PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ADMELOG

(insulin lispro injection)

Solution for Injection, 100 units/mL

Anti-Diabetic Agent

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Date of Approval:

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ADMELOG™

(insulin lispro injection)

ADMELOG (insulin lispro) is a biosimilar biologic drug (biosimilar) to HUMALOG (Eli Lily Inc.)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Parenteral Subcutaneous injection	Solution for Injection, 100 units/mL	m-Cresol [3.15 mg/ml] Glycerol Dibasic sodium phosphate Zinc oxide Water for injection Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

INDICATIONS AND CLINICAL USE

The indications have been granted on the basis of similarity between ADMELOG and the reference biologic drug, HUMALOG.

ADMELOG™ (insulin lispro injection), is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. ADMELOG insulin is also indicated for the initial stabilization of diabetes mellitus. ADMELOG (insulin lispro injection) is a short acting insulin analogue and is for use in conjunction with a longer acting insulin, except when used in a subcutaneous insulin infusion pump.

CONTRAINDICATIONS

ADMELOG (insulin lispro injection) 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

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect associated with insulins, including ADMELOG. 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 their quick onset of action, ADMELOG (insulin lispro) should be given within 15 minutes before a meal.
- When necessary, ADMELOG (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, ADMELOG (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 Patient Medication 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).
- ADMELOG 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 ADMELOG 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 ADMELOG. 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.

Insulin lispro had a similar safety profile to HUMULIN® R (insulin injection (rDNA origin)

Regular) over the course of the clinical studies with insulin lispro 100 units/mL. Insulin lispro 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 ADMELOG, 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 ADMELOG, 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 ADMELOG, is contemplated.

Transferring Patients from Other Insulins:
Patients switching to ADMELOG 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 ADMELOG. 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 ADMELOG 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 ADMELOG (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 Patient Medication 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 ADMELOG, 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/Pancreas
Although impaired hepatic function does not affect the absorption or disposition of ADMELOG, careful glucose monitoring and dose adjustments of insulin, including ADMELOG, may be necessary.

Immune
Local Allergic Reactions:
With insulin therapies including ADMELOG, 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 ADMELOG, 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 ADMELOG(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). Anti-insulin antibodies are frequently cross-reactive. Patients who have demonstrated an allergic reaction to other insulin products may demonstrate an allergic reaction to ADMELOG.

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

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

Information for Patients
Patients should be informed about potential advantages and disadvantages of ADMELOG 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 Patient Medication 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 Patient Medication Information).

Special Populations

Pregnant Women:
ADMELOG can be used in pregnancy if clinically indicated. Data on a large number of pregnancies exposed to HUMALOG 100 units/mL do not indicate any adverse effect of insulin lispro 100 units/mL on pregnancy or on the health of the fetus /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 insulin lispro insulins 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 insulin lispro 100 units/mL to regular human insulin. Insulin lispro 100 units/mL showed better postprandial blood glucose control while maintaining a similar safety profile.

As in adults, ADMELOG 100 units/mL should be given within 15 minutes before a meal. When necessary, ADMELOG 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):
ADMELOG may be used in elderly patients, if clinically indicated.
Information on the effect of age and gender on the pharmacokinetics of insulin lispro 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 insulin lispro 100 units/mL and regular human insulin.

In clinical studies with insulin lispro 100 units/mL, glycosylated hemoglobin (HbA1c) 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 ADMELOG, the need for regular blood glucose self-monitoring should be considered to obtain optimal glycemic control (see Patient Medication Information). HbA1c should be measured every 3 to 4 months in all patients taking insulin products.

ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared ADMELOG to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

Adverse Drug 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, pruritus, 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 – insulin lispro 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 insulin lispro 100 units/mL, insulin aspart and insulin glulisine (Figure 1).

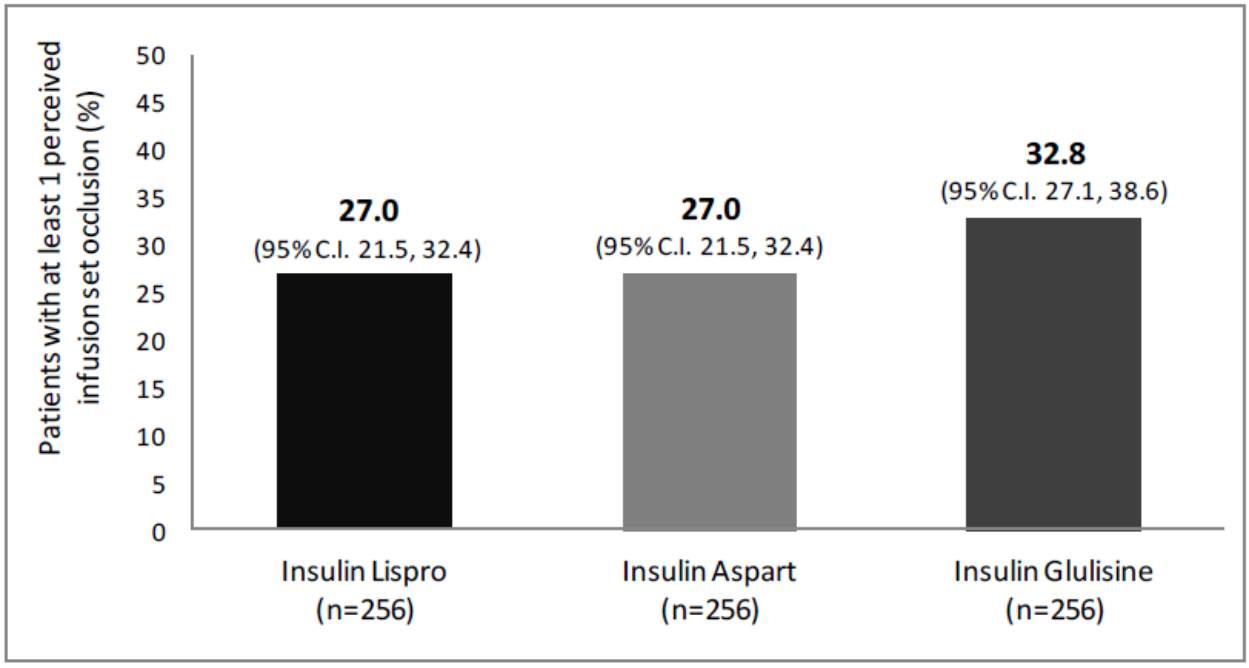


Figure 1 –Patients (%) with at least 1 perceived set occlusion over 13 weeks.

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 insulin lispro 100 units/mL and regular human insulin treated patients (Table 1).

Table 1 –Rates of Catheter Occlusions and Infusion Site Reactions

	Insulin lispro 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 Reactions
Cases of edema have been reported with insulin therapy, including insulin lispro 100 units/mL, particularly if previous poor metabolic control is improved by intensified insulin therapy.

DRUG INTERACTIONS

Drug-Drug Interactions
Drug interactions with insulin formulations including insulin lispro 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.

Certain drugs 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 ADMELOG.

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 ADMELOG is determined by a physician in accordance with the requirements of the patient.

Although insulin lispro has a quicker onset of action and shorter duration of activity, dosing is comparable to regular human insulin. The dosage of ADMELOG, 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 ADMELOG 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 ADMELOG, use the same dose and dosage schedule. However, some patients transferring to ADMELOG 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 insulin lispro 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 insulin lispro 100 units/mL and HUMULIN R.

