HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADMELOG safely and effectively. See full prescribing information for ADMELOG®.

ADMELOG® (insulin lispro) injection, for subcutaneous or intravenous use

Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ADMELOG is a rapid-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus. (1)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for important preparation and administration instructions. (2.1, 2.2, 2.3, 2.4)
- Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis. (2.2)
- Subcutaneous injection (2.2):
  - Administer ADMELOG by subcutaneous injection into the abdominal wall, thigh, upper arm, or buttocks within 15 minutes before a meal or immediately after a meal.
  - Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
- Continuous subcutaneous infusion (Insulin Pump) (2.2):
  - Refer to the insulin infusion pump user manual to see if ADMELOG can be used. Use in accordance with the insulin pump instructions for use.
  - Administer ADMELOG by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer.
  - Rotate infusion sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis.
  - Do not mix with other insulins or diluents in the pump.
- Intravenous Infusion: Administer ADMELOG by intravenous infusion ONLY after dilution and under medical supervision. (2.2)
- The dosage of ADMELOG must be individualized based on the route of administration and the patient's metabolic needs, blood glucose monitoring results and glycemic control goal. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) is available as: (3)

- 10 mL multiple-dose vials
- 3 mL multiple-dose vials
- 3 mL single-patient-use SoloStar® prefilled pens

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to insulin lispro or any of the excipients in ADMELOG. (4)

WARNINGS AND PRECAUTIONS

- *Never share* an ADMELOG SoloStar disposable prefilled pen or syringe between patients, even if the needle is changed. (5.1)
- *Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. (5.2)
- *Hypoglycemia:* May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3, 6, 7, 8.6, 8.7)
- *Hypoglycemia Due to Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- *Hypersensitivity Reactions:* May be life-threatening. Discontinue ADMELOG, monitor and treat if indicated. (5.5)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
- *Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)
- *Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:* Monitor glucose and administer ADMELOG by subcutaneous injection if pump malfunction occurs. (5.8)

ADVERSE REACTIONS

Adverse reactions associated with ADMELOG include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Drugs that may increase the risk of hypoglycemia:* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics (7).
- *Drugs that may decrease the blood glucose lowering effect:* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7).
- *Drugs that may increase or decrease the blood glucose lowering effect:* alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7).
- *Drugs that may blunt the signs and symptoms of hypoglycemia:* beta-blockers, clonidine, guanethidine, and reserpine (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADMELOG is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Preparation and Administration Instructions

- Always check insulin labels before administration *[see Warnings and Precautions (5.4)]*.
- Inspect ADMELOG visually before use. It should appear clear and colorless. Do not use ADMELOG if particulate matter or coloration is seen.
- Use ADMELOG SoloStar prefilled pen with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
- Do NOT mix ADMELOG with other insulins when administering using a continuous subcutaneous infusion pump.

2.2 Preparation and Administration Instructions for the Approved Routes of Administration

Subcutaneous Injection

- Administer the dose of ADMELOG subcutaneously within fifteen minutes before a meal or immediately after a meal into the abdominal wall, thigh, upper arm, or buttocks.
- Rotate injection site within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2), Adverse Reactions (6)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- ADMELOG administered by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin.
- The ADMELOG SoloStar prefilled pen dials in 1-unit increments.
- Prior to subcutaneous use, ADMELOG may be diluted with sterile 0.9% Sodium Chloride Injection. Dilute one-part ADMELOG to one-part 0.9% Sodium Chloride Injection to yield a concentration one-half that of ADMELOG (equivalent to U-50). If diluted ADMELOG is not used immediately, refrigerate at 2°C to 8°C (36°F to 46°F) for no more than 24 hours or store at room temperature up to 30°C (86°F) for 4 hours. Discard the unused diluted ADEMLOG after 24 hours if refrigerated or after 4 hours if stored at room temperature.

Continuous Subcutaneous Infusion (Insulin Pump)

- Refer to the continuous subcutaneous insulin infusion pump user manual to see if ADMELOG can be used with the insulin pump. Use ADMELOG in accordance with the insulin pump system's instructions for use.
- Administer ADMELOG by continuous subcutaneous infusion in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2), Adverse Reactions (6)]*.
- Train patients using continuous subcutaneous insulin infusion therapy to administer insulin by injection and have alternate insulin therapy available in case of insulin pump failure *[see Warnings and Precautions (5.8)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Change ADMELOG in the pump reservoir at least every 7 days or according to the pump user manual, whichever is shorter.
- Change the infusion sets and the infusion set insertion site according to the manufacturer's user manual.
- Do NOT dilute or mix ADMELOG when administering by continuous subcutaneous infusion.
- Do NOT expose ADMELOG in the pump reservoir to temperatures greater than 98.6°F (37°C).

Intravenous Administration

- Administer ADMELOG intravenously ONLY under medical supervision *[see Warnings and Precautions (5.3, 5.6)]*.
- Dilute ADMELOG to concentrations from 0.1 unit/mL to 1 unit/mL using 0.9% Sodium Chloride Injection, USP *[see How Supplied/Storage and Handling (16.2)]*.
- Closely monitor of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*.

2.3 Dosage Recommendations

- Individualize and adjust the dosage of ADMELOG based on the route of administration, the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dosage modifications may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function, or during acute illness *[see Warnings and Precautions (5.2, 5.3) and Use in Specific Populations (8.6, 8.7)]*.
- When switching from another insulin lispro product to ADMELOG, the dose of ADMELOG should be the same as the other insulin lispro product *[see Warnings and Precautions (5.2)]*.
- When switching from other insulins to ADMELOG, the ADMELOG dosage may need to be adjusted *[see Warnings and Precautions (5.2)]*.

