You have been instructed to test your blood and/or your urine regularly for glucose. If your blood tests consistently show above- or below-normal glucose levels or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your doctor know.

When it should not be used:

- When your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of LIPRELOG.
- If you are allergic to anything in LIPRELOG. A complete list of ingredients in LIPRELOG is provided below.

What the medicinal ingredient is:

LIPRELOG contains 100 units/mL of Human Insulin Analogue.

LIPRELOG contains insulin lispro injection.

What the non-medicinal ingredients are:

LIPRELOG contains glycerol, dibasic sodium phosphate, m-cresol, zinc (as ion) and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

What dosage forms it comes in:

LIPRELOG is a sterile solution containing insulin lispro injection. It is available in:
- Cartridge, 3 mL
- KwikPen, 3 mL prefilled pen
- Junior KwikPen, 3 mL prefilled pen

LIPRELOG is also available in:
- Vial, 10 mL

LIPRELOG prefilled pens and cartridges are available in boxes of 5. LIPRELOG cartridges are designed for use with Lilly injector systems. The cartridge or prefilled pen containing LIPRELOG is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge or prefilled pen to be reused.

For guidance on the use of the Pen (prefilled, disposable insulin injector), please refer to the separate Instructions for Use enclosed within the packaging.

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

Always keep an extra supply of LIPRELOG i.e. a spare pen and cartridge or prefilled pen on hand. Always wear identification to indicate that you have diabetes so that

appropriate treatment can be given if complications occur away from home.

When you receive your insulin from the pharmacy, always check to see that:

1. The name LIPRELOG appears on the carton and cartridge or prefilled pen label.
2. The carton and cartridge or prefilled pen label is correct for your type of insulin.
3. The insulin strength is U-100.
4. The expiration date on the package will allow you to use the insulin before that date.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hypoglycemia or low blood sugar is the most common adverse effect experienced by insulin users. Blood glucose monitoring is recommended for all patients with diabetes. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. Information on how to recognize these symptoms is provided below.
- This Lilly human insulin analogue differs from other insulins because it has a unique structure, a very quick onset of action and a short duration of activity. LIPRELOG should be given within 15 minutes before a meal or when necessary shortly after a meal instead (within 20 minutes of the start of the meal). The short duration of action of LIPRELOG means that if you have Type 1 diabetes you also need to use a longer acting insulin, such as HUMULIN N to give the best glucose control (except when using an insulin infusion pump).
- LIPRELOG should not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the cartridge.
- Any change of insulin should be made cautiously and only under medical supervision. Changes in purity, strength, brand (manufacturer), type (regular, NPH, etc), species (beef, pork, beef-pork, human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.
- Mixing of LIPRELOG with either animal insulins or insulin preparations produced by other manufacturers is not recommended.
- Patients taking LIPRELOG may require a change in dosage from that used with other insulins. If an adjustment is needed, it may occur with the first dose or over a period of several weeks.
- Insulin infusion pump: when used in an insulin infusion pump, LIPRELOG should not be diluted or mixed with any other insulin. Carefully read and follow the insulin infusion pump manufacturer's instructions and this insert before using LIPRELOG.

BEFORE you use LIPRELOG talk to your doctor or pharmacist if:

- You have trouble with your kidneys or liver, your doctor may decide to alter your insulin dose.
- You drink alcohol (including wine and beer): watch for signs of hypoglycemia and never drink alcohol on an empty stomach.
- You exercise more than usual or if you want to change your usual diet. Exercise may lower your body's need for insulin during and for some time after the activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site.
- You are ill. Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently.
- You are travelling across more than 2 time zones. You should consult your doctor concerning adjustments in your insulin schedule.
- You are pregnant. LIPRELOG can be used in pregnancy if clinically indicated. Data on a large number of exposed pregnancies do not indicate any adverse effect of LIPRELOG on pregnancy or on the health of the foetus/newborn. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor.
- When you use other medicines. Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

INTERACTIONS WITH THIS MEDICATION

Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives (for example, birth control pills, injections and patches), corticosteroids, or thyroid replacement therapy. Insulin requirements may be decreased in the presence of agents such as oral antidiabetic agents, salicylates (aspirin), sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), beta-blockers, alcohol, ACE-inhibitors and angiotensin II receptor blockers. Always discuss any medications you are taking with your doctor.

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise

intolerance, or swelling of the lower extremities while you are on these agents.

PROPER USE OF THIS MEDICATION

LIPRELOG is a sterile solution. LIPRELOG should be given by subcutaneous injection, or by continuous subcutaneous insulin infusion pump. The concentration of LIPRELOG in 3 mL cartridges or prefilled pens is 100 units/mL (U-100).

When used as a meal-time insulin, LIPRELOG should be given within 15 minutes before a meal, or when necessary shortly after a meal instead (within 20 minutes of the start of the meal).