Transferring a patient from HUMALOG to ADMELOG can be done unit-to-unit based on the previous rapid-acting insulin dose.

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 ADMELOG.

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

Administration

ADMELOG is a clear, colourless solution. It is important to always examine the appearance of the vial or cartridge of ADMELOG 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.

ADMELOG 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 ADMELOG 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, ADMELOG 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, insulin lispro 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 an ADMELOG pen or cartridge between patients, even if the needle on the delivery device is changed.

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

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

ADMELOG in cartridges
The ADMELOG cartridges should only be used with the following pens:
- JuniorSTAR which delivers ADMELOG in 0.5 unit dose increments
- ClikSTAR which delivers ADMELOG in 1 unit dose increments.

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

OVERDOSAGE

With the rapid onset of activity of ADMELOG, it is important that the insulin analogue be given close to mealtime (within 15 minutes before a meal). When necessary, ADMELOG 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 ADMELOG 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 ADMELOG 100 units/mL, 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 ADMELOG, 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

Insulin lispro 100 units/mL

Insulin lispro 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, ADMELOG should be given within 15 minutes before a meal. When necessary, ADMELOG 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), insulin lispro 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 insulin lispro 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. Insulin lispro 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 (Table 2, Table 3).

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

Mean	Insulin lispro 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 – Pharmacokinetic of insulin lispro 100 units/mL Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Mean	Insulin lispro 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 insulin lispro 100 units/mL when compared to HUMULIN R (Figure 2).

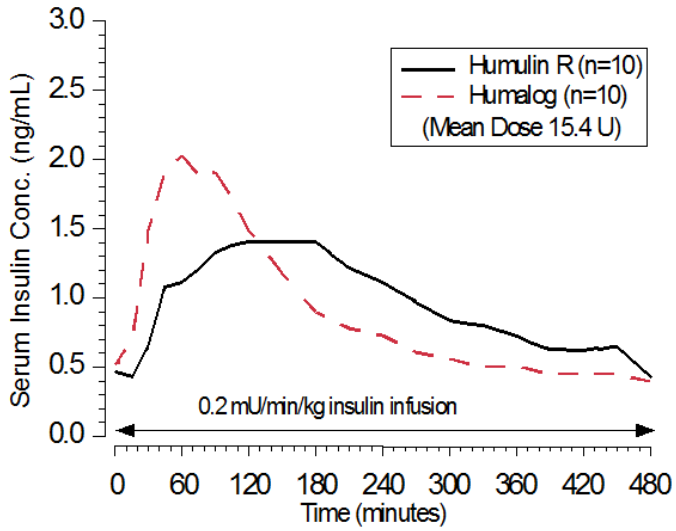


Figure 2 – Mean Serum Insulin Concentrations in type 1 Patients Following Injection of HUMULIN R and insulin lispro 100 units/mL (Basal 0.2mU/min/kg insulin infusion).

Postprandial and overall glycemic control: In clinical studies after one year, the decrease in glucose excursion during and after meals with insulin lispro 100 units/mL was consistent, although not always significant, when compared to HUMULIN R. However, there was no significant difference in HbA1c 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, insulin lispro 100 units/mL controls postprandial glucose and contributes to lower HbA1c 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 (insulin lispro 100 units/mL), n=543; HUMULIN R, n=561, but was significantly less with insulin lispro therapy in a six-month crossover study in type 1 patients (n=1008) which also demonstrated a significant reduction in nocturnal hypoglycemia with insulin lispro.

Use in Pumps:
When used in subcutaneous insulin infusion pumps, treatment with insulin lispro 100 units/mL has been shown to result in lower HbA1c levels compared to regular human insulin without increasing the risk of hypoglycemia. In clinical trials that compared insulin lispro 100 units/mL with regular human insulin, insulin lispro 100 units/mL consistently showed significant HbA1c 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 insulin lispro when compared to patients with no history of hepatic dysfunction. In that study, insulin lispro maintained its more rapid absorption and elimination when compared to human regular insulin. Careful glucose monitoring and dose adjustments of insulin, including ADMELOG, 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 insulin lispro 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 ADMELOG, may be necessary in patients with renal dysfunction.

STORAGE AND STABILITY

Do not use after the expiration date.

Not in-use (unopened) ADMELOG must be stored in a refrigerator (2° to 8°C), but not in the freezer. Protect from light. Do not use ADMELOG if it has been frozen.

In-use (opened) ADMELOG vials, cartridges and ADMELOG SoloSTAR should be stored at room temperature, below 30°C and must be used within 28 days or be discarded, even if they still contain ADMELOG. Protect from direct heat and light.

When administered by continuous subcutaneous infusion by an external insulin pump, the ADMELOG 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

ADMELOG (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, 1 vial/box
- Cartridge, 3 mL, 5 cartridges/box
- Disposable SoloSTAR, 3 mL prefilled pen, 5 pens/box

Active ingredient: insulin lispro 100 units/ml

1 ml contains 3.5 mg insulin lispro, corresponding to 100 units of insulin lispro.

Non-medicinal Ingredients:
ADMELOG 100 units/mL contains m-Cresol [3.15 mg/ml]; glycerol; dibasic sodium phosphate; zinc oxide; water for injection. Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

PART II: SCIENTIFIC INFORMATION

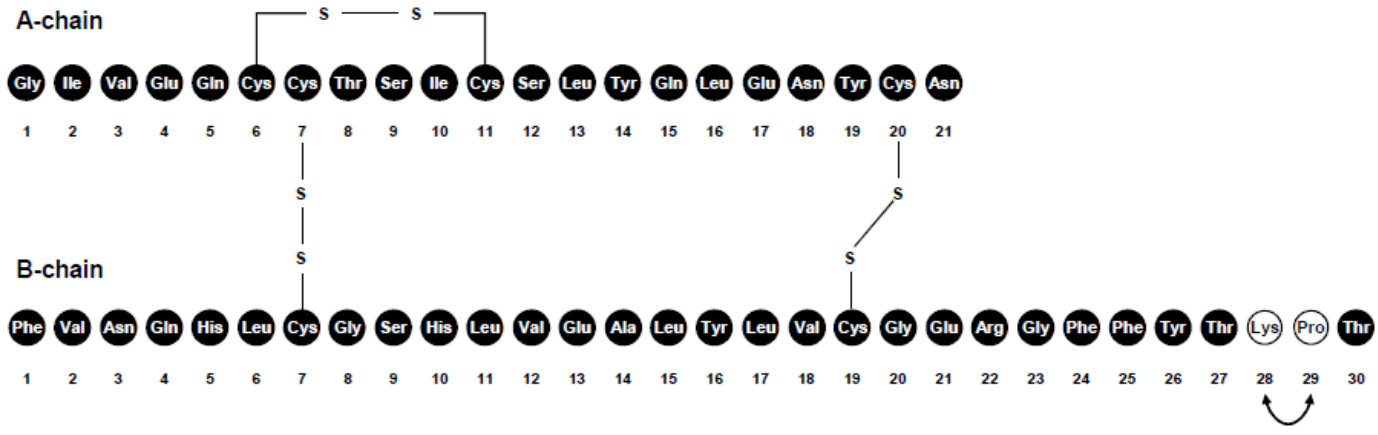
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Insulin lispro
Chemical name:	28B-L-Lysine-29B-L-proline insulin (human) Recombinant human insulin analogue
Molecular formula:	$C_{257}H_{383}N_{65}O_{77}S_6$
Molecular mass:	5807.6
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).