2.4 Dosage Adjustment for Drug Interactions

- Dosage modification may be needed when ADMELOG is coadministered with certain drugs *[see Drug Interactions (7)]*.
- Do NOT mix ADMELOG with any other insulin.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) is a clear and colorless solution available as:

- 10 mL multiple-dose vials
- 3 mL multiple-dose vials
- 3 mL single-patient-use SoloStar prefilled pens

4 CONTRAINDICATIONS

ADMELOG is contraindicated:

- during episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- in patients who are hypersensitive to insulin lispro or to any of the excipients in ADMELOG *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share an ADMELOG SoloStar Pen or Syringe Between Patients

ADMELOG SoloStar prefilled pen must never be shared between patients, even if the needle is changed. Patients using ADMELOG vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to unaffected area) has been reported to result in hypoglycemia *[see Adverse Reactions (6)]*.

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant anti-diabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including ADMELOG.

Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly, and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulins, the glucose lowering effect time course of ADMELOG may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature *[see Clinical Pharmacology (12.2)]*. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between ADMELOG and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including ADMELOG. If hypersensitivity reactions occur, discontinue ADMELOG; treat per standard of care and monitor until symptoms and signs resolve *[see Adverse Reactions (6.1)]*. ADMELOG is contraindicated in patients who have had hypersensitivity reactions to insulin lispro or any of the excipients in ADMELOG *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulins, including ADMELOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including ADMELOG, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction

Malfunction of the insulin pump or insulin infusion set or insulin degradation can rapidly lead to hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with ADMELOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure *[see How Supplied/Storage and Handling (16.2) and Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypoglycemia Due to Medication Errors *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions with Subcutaneous Injections of ADMELOG

Two clinical trials with ADMELOG were conducted: one in patients with type 1 diabetes and one in patients with type 2 diabetes *[see Clinical Studies (14)]*.

- The data in Table 1 reflect the exposure of 252 patients with type 1 diabetes to ADMELOG with mean exposure duration of 49 weeks. The type 1 diabetes population had the following characteristics: Mean age was 43 years and mean duration of diabetes was 20 years. Fifty-nine percent were male, 80% were White, 6% were Black or African American and 7% were Hispanic. At baseline, the mean eGFR was 90 mL/min/1.73 m^2 and 49% of patients had eGFR ≥90 mL/min/1.73 m^2. The mean BMI was 26 kg/m^2. The mean HbA1c at baseline was 8.07%.
- Two hundred fifty-three patients with type 2 diabetes were exposed to ADMELOG with mean exposure duration of 25 weeks. The type 2 diabetes population had the following characteristics: Mean age was 62 years and mean duration of diabetes was 17 years. Fifty-four percent were male, 90% were White, 6% were Black or African American and 17% were Hispanic. At baseline, the mean eGFR was 77 mL/min/1.73 m^2 and 27% of patients had eGFR ≥90 mL/min/1.73 m^2. The mean BMI was 32 kg/m^2. The mean HbA1c at baseline was 7.99%.

Common adverse reactions were defined as reactions that occurred in ≥5% of the population studied.

Common adverse reactions (other than hypoglycemia) during a clinical trial in patients with type 1 diabetes mellitus are listed in Table 1. In a 26-week clinical trial in patients with type 2 diabetes mellitus, no adverse reactions (other than hypoglycemia) occurred in ≥5% of ADMELOG-treated patients (n=253) were observed.

Table 1: Adverse Reactions that Occurred in ≥5% of ADMELOG-Treated Patients with Type 1 Diabetes in a 52-Week Trial

	ADMELOG + Insulin Glargine (100 units/mL), % (n=252)
Nasopharyngitis	13%
Upper respiratory tract infection	6%

Severe Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including ADMELOG *[see Warnings and Precautions (5.3)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for ADMELOG with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the ADMELOG trials, severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. The incidence of severe hypoglycemia in patients receiving ADMELOG with type 1 diabetes mellitus and type 2 diabetes mellitus was 13.5% at 52 weeks and 2.4% at 26 weeks, respectively *[see Clinical Studies (14)]*.

Adverse Reactions Associated with Insulin Initiation and Intensification of Glucose Control

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

Lipodystrophy

Long-term use of insulin, including ADMELOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect insulin absorption *[see Dosage and Administration (2.2)]*.

Weight Gain

Weight gain can occur with insulins, including ADMELOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulins, including ADMELOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII) of ADMELOG

In a randomized, open-label crossover study in adult patients with type 1 diabetes treated over two 4-week periods, the incidence of infusion set occlusions (defined as failure to correct hyperglycemia [plasma glucose ≥300 mg/dL] by insulin bolus via insulin pump) in ADMELOG-treated patients (n=25) was evaluated. Infusion set occlusions were reported by 24% of patients.

In a randomized, 16-week, open-label, parallel design study of pediatric patients with type 1 diabetes, adverse reactions related to infusion site-related reactions for another insulin lispro product, 100 units/mL, occurred in 21% of patients. The most frequently reported infusion site-related reactions were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy

As with any insulin therapy, patients taking ADMELOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions may require discontinuation of ADMELOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including ADMELOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

Localized reactions and generalized myalgias have been reported with injected meta-cresol, which is an excipient in ADMELOG *[see Contraindications (4)]*.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADMELOG in the studies described below with the incidence of antibodies in other studies or to other insulin products may be misleading.