LIPRELOG is a clear and colourless liquid with a water-like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly coloured or if solid particles are visible. Always check the appearance of your cartridge or prefilled pen of LIPRELOG before using, and if you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

Injection Procedure

Preparing a Cartridge of LIPRELOG for Insertion in a Pen:

1. Wash your hands.
2. Before inserting the LIPRELOG cartridge into the pen, inspect it to make sure the contents look clear and colourless. Do not use the LIPRELOG cartridge if it appears cloudy, thickened, or slightly coloured or if solid particles are visible or if the cartridge is cracked or broken.
3. Follow the pen manufacturer's directions carefully for loading the cartridge into the pen.

Injecting the Dose:

1. Wash your hands.
2. Use an alcohol swab to wipe the exposed rubber surface on the metal cap end of the cartridge or prefilled pen.
3. Inspect the LIPRELOG in the cartridge. It should look clear and colourless. Do not use LIPRELOG if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.
4. Follow pen manufacturer's directions for attaching needle.
5. Hold the pen with needle pointing straight up. If there are large bubbles, tap the side of the pen until they float to the top. Remove the bubbles and the air in the needle by setting the pen to a 2-unit dose and depressing the plunger. Repeat this step if necessary until a drop of LIPRELOG appears at the end of the needle.
6. To avoid tissue damage, injection sites can be rotated so that the same site is not used more than approximately once a month.
7. Prepare the injection site as directed by your healthcare professional.
8. Insert the needle as instructed by your doctor.
9. To inject LIPRELOG, follow the pen manufacturer's instructions.
10. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.
11. Immediately after an injection, remove the needle from the pen. This will guard against contamination and prevent leakage, re-entry of air, and potential needle clogs. Dispose of the needle in a closable, puncture-resistant sharps container (like a biohazard container) or as directed by your healthcare professional. Do not reuse needle. NEEDLES, CARTRIDGES, AND PENS MUST NOT BE SHARED. To prevent the possible transmission of disease, never share a LIPRELOG pen or cartridge between patients, even if the needle on the delivery device is changed.
12. Use the gauge on the side of the 3 mL cartridge to help you judge how much LIPRELOG remains. The distance between each mark is approximately 20 units for 3 mL cartridges. When the leading edge of the plunger reaches the last mark on the gauge there is approximately 20 units of LIPRELOG remaining in the cartridge. You may continue to use the cartridge until the plunger will no longer advance. See injection instructions accompanying the pen to ensure that a complete dose is obtained.

Usual dose

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual LIPRELOG dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your LIPRELOG dose are illness, pregnancy, medication, exercise and travel.

Overdose

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates, sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

Dietary Implications:

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal

on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Hypoglycemia:

One of the most frequent adverse events experienced by insulin users is hypoglycemia (see PROPER USE OF THIS MEDICATION).

Diabetic Acidosis and Coma:

Diabetic acidosis may develop if your body has too little insulin (this is the opposite of insulin reaction, which is the result of too much insulin in the blood). Diabetic acidosis may be brought on if you omit your insulin or take less than the doctor has prescribed, eat significantly more than your diet calls for, or develop a fever or infection. With acidosis, urine tests show a large amount of sugar and acetone.

The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Heavy breathing and a rapid pulse are more severe symptoms.

If uncorrected, loss of consciousness, coma, or death can result. Therefore, it is important that you obtain medical assistance immediately.

Lipoatrophy:

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy to Insulin:

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. If you have local reactions, contact your doctor, who may recommend a change in the type or species of insulin.

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately. Your doctor may recommend skin testing, that is, injecting small doses of other insulins into the skin, in order to select the best insulin for you to use. Patients who have had severe generalized allergic reactions to insulin should be skin tested with each new preparation to be used before treatment with that preparation is started.

This is not a complete list of side effects. For any unexpected effects while taking LIPRELOG, contact your doctor or pharmacist.

HOW TO STORE IT

Prior to first use, LIPRELOG insulin cartridges or prefilled pens should be stored in a refrigerator between 2° and 8°C. Do not freeze. Do not expose to excessive heat or sunlight. The pen and cartridge of LIPRELOG that you are currently using should not be refrigerated but should be kept as cool as possible (below 30°C) and away from direct heat and light. Do not use LIPRELOG if it has been frozen. Cartridges or prefilled pens in use, or not refrigerated, should be discarded after 28 days, even if they still contain LIPRELOG.

Inspection of Cartridge:

LIPRELOG should be clear and colourless. DO NOT USE a cartridge or KwikPen of LIPRELOG if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A cartridge or KwikPen that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional.

DO NOT USE A CARTRIDGE OR PREFILLED PEN OF LIPRELOG AFTER THE EXPIRATION DATE STAMPED ON THE LABEL.

Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.

Dispose of used pens as instructed by your healthcare professional and without the needle attached.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at:

1-888-545-5972 or visit the website at 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.

This leaflet was prepared by Eli Lilly Canada Inc.

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

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