Insulin lispro is produced by recombinant DNA technology utilising Escherichia coli (K12 strain) as the production organism.

Figure 3 – Schematic amino acid sequence indicating the change in comparison to human insulin.



Product Characteristics

Description:	Insulin lispro is a white or almost white powder.
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 5.9 (calculated 5.4)

COMPARATIVE CLINICAL TRIALS

Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between ADMELOG and the reference biologic drug included:

- PDY12704, a randomized study performed in T1DM patients to demonstrate similarity in pharmacokinetic (PK) exposure and pharmacodynamic (PD) activity between ADMELOG and Humalog.
- EFC12619 (SORELLA 1), a randomized study performed in T1DM patients comparing the safety and efficacy of ADMELOG to Humalog.
- EFC13403 (SORELLA 2) a randomized study performed in T2DM patients comparing the safety and efficacy of ADMELOG to Humalog.

An overview of the study designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 4.

Table 4 - Summary of trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender (M/F)
PDY12704	Phase 1, randomized, double-blind, controlled, 3 treatment, 3-period, 6-sequence cross over study to compare exposure and activity of ADMELOG to Humalog, using the euglycemic clamp technique, in patients with T1DM	Single subcutaneous injection of 0.3U/kg per period. Duration: 3 periods of one day	ADMELOG: 29 Humalog US: 29 Humalog EU: 29 Total: 30	44.0±9.4 (20-59)	30/0

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender (M/F)
EFC12619 (SORELLA 1)	Phase 3, randomized, open-label, multicenter, 2-arm parallel study to compare the safety and efficacy of ADMELOG and HUMALOG, both in combination with insulin glargine, in adult patients with T1DM.	SC injection before or immediately after each meal in order to achieve a 2h postprandial plasma glucose of 6.7 to 8.9 mmol/L while avoiding hypoglycemia 26 weeks + 26 weeks safety extension	Randomized: ADMELOG: 253; Humalog: 254 (Humalog US: 140/ Humalog EU: 114)	43.0±14.2 (18-84)	302/205
EFC13403 (SORELLA 2)	Phase 3, randomized, open-label, multicenter, 2-arm parallel study to compare the safety and efficacy of ADMELOG and HUMALOG, both in combination with insulin glargine, in adult patients with T2DM.	SC injection before or immediately after each meal in order to achieve a 2 h postprandial plasma glucose of 6.7 to 8.9 mmol/L while avoiding hypoglycemia 26 weeks	Randomized: ADMELOG:253 ; Humalog: 252 (Humalog US: 120/ Humalog EU: 132)	62.5±9.1 (35-88)	268/237

SC: subcutaneous; T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus

The pharmacokinetics (PK) and pharmacodynamics (PD) of single dose (0.3 U/kg) insulin lispro administration were compared between ADMELOG and each reference product (Humalog sourced from the EU and the USA). The study, PDY12704, was a randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study conducted under fasted conditions. The study enrolled 30 male patients and two patients did not receive all 3 treatments, which resulted in 29 patients included in each statistical comparison. Treatments were separated by a minimum washout period of 5 days. A euglycemic glucose clamp procedure, lasting up to 12 hours, was conducted to assess and compare the PD effects. The primary PD parameter was Glucose Infusion Rate (GIR)-$AUC_{0\text{-}12}$. A key secondary PD endpoint was the maximum glucose infusion rate (GIR_{max}). Serial blood samples were collected pre-dose and at time points up to 12 hours post-dose to assess PK. The PD and PK parameters are summarized in Table 5 and Pharmacokinetics

Table 6 respectively. ADMELOG was determined to have similar PD properties compared to the reference products, displaying a short-time acting profile. PK properties were found to be comparable between ADMELOG and the reference products.

Two multinational, open-label, randomized, controlled Phase 3 studies were conducted in patients with T1DM (EFC12619) or patients with T2DM (EFC13403) to compare the efficacy and safety of ADMELOG to Humalog (100 U/mL), both in combination with LANTUS (insulin glargine 100 U/mL).

In both studies, treatment assignment was stratified on the basis of HbA1c value at screening (<8.0%, ≥8.0%) and prior use of Humalog (yes, no). In addition, study EFC12619 included geographical region (Non Japan, Japan) as a stratification factor. Patients randomized to Humalog received the regionally approved product, Humalog US or Humalog EU.

The treatment duration of the Phase 3 studies was 6 months (main 6-month treatment period) followed by a 6-month comparative safety extension period for study EFC12619.

In both studies the primary efficacy objective was to test non-inferiority of ADMELOG compared to Humalog in terms of HbA1c change from baseline to Week 26. A non-inferiority margin of 0.3% HbA1c was pre-defined.

In study EFC12619, 507 adults with type 1 diabetes were randomized (ADMELOG: 253 Humalog 254). The mean age was 43 years and the mean duration of diabetes was 19 years. The majority of patients were Caucasian (82.1%) with 4.7% of patients Black or African American and 5.3 % Hispanic. 48.7% of patients had a glomerular filtration rate (GFR) ≥ 90 mL/min/1.73m^2. The mean BMI was approximately 26 kg/m^2. Prior to randomization, 60.6%, 37.5% and 2.0% of the patients were taking the reference product or insulin aspart 100 units/ml or both, respectively. These patients were switched to ADMELOG or reference product with a unit to unit conversion from the rapid-acting insulin dose used prior to the trial or with a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization. ADMELOG or reference product were administered by subcutaneous injection immediately prior to meals.

In study EFC13403, 505 adults with type 2 diabetes were randomized (ADMELOG: 253 Humalog 252). The mean age was 62.5 years and the mean duration of diabetes was 17.1 years. The majority of patients were Caucasian (88.3%) with 6.1% Black or African American and 17.8% Hispanic. 26.9% of patients had GFR ≥ 90 mL/min/1.73m^2. The mean BMI was approximately 32.2 kg/m^2. At time of randomization, all patients were treated with LANTUS and short-acting mealtime insulin analogues. Prior to randomization, 51.4%, 48.2% and 0.4% of the patients were taking the reference product or insulin aspart 100 units/ml or both, respectively. These patients were switched to ADMELOG or reference product with a unit to unit conversion from the rapid-acting insulin dose used prior to the trial or with a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization. ADMELOG or reference product was administered by subcutaneous injection immediately prior to meals.

Comparative Study Results

Comparative Bioavailability Studies

Pharmacodynamics

Table 5 – Comparative PD data for ADMELOG versus reference products in patients with T1DM after single dose administration.

PARAMETER	ADMELOG N=29	Reference product Humalog US N=29	Reference product Humalog EU N=29
GIR-AUC_{0-12h} (mg/kg)			
Mean (SD)	1953.50 (547.32)	1993.09 (551.08)	1904.57 (566.39)
Point estimates of treatment ratio (95% confidence intervals) ADMELOG vs Humalog US or EU		1.00 (0.93 to 1.08)	1.06 (0.95 to 1.17)
GIR_{max} (mg/kg/min)			
Mean (SD)	9.97 (2.37)	9.79 (2.41)	9.50 (2.09)
Point estimates of treatment ratio (95% confidence intervals) ADMELOG vs Humalog US or EU		1.04 (0.96 to 1.12)	1.07 (0.98 to 1.16)
GIR-t_{max} (hours)			
Mean (SD)	2.07 (0.78)	2.30 (0.83)	2.37 (0.85)
Point estimates of treatment difference (95% confidence intervals) ADMELOG vs Humalog US or EU		-0.30 (-0.64 , 0.02)	-0.26 (-0.67 , 0.05)

GIR: Glucose Infusion Rate; SD: Standard Deviation
GIR_{max} and GIR t_{max} parameters were derived based on locally weighted regression in smoothing scatter plots (LOESS) smoothing technique for the raw body weight standardized GIR data (LOESS smoothing factor of 0.06).