In a 52-week study of ADMELOG in type 1 diabetes patients, 49.4% were positive at baseline and 22.6% had treatment-emergent ADA (i.e., either new ADA, or increase in titer of at least 4-fold).

In a 26-week study of ADMELOG in type 2 diabetes patients, 26.4% were positive at baseline and 18.8% had treatment-emergent ADA (i.e., either new ADA, or increase in titer of at least 4-fold).

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of another insulin lispro product, 100 units/mL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for another insulin lispro product, 100 units/mL, have been identified during post approval use.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7 DRUG INTERACTIONS

Table 2 presents clinically significant drug interactions with ADMELOG.

Table 2: Clinically Significant Drug Interactions with ADMELOG

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is concomitantly administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of ADMELOG	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is concomitantly administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of ADMELOG	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is concomitantly administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when ADMELOG is concomitantly administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies with another insulin lispro product used during pregnancy have not reported an association between insulin lispro and the induction of major birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Pregnant rats and rabbits were exposed to another insulin lispro product in animal reproduction studies during organogenesis. Fetal growth retardation was observed in

offspring of rats exposed to insulin lispro at a dose approximately 3 times the human subcutaneous dose of 1.0 unit/kg/day. No adverse effects on embryo-fetal development were observed in offspring of rabbits exposed to insulin lispro at doses up to approximately 0.24 times the human subcutaneous dose of 1.0 unit/kg/day *[see Data]*.

The estimated background risk of major birth defects is 6%–10% in women with pregestational diabetes with a HbA1c >7% and has been reported to be as high as 20%–25% in women with a HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human data

Published data from retrospective studies and meta-analyses do not report an association with another insulin lispro product and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin lispro is used during pregnancy. However, these studies cannot definitely establish or exclude the absence of any risk because of methodological limitations including small sample size, selection bias, confounding by unmeasured factors, and some lacking comparator groups.

Animal data

In a combined fertility and embryo-fetal development study with another insulin lispro product, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was observed at the 20 units/kg/day dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits with another insulin lispro product, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation Days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

8.2 Lactation

Risk Summary

Available data from published literature suggest that exogenous human insulin products, including insulin lispro, are transferred into human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including insulin lispro, on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADMELOG and any potential adverse effects on the breastfed child from ADMELOG or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ADMELOG to improve glycemic control have been established in pediatric patients with diabetes mellitus. Use of ADMELOG for this indication is supported by evidence from an adequate and well-controlled study with another insulin lispro product, 100 units/ml, in 60 pediatric patients 3 years of age and older with type 1 diabetes mellitus and studies in adult patients with diabetes mellitus *[see Clinical Studies (14)]*.

8.5 Geriatric Use

Of the total number of patients (n=2,834) in eight clinical studies of another insulin lispro product, 100 units/mL, 12% (n=338) were 65 years of age or over. The majority of these patients had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age.

Of the total number of patients (n=1,011) in clinical studies of ADMELOG or another insulin lispro product, 100 units/mL, 26.5% (n=268) were 65 years of age or over. The majority of these patients had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age.

Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of ADMELOG action have not been performed.

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent ADMELOG dose adjustment and more frequent blood glucose monitoring *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent ADMELOG dose adjustment and more frequent blood glucose monitoring *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with a glucagon product for emergency use or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

Insulin lispro is a rapid-acting human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Insulin lispro has a molecular weight of 5808 Da, identical to that of human insulin.

ADMELOG (insulin lispro) injection is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous use. Each mL of ADMELOG contains 100 units of insulin lispro, and the inactive ingredients: dibasic sodium phosphate (1.88 mg), glycerin (16 mg), metacresol (3.15 mg), zinc oxide (content adjusted to provide 0.0197 mg zinc ion), and Water for Injection, USP. Insulin lispro has a pH of 7.0 to 7.8. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide. ADMELOG is latex free.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

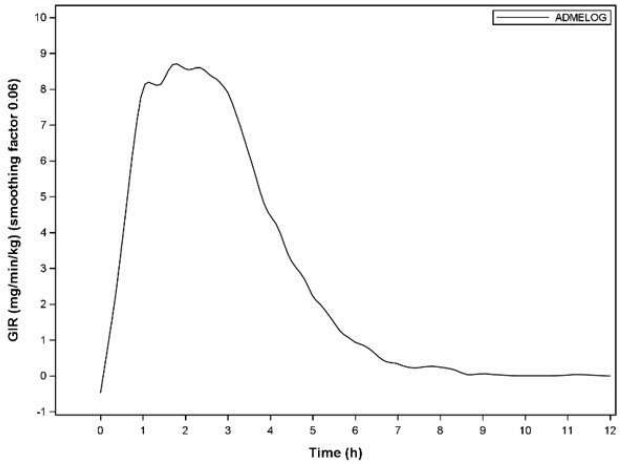
Regulation of glucose metabolism is the primary activity of insulins and insulin analogs, including insulin lispro products. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis and enhance protein synthesis.

12.2 Pharmacodynamics

Pharmacodynamics of ADMELOG After Subcutaneous Injection

The pharmacodynamic profile of a single 0.3 unit/kg dose of ADMELOG administered subcutaneously was evaluated in a euglycemic clamp study enrolling 30 patients with type 1 diabetes. In this study, the mean (SD) time to maximum effect of ADMELOG (measured by the peak rate of glucose infusion) was approximately 2.1 (0.8) hours. The mean (SD) area under the glucose infusion rate curves (measure of overall pharmacodynamic effect) and mean (SD) maximum glucose infusion rate were 1953.5 (547.3) mg/kg and 9.97 (2.37) mg/min/kg, respectively (see Figure 1).

Figure 1: Mean Smoothed Glucose Infusion Rate* after Subcutaneous Injection of ADMELOG (0.3 unit/kg) in Patients with Type 1 Diabetes



*Body Weight Standardized

The time course of action of insulin and insulin analogs, including insulin lispro products, may vary considerably in different individuals or within the same individual. The rate of insulin absorption and, consequently, the onset of activity are known to be affected by the site of injection, exercise, and other variables *[see Warnings and Precautions (5.2)]*.

Pharmacodynamics of AMELOG after Intravenous Administration

The glucose lowering effect of intravenous administration of another insulin lispro product, 100 units/mL, was tested in 21 patients with type 1 diabetes. For the study, the patients' usual doses of insulin were held, and blood glucose concentrations were allowed to reach a stable range of 200 to 260 mg/dL during a one to three-hour run-in phase. The run-in phase was followed by a 6-hour assessment phase. During the assessment phase, patients received intravenous infusion of another insulin lispro product, 100 units/mL, at an initial infusion rate of 0.5 units/hour. The infusion rate could be adjusted at regular timed intervals to achieve and maintain blood glucose concentrations between 100 to 160 mg/dL.

The mean blood glucose levels during the assessment phase for patients on another insulin lispro product, 100 units/mL, therapy are summarized below in Table 3. All patients achieved the targeted glucose range at some point during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 17 of 20 patients treated with another insulin lispro product, 100 units/mL. The average time (±SE) required to attain near normoglycemia was 129 ± 14 minutes for another insulin lispro product, 100 units/mL.

Table 3: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of Another Insulin Lispro Product, 100 units/mL in Patients with Type 1 Diabetes

Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous*
0	224 ± 16
30	205 ± 21
60	195 ± 20
120	165 ± 26
180	140 ± 26
240	123 ± 20

Table 3: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of Another Insulin Lispro Product, 100 units/mL in Patients with Type 1 Diabetes (continued)

Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous*
300	120 ± 27
360	122 ± 25

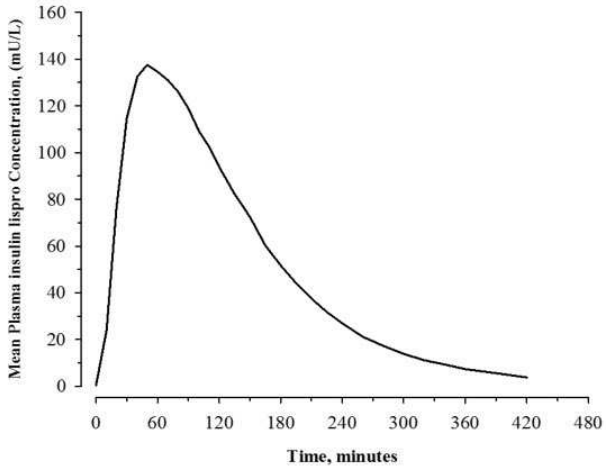
*Results shown as mean ± SD.

12.3 Pharmacokinetics

Absorption

The pharmacokinetic profile of a single 0.3 unit/kg dose of ADMELOG administered subcutaneously was evaluated in a study enrolling 30 patients with type 1 diabetes. In this study, the mean observed area under the plasma insulin lispro concentration-time curve from time zero to infinity and peak plasma insulin lispro concentration were 12800 pg·hr/mL and 5070 pg/mL, respectively. The median time to maximum plasma insulin lispro concentration was 0.83 hours after injection (see Figure 2).

Figure 2: Mean Plasma Concentrations of ADMELOG after a Single Subcutaneous Administration of ADMELOG (0.3 unit/kg) in Patients with Type 1 Diabetes



The absolute bioavailability of another insulin lispro product, 100 units/mL, after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

Distribution

When administered intravenously as bolus injections of 0.1 and 0.2 unit/kg dose in two separate groups of healthy subjects, the mean volume of distribution of another insulin lispro product, 100 units/mL, appeared to decrease with increase in dose (1.55 and 0.72 L/kg, respectively).

Elimination

Metabolism

Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of another insulin lispro product, 100 units/mL, is identical to that of regular human insulin.

Excretion

When administered intravenously, another insulin lispro product, 100 units/mL demonstrated dose-dependent clearance, with a mean clearance of 21.0 mL/min/kg (0.1 unit/kg dose), and 9.6 mL/min/kg (0.2 unit/kg dose). Another insulin lispro product, 100 units/mL, demonstrated a mean $t_{1/2}$ of 0.85 hours (51 minutes) and 0.92 hours (55 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses.

Specific Populations

The effects of age, gender, race, obesity, pregnancy, or smoking on the pharmacokinetics of ADMELOG have not been studied.