Pharmacokinetics

Table 6 - Comparative PK data for ADMELOG versus reference products in patients with T1DM after single dose administration

PARAMETER	ADMELOG N=29	Reference Product Humalog US N=29	Reference Product Humalog EU N=29
INS-C_{max} (pg/mL)			
Mean (SD)	5070 (1420)	5170 (1290)	5310 (1600)
Point estimates of treatment ratio (90% confidence intervals) ADMELOG vs Humalog US or EU		0.97 (0.89 to 1.05)	0.96 (0.89 to 1.04)

INS-AUC$_{last}$ (pg.h/mL)			
Mean (SD)	12500 (3560)	13100 (3450)	12800 (3510)
Point estimates of treatment ratio (90% confidence intervals) ADMELOG vs Humalog US or EU		0.95 (0.91 to 0.99)	0.97 (0.94 to 1.01)
INS-AUC (pg.h/mL)			
Mean (SD)	12800 (3720)	13400 (3620)	13100 (3680)
Point estimates of treatment ratio (90% confidence intervals) ADMELOG vs Humalog US or EU		0.95 (0.92 to 0.99)	0.97 (0.94 to 1.00)

INS: insulin: SD: Standard Deviation; AUC: Area Under the Curve

Comparative Safety and Efficacy

Efficacy Results

Type 1 Adult Diabetes

ADMELOG was non-inferior to Humalog in terms of the change in HbA1c from baseline to week 26 at the 0.3% non-inferiority margin.

Table 7 – Study EFC12619: Summary of the Efficacy results for ADMELOG vs Humalog at Week 26 in T1DM

	ADMELOG	Humalog
Treatment in combination with	LANTUS	
Number of subjects randomized (ITT[a])	253	254
HbA1c (%)		
Number of subjects	247	249
Baseline mean	8.08	7.99
LS Mean change from baseline[b]	-0.42	-0.47
LS mean difference[b]	0.06	
[95% Confidence Interval][c]	[-0.084 to 0.197]	
Daily mealtime insulin dose (U/kg/day)		
Baseline mean [n]	0.364 [240]	0.355 [244]
Week 26 (mean) [n]	0.367 [222]	0.349[229]
Mean change from baseline [n]	0.005[217]	-0.005[222]
Daily total insulin dose (U/kg/day)		
Baseline mean [n]	0.705 [238]	0.685[241]
Week 26 (mean) [n]	0.733[221]	0.694[228]
Mean change from baseline [n]	0.019[215]	0.010[220]

a ITT: Intent-to-treat

b Mixed-effect model for repeated measure (MMRM) with treatment group (ADMELOG, Humalog), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, Non-Japan), visit (Week 12, Week 26) and treatment-by-visit interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by –visit interaction as continuous fixed covariates.

c ADMELOG was non-inferior to HUMALOG in the primary comparison at the 0.3% non-inferiority margin.

Type 2 Adult Diabetes

ADMELOG was non-inferior to Humalog in terms of change in HbA1c from baseline to week 26 at the 0.3% non-inferiority margin.

Table 8 – Study EFC13403: Summary of the Efficacy results for ADMELOG vs Humalog at Week 26 (end of study) in T2DM

	ADMELOG	Humalog
Treatment in combination with	LANTUS	
Number of subjects randomized (ITT[a])	253	252
HbA1c (%)		
Number of subjects	239	246
Baseline mean	8.00	8.03
LS mean change from baseline[b]	-0.92	-0.85
LS mean difference[b]	-0.07	
[95% Confidence Interval][c]	[-0.215 to 0.067]	
Daily mealtime insulin dose (U/kg/day)		
Baseline mean [n]	0.449[231]	0.433[243]
End of study (mean) [n]	0.524[214]	0.512[223]
Mean change from baseline [n]	0.087[197]	0.080[218]
Daily total insulin dose (U/kg/day)		
Baseline mean [n]	0.927[230]	0.888[242]
End of study (mean) [n]	1.077[213]	1.038[222]
Mean change from baseline [n]	0.172[196]	0.151[216]

a ITT: Intent-to-treat

b MMRM with treatment group (ADMELOG, Humalog), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No) , visit (Week 12, Week 26) and treatment-by-visit interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by –visit interaction as continuous fixed covariates.

c ADMELOG was non-inferior to HUMALOG in the primary comparison at the 0.3% non-inferiority margin.

Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Immunogenicity

Anti-insulin lispro antibodies were determined in studies EFC12619 (T1DM) and EFC13403 (T2DM) at baseline, Week 4, Week 12, Week 26 and Week 52 (for EFC12619 only) at a centralized laboratory blinded to treatment groups using a validated radioimmuno-assay. Results from studies comparing ADMELOG and Humalog showed similarity in terms of the development of insulin antibodies (Table 9). No effect on efficacy, safety or insulin dose was observed. The prevalence of AIA (defined as patients with at least one positive AIA over the treatment period) was 62.5% with ADMELOG and 63.1% with Humalog in study EFC12619 after 12 months, and 38.4% with ADMELOG and 36.7% with Humalog in study EFC13403 after 6 months.

Table 9 - Patients with treatment-emergent anti-insulin antibodies (AIAs)

	EFC12619 T1DM; 6-month period		EFC12619 T1DM; 12-month period		EFC13403. T2DM; 6-month study	
	ADMELOG (N=247)	**Humalog (N=252)**	**ADMELOG (N=248)**	**Humalog (N=252)**	**ADMELOG (N=245)**	**Humalog (N=248)**
Patients with treatment-emergent AIA (incidence) [n(%)][a]	43/247 (17.4%)	44/252 (17.5%)	56/248 (22.6%)	61/252 (24.2%)	46/245 (18.8%)	36/248 (14.5%)

a) Patients with treatment-emergent AIAs (AIA incidence) over the treatment period: Patients with treatment-induced or treatment-boosted AIAs.

Treatment-boosted AIAs are defined as pre-existing AIAs that were boosted to a significant higher titer following the IMP administration (≥4-fold increase in titer). Treatment-induced AIAs are defined as AIAs that developed de novo (seroconversion) following the IMP administration.

The AIA population was defined as all patients randomized and exposed, with at least one AIA sample available for analysis during the on-treatment period

COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

Comparative Non-clinical Pharmacodynamics

In vitro pharmacology studies: ADMELOG was tested in comparison with the reference product (HUMALOG) in *in vitro* non-clinical pharmacology studies focusing on insulin receptor A and insulin receptor B binding affinity and binding kinetics, insulin receptor A and insulin receptor B activation, metabolic responses, insulin-like growth factor-1 receptor binding and activation and mitogenic activities.

ADMELOG binds to insulin receptor A and insulin receptor B and stimulates autophosphorylation of both receptors and metabolic responses in three different study setups ((1) inhibition of lipolysis in human adipocytes, (2) stimulation of glucose uptake in rat myocytes and (3) gene regulation of glucose 6-phosphatase in primary human hepatocytes) with an activity similar to HUMALOG. Also, the binding kinetics of ADMELOG to insulin receptor A and insulin receptor B is similar to that of HUMALOG. For the insulin-like growth factor-1 receptor, ADMELOG shows affinity and autophosphorylation of the receptor similar to that of HUMALOG, which is reflected as well in a similar stimulation of mitogenic response (stimulation of radiolabeled thymidine incorporation into DNA of human breast cancer cells). Overall, regarding described *in vitro* non-clinical pharmacology studies ADMELOG and HUMALOG were similar.