Patients with Renal Impairment

Type 2 diabetic patients with varying degrees of renal impairment showed no difference in pharmacokinetics of another insulin lispro product, 100 units/mL. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Type 2 diabetic patients with impaired hepatic function showed no effect on the pharmacokinetics of another insulin lispro product, 100 units/mL, as compared to patients with no hepatic dysfunction. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. In Fischer 344 rats, a 12-month repeat-dose toxicity study was conducted with insulin lispro at subcutaneous doses of 20 and 200 units/kg/day (approximately 3 and 32 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area). Insulin lispro did not produce important target organ toxicity including mammary tumors at any dose.

Insulin lispro was not mutagenic in the following genetic toxicity assays: bacterial mutation, unscheduled DNA synthesis, mouse lymphoma, chromosomal aberration, and micronucleus assays.

Male fertility was not compromised when male rats given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area) for 6 months were mated with untreated female rats. In a combined fertility, perinatal, and postnatal study in male and female rats given 1, 5, and 20 units/kg/day subcutaneously (0.16, 0.8, and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area), mating and fertility were not adversely affected in either gender at any dose.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The safety and effectiveness of ADMELOG to improve glycemic control in adult and pediatric patients with diabetes mellitus have been established based on adequate and well-controlled studies of ADMELOG in adult patients with type 1 and type 2 diabetes mellitus, and based on adequate and well-controlled studies of another insulin lispro product, 100 units/mL, in adult and pediatric patients 3 years of age and older with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus.

The safety and effectiveness of:

- ADMELOG were studied in 507 adult patients with type 1 diabetes and 505 adult patients with type 2 diabetes.
- Another insulin lispro product, 100 units/mL, were studied in 1,087 adult and pediatric patients with type 1 diabetes and in 722 adult patients with type 2 diabetes.

14.2 Type 1 Diabetes Mellitus – Subcutaneous Injection

ADMELOG: Study in Adult Patients

A 26-week open-label, active-controlled study (NCT02273180) evaluated the glucose lowering effect of ADMELOG plus insulin glargine, 100 units/mL, compared to that of Comparator (another insulin lispro product, 100 units/mL, or a non–U.S.-licensed insulin lispro product, 100 units/mL), plus insulin glargine, 100 units/mL. A total of 507 patients with type 1 diabetes mellitus treated with insulin glargine 100 units/mL and rapid-acting mealtime insulin analogs participated in the study. Patients were randomized to ADMELOG (n=253) or Comparator (n=254). ADMELOG or Comparator was administered by subcutaneous injection immediately prior to meals.

The mean age of these patients was 43 years old, and 60% were male. The population was 82% White, 5% Black or African American and 5% were Hispanic. The population had type 1 diabetes mellitus for a mean duration of 19 years. The mean eGFR was 90.6 mL/min/1.73 m^2 and 48.7% of patients had GFR ≥90 mL/min/1.73 m^2. The mean BMI was approximately 26 kg/m^2. At baseline, 61%, 38% and 2% of the patients were using other insulin lispro products, 100 units/mL, insulin aspart, 100 units/mL, or both, respectively.

At week 26, treatment with ADMELOG provided a mean reduction in HbA1c that was non-inferior to that achieved with the Comparator (see Table 4).

Table 4: 26 Week Type 1 Diabetes Mellitus Trial in Adults – Mean Change in HbA1c (ADMELOG plus Insulin Glargine, 100 units/mL, versus Comparator plus Insulin Glargine, 100 units/mL)

	ADMELOG + Insulin Glargine	Comparator + Insulin Glargine
N*	253	254
HbA1c (%)		
Baseline (mean)	8.08	7.99
Adjusted mean change from baseline†	-0.40	-0.46
Adjusted mean difference‡ (95% CI)	0.06 (-0.086 to 0.201)	

*ITT: Intent-to-treat; all randomized patients.

†Estimated using a multiple imputation method that models a "return to baseline" for patients having missing data who discontinued treatment. ANCOVA was used with treatment and stratification groups as fixed factors and baseline HbA1c as a covariate.

‡Treatment difference: ADMELOG - Comparator.

Another Insulin Lispro Product, 100 units/mL: Study in Adult and Pediatric Patients 12 Years of Age and Older

A 12-month, randomized, parallel, open-label, active-controlled study was conducted in 167 patients with type 1 diabetes to assess the safety and efficacy of another insulin lispro product, 100 units/mL (n=81), compared with regular human insulin, 100 units/mL (n=86). This other insulin lispro product was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered 30 to 45 minutes before meals. Human insulin extended zinc suspension was administered once or twice daily as the basal insulin in both treatment groups. There was a 2 to 4-week run-in period with regular human insulin and human insulin extended zinc suspension before randomization.

The mean age of these patients was 31 years (range 12 to 70 years), and 47% were male. The population was 97% White.

Table 5: 12 Month Type 1 Diabetes Mellitus Trial in Adults and Pediatric Patients 12 Years of Age and Older – Mean Change in HbA1c% (another insulin lispro product, 100 units/mL, versus regular human insulin, 100 units/mL)

	Another Insulin Lispro Product + Human Insulin Extended Zinc	Regular Human Insulin + Human Insulin Extended Zinc
N	81	86
Baseline HbA1c (%)*	8.2 ± 1.4	8.3 ± 1.7
Change from baseline HbA1c (%)*	-0.1 ± 0.9	0.1 ± 1.1

Table 5: 12 Month Type 1 Diabetes Mellitus Trial in Adults and Pediatric Patients 12 Years of Age and Older – Mean Change in HbA1c% (another insulin lispro product, 100 units/mL, versus regular human insulin, 100 units/mL) (continued)

	Another Insulin Lispro Product + Human Insulin Extended Zinc	Regular Human Insulin + Human Insulin Extended Zinc
Treatment difference in HbA1c mean (95% confidence interval)	0.4 (0.0; 0.8)	

*Values are Mean ± SD.