Non-clinical toxicology studies: The non-clinical toxicological program consisted of two 1-month repeated-dose toxicity studies in rats using twice daily SC dosing at dose levels up to 200 U/kg/day, and a local tolerability study in rabbits comparing ADMELOG with the reference product (HUMALOG).

In the rat toxicity study, similar exposure in terms of the maximum observed concentration within the 0 to 4 hours sampling period ($C_{max,1}$) and the area under the concentration versus time

curve from time 0 to 8 hours (AUC_{0-8h}) was observed for equivalent doses of ADMELOG and HUMALOG and the toxicity profile was comparable between treatments as well. In summary, with regard to the described toxicology studies ADMELOG and HUMALOG were considered to be similar.

CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

Clinical Pharmacology:

Glucose Clamp Studies: Comparison of the insulin lispro100 units/mL) to Regular Insulin

A glucose clamp study was performed, in healthy volunteers, in which a 10 U dose of insulin lispro 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 10**Error! Reference source not found.**).

Insulin lispro 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 10 – Pharmacokinetics of insulin lispro 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)**
insulin lispro 100 units/mL, 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.
SC: subcutaneous; IV: intravenous; C_{max}: maximum concentration; t_{max}: time to maximum concentration; AUC: area under the curve

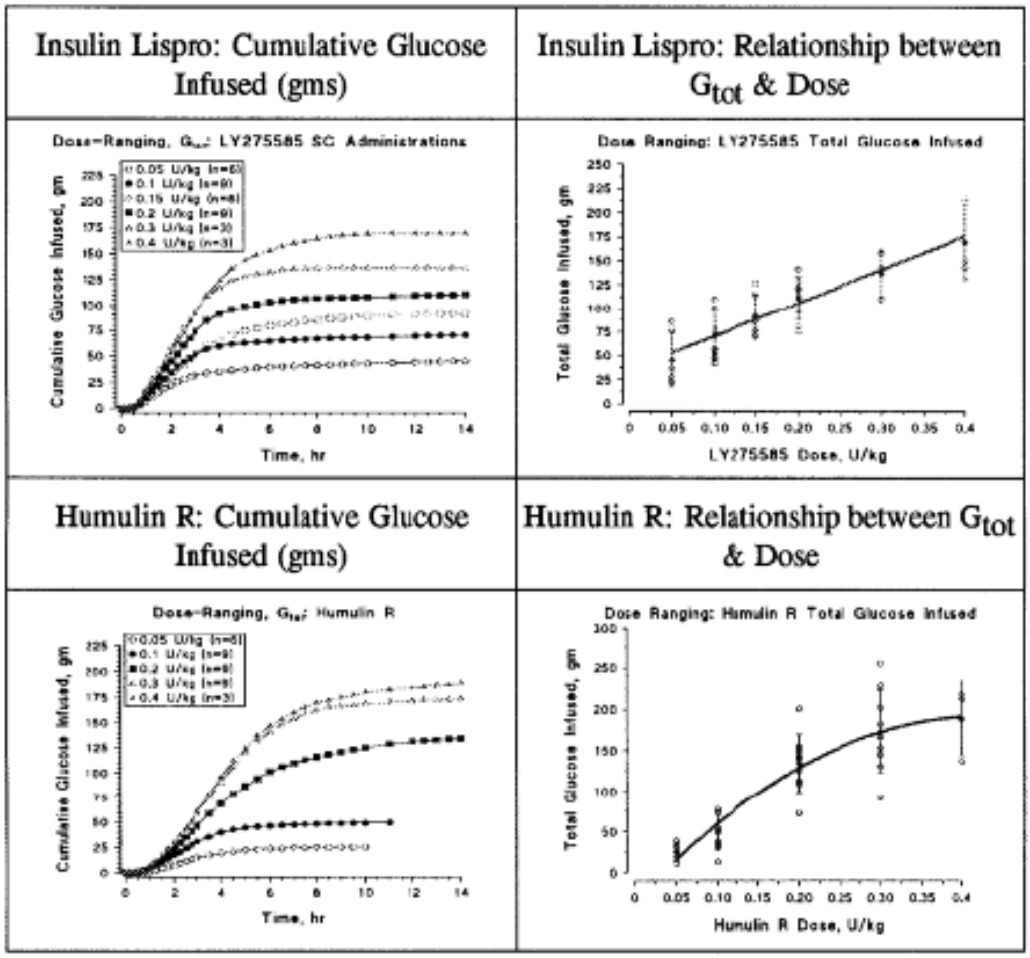
Glucodynamic data from the same study showed slightly lower maximum glucose infusion rate (R_{max}) values for HUMULIN R when compared to insulin lispro 100 units/mL, although this comparison was not statistically different. However, the time required to achieve this maximum infusion rate (TR_{max}) was significantly earlier for insulin lispro 100 units/mL. The total glucose demand induced by any of the subcutaneous administrations (G_{tot}) were comparable (Table 11).

Table 11 – Glucodynamics of insulin lispro (100 units/mL) Compared with HUMULIN R 100 units/mL in Healthy Volunteers.

Treatment	R_{max} (mg/min)	TR_{max} (min)	G_{tot} (gm)
Insulin lispro, 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.
SC: subcutaneous; IV: intravenous; R_{max}: maximal glucose infusion rate; TR_{max}: time to $_{Rmax}$; G_{tot}: total glucose infused

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 insulin lispro 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 insulin lispro whereas the relationship was nonlinear for HUMULIN R. This implies that insulin lispro might have a more predictable effect upon glucose levels across the dosage range (Figure 4).



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

Figure 4 – Dose Ranging Studies in Healthy Volunteers

A study was performed comparing the abilities of insulin lispro 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 insulin lispro 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/ insulin lispro 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/ insulin lispro 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 insulin lispro concentrations.

The serum drug concentrations confirmed the glucose clamp trial performed in healthy volunteers (Figure 5, Table 12), and shows a more rapid absorption, with insulin lispro 100 units/mL peaking higher and earlier than HUMULIN R. Total absorption was comparable.

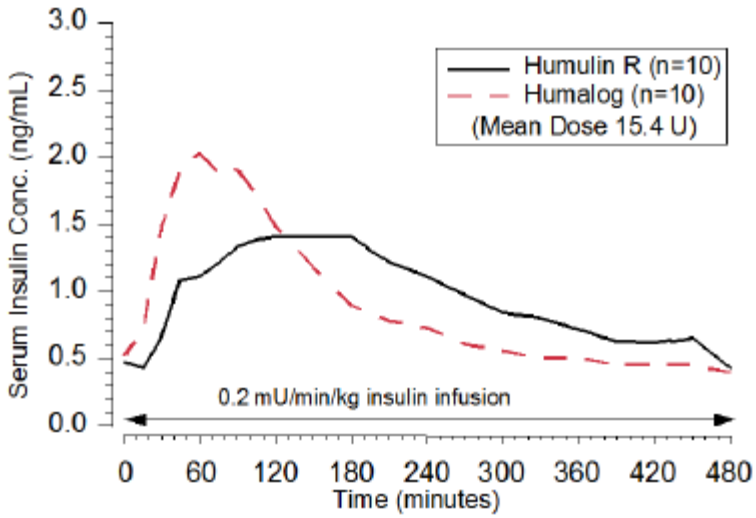


Figure 5 – Mean Serum Insulin Concentrations in type 1 Patients Following Injection of HUMULIN R and insulin lispro 100 units/mL (Basal 0.2 mU/min/kg insulin infusion).

Table 12 –Mean (+/-SD) Pharmacokinetic Parameters, insulin lispro 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**
insulin lispro	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

U: Unit; C_{max}: maximum concentration; t_{max}: time to maximum concentration; AUC: area under the curve

Glucose concentrations showed that insulin lispro 100 units/mL controlled the glucose excursions after this meal more completely than did regular insulin (Figure 6). Baseline blood glucose values were attained within 2 hours after meal consumption with insulin lispro 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.

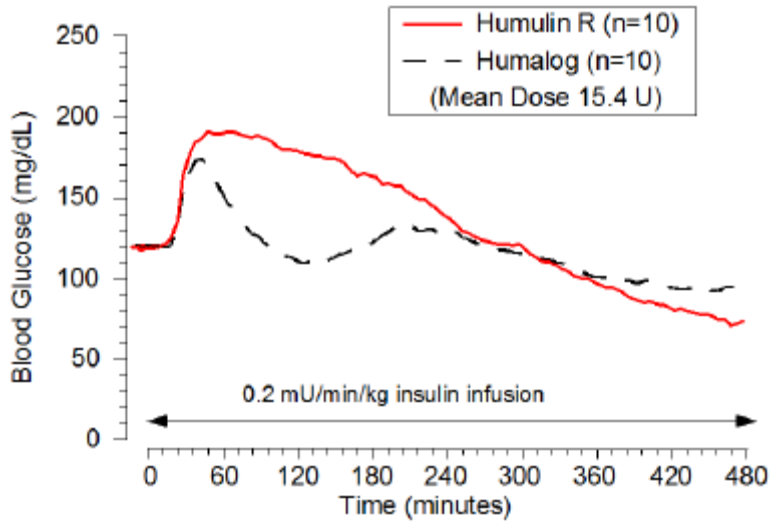


Figure 6 – Mean Blood Glucose Concentrations in type 1 Patients Following Injection of HUMULIN R and insulin lispro 100 units/mL Immediately Prior to a Meal.

NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG

Acute Toxicity

Table 13 – 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.

Table 14. Results of Subchronic/Chronic Toxicity Studies with Insulin Lispro

Species, Strain	No./ Sex/ Group; Age	Dose (U/kg)	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).
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.

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 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 similar 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 [14C]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 [3H] 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 (ED50 ± 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 0.1U/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 (300mU/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.

SUPPORTING PRODUCT MONOGRAPHS

1. HUMALOG Solution for injection, 100 units/mL, Lilly Standard, submission control no. 175085, Product Monograph, ELI LILLY CANADA INC. (March 30, 2015)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ADMELOG™ Vial (*Ad-mah-log*)
Insulin lispro

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

ADMELOG™ is a biosimilar biologic drug (biosimilar) to the reference biologic drug Humalog. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

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 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. ADMELOG 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 ADMELOG means that if you have Type 1 diabetes you also need to use a longer acting insulin, such as insulin NPH to give the best glucose control (except when using an insulin infusion pump).**
- **ADMELOG 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 ADMELOG with animal insulins is not recommended.**
- **Patients taking ADMELOG 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, ADMELOG 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 ADMELOG.**

What is ADMELOG 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.

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

The rapid onset of activity requires ADMELOG to be given within 15 minutes before a meal. When necessary, ADMELOG 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 ADMELOG 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.

What are the ingredients in ADMELOG?

Medicinal ingredients: Human Insulin Analogue
Non-medicinal ingredients: m-Cresol [3.15 mg/ml]; Glycerol; Dibasic sodium phosphate; Water for injections; Zinc oxide.
Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

ADMELOG comes in the following dosage forms:

ADMELOG is a sterile solution containing insulin lispro injection. It is available in:
10 mL vial

ADMELOG is also available in:
3 mL cartridge (for use only with JuniorSTAR and ClikSTAR reusable pens)
3 mL disposable prefilled SoloSTAR injection pen.

Always keep an extra supply of ADMELOG 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 ADMELOG 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 expiration date on the package will allow you to use the insulin before that date.

Do not use ADMELOG if:

- Your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of ADMELOG.
- You are allergic to anything in ADMELOG. A complete list of ingredients in ADMELOG is provided above.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADMELOG. Talk about any health conditions or problems you may have, including if you:

- have trouble with your kidneys or liver, your doctor may decide to alter your insulin dose.
- drink alcohol (including wine and beer): watch for signs of hypoglycemia and never drink alcohol on an empty stomach.
- 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.
- 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.
- are travelling across more than 2 time zones. You should consult your doctor concerning adjustments in your insulin schedule.
- are pregnant. ADMELOG can be used in pregnancy if clinically indicated. Data on a large number of pregnancies exposed to insulin lispro (100 U/mL) do not indicate any adverse effect 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.
- use other medicines. Many medicines affect the way glucose works in your body and this may influence your insulin dose. Medicines that may affect your insulin treatment are noted in the following sections. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

Other warnings you should know about:
DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

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

The following may interact with ADMELOG:
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.

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

When used as a meal-time insulin, ADMELOG 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). ADMELOG 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 ADMELOG 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:
It is important to use a syringe that is marked for U-100 insulin preparations since ADMELOG contains 100 units/mL. Using an incorrect syringe could lead to a mistake in dosing and cause serious medical 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. To avoid medication errors, check the vial label of the insulin before each injection.
2. Inspect the insulin. ADMELOG should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. Flip off the plastic protective cap but do not remove the stopper if using a new vial.
6. Wipe the top of the vial with an alcohol swab.
7. If you are mixing insulins, refer to the instructions for mixing below.
8. A new sterile syringe must be used.
9. Remove the cover from the needle. Draw air into the syringe equal to your ADMELOG dose. Put the needle through the rubber top of the ADMELOG vial and inject the air into the vial.
10. Turn the vial and syringe upside down. Hold the vial and syringe firmly in one hand.
11. Making sure the tip of the needle is in the ADMELOG vial, withdraw the correct dose into the syringe.
12. Before removing the needle from the vial, check your syringe for air bubbles, which reduce the amount of ADMELOG. 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.
13. Remove the needle from the vial and lay the syringe down so that the needle does not touch anything.
14. An empty vial must never be reused and must be properly discarded.

Mixing ADMELOG With Longer-Acting Insulin Formulations (insulin NPH)
MIXING ADMELOG WITH ANIMAL INSULINS IS NOT RECOMMENDED.

1. ADMELOG should be mixed with longer-acting insulins such as insulin NPH only on the advice of your doctor.
2. Draw air into your syringe equal to the amount of longer-acting insulin (insulin NPH) 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 ADMELOG 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 ADMELOG, withdraw the correct dose of ADMELOG into the syringe.
6. Before removing the needle from the vial of ADMELOG, check your syringe for air bubbles, which reduce the amount of ADMELOG 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 insulin(insulin NPH) vial until the insulin is mixed.
7. Remove the needle from the vial of ADMELOG and insert it into the vial of the longer-acting insulin (insulin NPH). Turn the vial and syringe upside down. Making sure the tip of the needle is in the insulin, withdraw your dose of longer-acting 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. ADMELOG 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 ADMELOG in an Insulin Infusion Pump:
1. Health Canada approved insulin infusion pumps may be used to infuse ADMELOG 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 ADMELOG 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, ADMELOG 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 ADMELOG 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 ADMELOG 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.