Another Insulin Lispro Product, 100 units/mL: Studies in Pediatric Patients 3 Years of Age and Older

An 8-month, crossover study of pediatric patients with type 1 diabetes (n=463), aged 9 to 19 years, compared two subcutaneous multiple-dose treatment regimens: another insulin lispro product, 100 units/mL, or regular human insulin, 100 units/mL, both administered with NPH human insulin isophane suspension as the basal insulin. Insulin lispro achieved glycemic control comparable to regular human insulin, as measured by HbA1c (see Table 6).

Table 6: Type 1 Diabetes Mellitus Trial in Pediatric Patients 9 Years of Age and Older – Mean Change in HbA1c (%) (another insulin lispro product, 100 units/mL, versus regular human insulin, 100 units/mL)

	Baseline	Another Insulin Lispro Product + NPH	Regular Human Insulin + NPH
HbA1c (%)*	8.6 ± 1.5	8.7 ± 1.5	8.7 ± 1.6
Change from baseline HbA1c (%)*	-	0.1 ± 1.1	0.1 ± 1.3

*Values are Mean ± SD.

In a 9-month, crossover study of pediatric patients with type 1 diabetes mellitus (n=60), aged 3 to 11 years, compared three subcutaneous injection regimens: another insulin lispro product, 100 units/mL, administered immediately before meals, this same insulin lispro product, 100 units/mL, administered immediately after meals and regular human insulin, 100 units/mL administered 30 minutes before meals resulted in similar glycemic control, as measured by HbA1c, regardless of treatment group.

14.3 Type 1 Diabetes Mellitus – Continuous Subcutaneous Infusion

Another Insulin Lispro Product, 100 units/mL: Studies in Adult and Pediatric Patients 15 Years of Age and Older

To evaluate the administration of another insulin lispro product, 100 units/mL, as a subcutaneous infusion via external insulin pumps, two open-label, crossover studies were performed in patients with type 1 diabetes mellitus.

- One study involved 39 patients, ages 19 to 58 years, treated for 24 weeks with another insulin lispro product, 100 units/mL, or regular human insulin 100 units/mL. After 12 weeks of treatment, the mean HbA1c values decreased from 7.8% to 7.2% in patients treated with another insulin lispro, and from 7.8% to 7.5% in the regular human insulin-treated patients.
- Another study involved 60 patients (mean age 39, range 15 to 58 years) treated for 24 weeks with either another insulin lispro product, 100 units/mL, or buffered regular human insulin, 100 units/mL. After 12 weeks of treatment, the mean HbA1c values decreased from 7.7% to 7.4% in patients treated with insulin lispro and remained unchanged from 7.7% in the buffered regular human insulin-treated patients.

Another Insulin Lispro Product, 100 units/mL: Study in Pediatric Patients 4 Years of Age and Older

A randomized, 16-week, open-label, parallel design, study of pediatric patients with type 1 diabetes mellitus (n=298), aged 4 to 18 years, compared two subcutaneous continuous infusion regimens administered via an external insulin pump: insulin aspart, 100 units/mL (n=198), or another insulin lispro product, 100 units/mL (n=100). These two treatments resulted in comparable changes from baseline in HbA1c after 16 weeks of treatment (see Table 7).

Table 7: 16 Week Type 1 Diabetes Mellitus Trial in Pediatric Patients 4 Years of Age and Older – Mean Change in HbA1c (%) (another insulin lispro product, 100 units/mL, versus insulin aspart, 100 units/mL) in Insulin Pump Study

	Another Insulin Lispro Product	Insulin Aspart
N	100	198
Baseline HbA1c (%)*	8.2 ± 0.8	8.0 ± 0.9
Change from Baseline HbA1c (%)	-0.1 ± 0.7	-0.1 ± 0.8
Treatment Difference in HbA1c, Mean (95% confidence interval)	0.1 (-0.3, 0.1)	

*Values are Mean ± SD.

14.4 Type 2 Diabetes Mellitus

ADMELOG: Study in Adult Patients

A 26-week open-label, active-controlled study (NCT02294474) evaluated the glucose lowering effect of ADMELOG plus insulin glargine, 100 units/mL, compared to that of Comparator (another insulin lispro product, 100 units/mL, or a non–U.S.-licensed insulin lispro, 100 units/mL) plus insulin glargine, 100 units/mL. A total of 505 patients with type 2 diabetes mellitus treated with insulin glargine, 100 units/mL, and rapid-acting mealtime insulin analogs participated in the study. Patients were randomized to ADMELOG, 100 units/mL (n=253) or Comparator (n=252). ADMELOG or Comparator, was administered by subcutaneous injection immediately prior to meals.

The mean age of these patients was 63 years, and 53% were male. The population was 88% White, 6% Black or African American and 18% were Hispanic. The population had type 2 diabetes mellitus for a mean duration of 17 years. The mean eGFR was 77.9 mL/min/1.73 m^2 and 26.9% of patients had GFR >90 mL/min/1.73 m^2. The mean BMI was approximately 32.2 kg/m^2. At baseline, 51%, 48%, and 0.4% of the patients were using other insulin lispro products, 100 units/mL, insulin aspart, 100 units/mL, or both, respectively.