If you think you have taken too much ADMELOG, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using ADMELOG?

These are not all the possible side effects you may feel when taking ADMELOG. If you experience any side effects not listed here, contact your healthcare professional. Please also see Serious Warnings and Precautions.

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.

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

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

- Visiting the Web page on Adverse Reaction Reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Prior to first use, ADMELOG 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 ADMELOG 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 ADMELOG. Do not use ADMELOG if it has been frozen.

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

Keep out of reach and sight of children.

If you want more information about ADMELOG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; Sanofi's website at Sanofi.ca, or by calling 1-888-852-6887.

This leaflet was prepared by sanofi-aventis Canada Inc.
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Last Revised October 30, 2017

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ADMELOG™ Cartridge (*Ad-mah-log*)
Insulin lispro

Cartridges are for use ONLY with ClikSTAR® and JuniorSTAR® pens.

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- **ADMELOG 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.**
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- **Mixing of ADMELOG with animal insulins is not recommended.**
- **Patients taking ADMELOG 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.**

What is ADMELOG 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.

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

The rapid onset of activity requires ADMELOG to be given within 15 minutes before a meal. When necessary, ADMELOG 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 ADMELOG 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.

What are the ingredients in ADMELOG?

Medicinal ingredients: Human Insulin Analogue
Non-medicinal ingredients: m-Cresol [3.15 mg/ml]; Glycerol;
Dibasic sodium phosphate; Water for injections; Zinc oxide.
Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

ADMELOG comes in the following dosage forms:

ADMELOG is a sterile solution containing insulin lispro injection. It is available in:
3 mL cartridge (for use only with JuniorSTAR and ClikSTAR reusable pens)

ADMELOG is also available in:

10 mL vial
3 mL disposable prefilled SoloSTAR injection pen.

Always keep an extra supply of ADMELOG i.e. a spare pen and cartridge 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 ADMELOG appears on the carton and cartridge label.
2. The carton and cartridge label is correct for your type of insulin.
3. The expiration date on the package will allow you to use the insulin before that date.

Do not use ADMELOG if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADMELOG. Talk about any health conditions or problems you may have, including if you:

- have trouble with your kidneys or liver, your doctor may decide to alter your insulin dose.
- drink alcohol (including wine and beer): watch for signs of hypoglycemia and never drink alcohol on an empty stomach.
- 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.
- 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.
- are travelling across more than 2 time zones. You should consult your doctor concerning adjustments in your insulin schedule.
- are pregnant. ADMELOG can be used in pregnancy if clinically indicated. Data on a large number of pregnancies exposed to insulin lispro (100 U/mL) do not indicate any adverse effect 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.
- use other medicines. Many medicines affect the way glucose works in your body and this may influence your insulin dose. Medicines that may affect your insulin treatment are noted in the following sections. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

Other warnings you should know about:

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR’S ADVICE AND

DIRECTION.

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

The following may interact with ADMELOG:
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.

How to take ADMELOG:
Use ADMELOG exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much ADMELOG to use and when to use it.

- Check your insulin label each time you give your injection to make sure you are using the correct insulin;
- **Use the ADMELOG cartridge only with ClikSTAR and JuniorSTAR pens.**
- **Do not** make any dose changes unless your healthcare provider tells you to;
- ADMELOG is injected under your skin (subcutaneously);
- Change (rotate) your injection sites within the area you chose with each dose;
- **Do not** use the exact spot for each injection;
- **Do not** inject ADMELOG into your vein (intravenously);
- **Keep ADMELOG and all medicines out of the reach of children.**

ADMELOG is a clear solution and looks like some long-acting insulins. Always check for the name of the insulin on your carton and your ADMELOG cartridge label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR ClikSTAR and JuniorSTAR, TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

× The ADMELOG cartridge is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.
✓Always perform a safety test.

✓Always carry a spare cartridge and spare needles in case they got lost or stop working.

As with all insulins, if patients are blind or have poor eyesight and cannot read the dose counter on the pen, they should get help from a person with good eyesight who is trained to use the insulin device.

Do not re-use the needle. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

Using the cartridge in any other injection pen not suitable for the ADMELOG cartridge could lead to a mistake in dosing and cause medical problems for you, such as a blood glucose level that is too low or too high.

JuniorSTAR delivers ADMELOG in 0.5 unit dose increments. ClikSTAR delivers ADMELOG in 1 unit dose increments.

Although rare, technical problems with the cartridge can occur which may prevent correct dosing. They include: broken, cracked or damaged cartridges, air bubbles or foam, and blocked needles. If technical problems occur or are suspected, contact the call center, your physician, pharmacist or nurse.

Injection Procedure

Preparing the ADMELOG Cartridge for Insertion into the injection pen

1. To avoid medication errors, check the cartridge label of the insulin before each insertion.
2. Inspect the insulin cartridge. ADMELOG should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. Carefully follow the injection pen directions for loading the cartridge into the injection pen.

Injecting the Dose:

1. Wash your hands.
2. Inspect the insulin. ADMELOG should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of solution.
3. It is not necessary to shake or rotate the cartridge inserted into the injection pen before use.
4. Remove the protective cap.
5. Follow the injection pen directions for attaching and changing the needle.
6. Check the cartridge inserted into the injection pen for air bubbles. If bubbles are present, remove them as instructed in the injection pen directions.
7. **Follow the injection pen directions for performing the Safety Test or Priming.**

8. Set the injection pen to the correct ADMELOG dose as instructed in the injection pen directions.
9. To avoid tissue damage, injection sites can be rotated so that the same site is not used more than approximately once a month.
10. Cleanse the skin with alcohol where the injection is to be made.
11. Pinch and hold the skin and insert the needle attached to the injection pen as instructed by your doctor or diabetes educator.
12. To inject ADMELOG, follow the directions for the injection pen.
13. Slowly count to 10 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.
14. Remove the needle from the injection pen immediately after each injection as instructed in the directions for the injection pen. Dispose of the needle appropriately. Do not reuse the needle.

If the injection pen malfunctions, ADMELOG may be drawn from the cartridge into an insulin syringe and injected. A new sterile syringe must be used at each injection.

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

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 ADMELOG 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 ADMELOG 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.

If you think you have taken too much ADMELOG, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using ADMELOG?

These are not all the possible side effects you may feel when taking ADMELOG. If you experience any side effects not listed here, contact your healthcare professional. Please also see Serious Warnings and Precautions.

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.

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

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

- Visiting the Web page on Adverse Reaction Reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Prior to first use, ADMELOG insulin cartridges 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 ADMELOG 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 ADMELOG if it has been frozen. Cartridges in use, or not refrigerated, should be discarded after 28 days, even if they still contain ADMELOG.

Inspection of Cartridge:
ADMELOG should be clear and colourless. DO NOT USE a cartridge of ADMELOG if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A cartridge 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 OF ADMELOG 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.

Keep out of reach and sight of children.