At week 26, treatment with ADMELOG provided a mean reduction in HbA1c that was non-inferior to that achieved with the Comparator (see Table 8).

Table 8: 26 Week Type 2 Diabetes Mellitus Trial in Adults – Mean Change in HbA1c (%) (ADMELOG plus insulin glargine, 100 units/mL, versus Comparator plus insulin glargine, 100 units/mL)

	ADMELOG + Insulin Glargine	Comparator + Insulin Glargine
N*	253	252
HbA1c (%)		
Baseline (mean)	8.00	8.03
Adjusted mean change from baseline†	-0.86	-0.80
Adjusted mean difference‡ (95% CI)	-0.06 (-0.209 to 0.091)	

*ITT: Intent-to-treat; all randomized patients.

†Estimated using a multiple imputation method that models a "return-to-baseline" for patients having missing data who discontinued treatment. ANCOVA was used with treatment and stratification groups as fixed factors and baseline HbA1c as a covariate.

‡Treatment difference: ADMELOG – Comparator.

Another Insulin Lispro Product, 100 units/mL: Study in Adult Patients

A 6-month randomized, crossover, open-label, active-controlled study was conducted in 722 patients with type 2 diabetes mellitus treated with insulin to assess the safety and efficacy of another insulin lispro product, 100 units/mL, for 3 months followed by regular human insulin, 100 units/mL, for 3 months or the reverse sequence. This other insulin lispro product was administered by subcutaneous injection immediately before meals and regular human insulin was administered 30 to 45 minutes before meals. NPH human insulin isophane suspension or human insulin extended zinc suspension was administered once or twice daily as the basal insulin in both treatment groups. All patients participated in a 2 to 4-week run-in period with regular human insulin and NPH human insulin isophane suspension or human insulin extended zinc suspension.

Most of the patients were White (88%), and the numbers of males and females in each group were approximately equal. The mean age was 59 years (range 24 to 85 years). The average body mass index (BMI) was 28.2 kg/m^2. During the study, the majority of patients used NPH human insulin isophane suspension (84%) compared with human insulin extended zinc suspension (16%) as their basal insulin. The reductions from baseline in HbA1c were similar between the two treatments from the combined groups (see Table 9).

Table 9: 3 Month Trial in Adults with Type 2 Diabetes Mellitus– Mean Change in HbA1c (%) (another insulin lispro product, 100 units/mL, versus regular human insulin, 100 units/mL)

	Baseline	Another Insulin Lispro Product + Basal Insulin	Regular Human Insulin + Basal Insulin
HbA1c (%)*	8.9 ± 1.7	8.2 ± 1.3	8.2 ± 1.4
Change from baseline HbA1c (%)*	-	-0.7 ± 1.4	-0.7 ± 1.3

*Values are Mean ± SD.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADMELOG (insulin lispro) injection 100 units/mL (U-100) is available as a clear and colorless solution in:

Dosage Unit	Package Size	NDC #
10 mL multiple-dose vials	Carton of 1	0024-5924-10
3 mL multiple-dose vials	Carton of 1	0024-5926-05
3 mL single-patient-use SoloStar prefilled pen	Carton of 5	0024-5925-05

Each prefilled SoloStar pen is for use by a single patient.

The ADMELOG SoloStar prefilled pen dials in 1-unit increments.

16.2 Storage and Handling

Dispense in the original sealed carton with the enclosed Instructions for Use.

Store ADMELOG according to the table below. Do not freeze and do not use ADMELOG if it has been frozen. Protect from direct heat and light.
In-use (opened) ADMELOG vials and ADMELOG SoloStar pens must be used within 28 days or be discarded, even if they still contain ADMELOG.

ADMELOG	Not In-Use (Unopened) Room Temperature (Up to 86°F [30°C])	Not In-Use (Unopened) Refrigerated (36°F–46°F [2°C–8°C])	In-Use (Opened) Room Temperature (Up to 86°F [30°C])
10 mL multiple-dose vial	28 days	Until expiration date	28 days refrigerated/room temperature
3 mL multiple-dose vial	28 days	Until expiration date	28 days refrigerated/room temperature
3 mL single-patient-use SoloStar prefilled pen	28 days	Until expiration date	28 days **Do not refrigerate.**

Use in an External Insulin Pump
Change the ADMELOG in the pump reservoir at least every 7 days or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 98.6°F (37°C).
Diluted ADMELOG for Subcutaneous Injection
Diluted ADMELOG may remain in patient use for up to 24 hours when stored in a refrigerator (36°F–46°F [2°C–8°C]) or for up to 4 hours when stored at room temperature (86°F [30°C]). Do not dilute ADMELOG used in an external insulin pump.
Admixture for Intravenous Administration
Infusion bags prepared with ADMELOG are stable when stored in a refrigerator (36°F–46°F [2°C–8°C]) for 24 hours or may be used at room temperature for up to 4 hours *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
Never Share an ADMELOG SoloStar Prefilled Pen or Syringe Between Patients
Advise patients that they must never share an ADMELOG SoloStar pen with another person, even if the needle is changed. Advise patients using ADMELOG vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.
Hyperglycemia or Hypoglycemia
Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of ADMELOG therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery *[see Warnings and Precautions (5.3)]*.
Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.
Hypoglycemia due to Medication Errors
Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products *[see Warnings and Precautions (5.4)]*.
Hypersensitivity Reactions
Advise patients that hypersensitivity reactions have occurred with ADMELOG. Inform patients on the symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.5)]*.
Instructions for Patients Using Continuous Subcutaneous Insulin Pumps