If you want more information about ADMELOG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; Sanofi's website at Sanofi.ca, or by calling 1-888-852-6887.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised October 30, 2017

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ADMELOG™ SoloSTAR® (Pre-filled disposable pen) (*Ad-mah-log*)
Insulin lispro

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

ADMELOG™ is a biosimilar biologic drug (biosimilar) to the reference biologic drug Humalog. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

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 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. ADMELOG 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 ADMELOG means that if you have Type 1 diabetes you also need to use a longer acting insulin such as insulin NPH to give the best glucose control (except when using an insulin infusion pump).**
- **ADMELOG SoloSTAR 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 prefilled pen 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.**
- **Patients taking ADMELOG 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.**

What is ADMELOG 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.

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

The rapid onset of activity requires ADMELOG to be given within 15 minutes before a meal. When necessary, ADMELOG 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 ADMELOG 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.

What are the ingredients in ADMELOG?

Medicinal ingredients: Human Insulin Analogue
Non-medicinal ingredients: m-Cresol [3.15 mg/ml]; Glycerol;
Dibasic sodium phosphate; Water for injections; Zinc oxide.
Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

ADMELOG comes in the following dosage forms:

ADMELOG is a sterile solution containing insulin lispro injection. It is available in:
3 mL disposable prefilled SoloSTAR injection pen.

ADMELOG is also available in:
10 mL vial
3 mL cartridge (for use only with JuniorSTAR and ClikSTAR reusable pens)
Always keep an extra supply of ADMELOG i.e. a spare 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 ADMELOG appears on the carton and prefilled pen label.
2. The carton and prefilled pen label is correct for your type of insulin.
3. The expiration date on the package will allow you to use the insulin before that date.

Do not use ADMELOG if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADMELOG. Talk about any health conditions or problems you may have, including if you:

- have trouble with your kidneys or liver, your doctor may decide to alter your insulin dose.
- drink alcohol (including wine and beer): watch for signs of hypoglycemia and never drink alcohol on an empty stomach.
- 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.
- 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.
- are travelling across more than 2 time zones. You should consult your doctor concerning adjustments in your insulin schedule.
- are pregnant. ADMELOG can be used in pregnancy if clinically indicated. Data on a large number of pregnancies exposed to insulin lispro (100 U/mL) do not indicate any adverse effect of ADMELOG 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.
- use other medicines. Many medicines affect the way glucose works in your body and this may influence your insulin dose. Medicines that may affect your insulin treatment are noted in the following sections. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

Other warnings you should know about:

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

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

The following may interact with ADMELOG:
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.

How to take ADMELOG:
Read the detailed Instructions for Use that come with your ADMELOG™ SoloStar® disposable prefilled pen. Use ADMELOG exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much ADMELOG to use and when to use it.

- Check your insulin label each time you give your injection to make sure you are using the correct insulin;
- ADMELOG comes in a SoloSTAR disposable prefilled pen that you must use to take your ADMELOG. The dose counter on your pen shows your dose of ADMELOG. **Do not** make any dose changes unless your healthcare provider tells you to;
- ADMELOG is injected under your skin (subcutaneously);
- Change (rotate) your injection sites within the area you chose with each dose;
- **Do not** use the exact spot for each injection;
- **Do not** inject ADMELOG into your vein (intravenously);
- **Keep ADMELOG and all medicines out of the reach of children.**

ADMELOG is a clear solution and looks like some long-acting insulins. Always check for the name of the insulin on your carton and your ADMELOG SoloSTAR pen label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR ADMELOG SoloSTAR PEN TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE**

× The injection pen is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.
×Never use your pen if it is damaged or if you are not sure that it is working properly.
✓Always perform a safety test.
✓Always carry a spare pen and spare needles in case they got lost or stop working.

The dose counter of the pen shows the number of units of ADMELOG to be injected.

As with all insulins, if patients are blind or have poor eyesight and cannot read the dose counter on the pen, they should get help from a person with good eyesight who is trained to use the insulin device.

Do not re-use the needle. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

Carefully read the "ADMELOG SoloSTAR pre-filled pen Instructions for Use" included in the package and use the pen as described. If you do not follow all of these instructions, you may get too much or too little insulin.

Injection Procedure

1. **Take the new pen out of the fridge at least 1 hour before you inject.** Make sure the insulin is at room temperature to minimize local irritation at the injection site; cold insulin is more painful to inject.
2. **Check the name and expiration date on the label of your pen.** To avoid medication errors between ADMELOG and other insulins, check the label on your ADMELOG SoloSTAR pen to make sure you have the correct insulin before every injection. Never use your pen after the expiration date.
3. **Check that the insulin is clear.** ADMELOG should be a clear and colorless solution with no visible particles. Do not use the pen if you notice anything unusual in the appearance of the solution.
4. **Wash your hands**.
5. **It is not necessary to shake or rotate the ADMELOG SoloSTAR pen before use.**
6. **Always attach a new needle.** Follow the ADMELOG SoloSTAR Instructions for Use for attaching and changing the needle.
7. **Pull off the protective cap and set it aside for later.**
8. **Do a safety test.** Always do a safety test before each injection to ensure your pen and needle are working correctly and to make sure that you get the correct insulin dose.
   - You may see air bubbles in the insulin – this is normal, they will not harm you.
9. **Select the correct dose.** Follow the steps included in your ADMELOG SoloSTAR Instructions for Use to ensure the correct dose of ADMELOG is selected.
   - Never select a dose or press the injection button without a needle attached – this may damage your pen.
10. **Choose a place to inject – upper arms, stomach, buttock or thighs.** There is no relevant difference in absorption of ADMELOG between your abdominal, thigh, buttock or upper arm subcutaneous injection areas.
    - Injection sites within an injection area (abdomen, thigh, buttock or upper arm) MUST be rotated from one injection to the next.

11. **Cleanse the skin with alcohol where the injection is to be made.**
12. **Push the needle into your skin as shown by your health provider.** Do not touch the injection button yet.
13. **Place your thumb on the injection button – press all the way in and hold.** Do not press at an angle – your thumb could block the dose selector from turning.
14. **Keep the injection button held in and when you see "0" in the dose window, slowly count to 5.** This will make sure you get your full dose. DO NOT RUB THE AREA.
15. **Remove the needle immediately after each injection**. Follow the steps included in your ADMELOG SoloSTAR Instructions for Use – do not re-use the needle.
    - Always take care when handling needles – this is to prevent injury and cross-infection. Never put the inner needle cap back on.
16. **Dispose of your needle appropriately.** Throw away the used needle in a puncture-resistant container or as instructed by your health provider or local authority.
17. **Put the pen cap back on.** Do not put the pen back in the fridge.

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

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 ADMELOG 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 ADMELOG 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.

If you think you have taken too much ADMELOG, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using ADMELOG?

These are not all the possible side effects you may feel when taking ADMELOG. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

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.

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

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

- Visiting the Web page on Adverse Reaction Reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Prior to first use, the ADMELOG SoloSTAR prefilled pen should be stored in a refrigerator between 2° and 8°C. Do not freeze. Do not expose to excessive heat or sunlight. The ADMELOG SoloSTAR prefilled pen 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 ADMELOG SoloSTAR if it has been frozen. Prefilled pens in use, or not refrigerated, should be discarded after 28 days, even if they still contain ADMELOG.

Inspection of the prefilled pen:
ADMELOG should be clear and colourless. DO NOT USE ADMELOG SoloSTAR if the liquid appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A prefilled pen cartridge 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 ADMELOG SOLOSTAR 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

Keep out of reach and sight of children.

If you want more information about ADMELOG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; Sanofi's website at Sanofi.ca, or by calling 1-888-852-6887.

This leaflet was prepared by sanofi-aventis Canada Inc.

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