- Train patients in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.
- Instruct patients to follow healthcare provider recommendations when setting pump basal rates and bolus settings.
- Refer to the continuous subcutaneous infusion pump user manual to see if ADMELOG can be used with the pump. See recommended reservoir and infusion sets in the insulin pump user manual.
- Instruct patients to replace insulin in the reservoir at least every 7 days, or according to the pump user manual, whichever is shorter. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin preservative.
- Instruct patients that infusion sets and infusion set insertion sites should be changed according to the manufacturer's user manual.
- Instruct patients to discard insulin exposed to temperatures higher than 98.6°F (37°C). The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat.
- Instruct patients to inform healthcare provider and select a new site for infusion if infusion site becomes erythematous, pruritic, or thickened.
- Instruct patients on the risk of rapid hyperglycemia and ketosis due to pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Instruct patients on the risk of hypoglycemia from pump malfunction. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their healthcare provider *[see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)]*.

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
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PATIENT INFORMATION
ADMELOG® (ad-mah-log)
(insulin lispro)
injection, for subcutaneous or intravenous use
100 units/mL (U-100)

Do not share your ADMELOG SoloStar® Pen or syringe with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is ADMELOG?

- ADMELOG is a man-made fast-acting insulin used to control high blood sugar in adults and children with diabetes mellitus.

Do not use ADMELOG if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to ADMELOG or any of the ingredients in ADMELOG. See the end of this Patient Information leaflet for a complete list of ingredients in ADMELOG.

Before using ADMELOG, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- take other medicines, especially ones commonly called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with ADMELOG.
- are pregnant, or plan to become pregnant. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. Talk to your healthcare provider about the best way to feed your baby while using ADMELOG.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Before you start using ADMELOG, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use ADMELOG?

- Read the detailed **Instructions for Use** that come with your 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.
- Know the type, strength, and amount of insulin you use. **Do not** change the type or amount of insulin you use unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take a different type of insulin.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.

- ADMELOG comes in a vial or in a SoloStar single-patient-use prefilled pen.
  Do not reuse needles. **Always use a new needle for each injection**. Reuse of needles increases your risk of having blocked needles, which may cause you to get the wrong dose of ADMELOG. Using a new needle for each injection also lowers your risk of getting an infection. If your needle is blocked, follow the instructions in Step 3 of the Instructions for Use of your pen.
- **ADMELOG starts acting fast. Inject ADMELOG within 15 minutes before eating or right after eating a meal.**
- Inject ADMELOG under the skin (subcutaneously) of your upper arms, thighs, buttocks, or stomach area (abdomen), or by continuous infusion under the skin (subcutaneously) through an insulin pump into an area of your body recommended in the instructions that come with your insulin pump.
- **Change (rotate) your injection site within the area you choose with each dose** to reduce your risk of getting pits in skin or thickened skin (lipodystrophy) and skin with lumps (localized cutaneous amyloidosis) at the injection sites.
  - **Do not** use the exact same spot for each injection.
  - **Do not** inject where the skin has pits, is thickened, or has lumps.
  - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

Keep ADMELOG and all medicines out of the reach of children.

Your dose of ADMELOG may need to change because of:
- a change in physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What should I avoid while using ADMELOG?
While using ADMELOG do not:
- drive or operate heavy machinery, until you know how ADMELOG affects you.
- drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of ADMELOG?
ADMELOG may cause serious side effects that can lead to death, including:
- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - headache
  - shakiness
  - irritability or mood changes
  - sweating
  - blurred vision
  - fast heartbeat
  - hunger
  - confusion
  - slurred speech
  - anxiety
- **serious allergic reactions (whole body reaction). Get medical help right away, if you have any of these signs or symptoms of a severe allergic reaction:**
  - a rash over your whole body
  - a fast heartbeat
  - sweating
  - trouble breathing
  - feel faint
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with ADMELOG may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with ADMELOG. Your healthcare provider should monitor you closely while you are taking TZDs with ADMELOG. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
  - shortness of breath
  - swelling of your ankles or feet
  - sudden weight gain.

  Treatment with TZDs and ADMELOG may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.
- **sudden onset of high blood sugar (hyperglycemia) and high amounts of ketones in the blood or urine (ketoacidosis) due to insulin pump problems.** If ADMELOG is given through an insulin pump and the pump is not working the right way or in case of handling errors, you may not get the right amount of insulin, which can cause a sudden onset of high blood sugar and high amounts of ketones in the blood or urine.

Get emergency medical help if you have:
- trouble breathing
- swelling of your face, tongue, or throat
- dizziness
- shortness of breath
- sweating
- confusion
- fast heartbeat
- extreme drowsiness

The most common side effects of ADMELOG include:
- low blood sugar (hypoglycemia), allergic reactions, including reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, and rash.

These are not all the possible side effects of ADMELOG. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ADMELOG.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use ADMELOG for a condition for which it was not prescribed. **Do not** give ADMELOG to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about ADMELOG that is written for health professionals. For more information, go to www.sanofi.com or call 1-800-633-1610.

What are the ingredients in ADMELOG?
Active ingredient: insulin lispro
Inactive ingredients: dibasic sodium phosphate, glycerin, metacresol, water for injection, and zinc oxide (zinc ion). Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

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This Patient Information has been approved by the U.S. Food and Drug Administration.
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