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: 1996

----------INDICATIONS AND USAGE----------

ADMELOG is a rapid-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus. (1)

----------DOSAGE AND ADMINISTRATION----------

- See Full Prescribing Information for important administration instructions. (2.1, 2.2, 2.3, 2.4)
- Subcutaneous injection: Administer ADMELOG by subcutaneous injection within 15 minutes before a meal or immediately after a meal. (2.2)
- Continuous subcutaneous infusion (Insulin Pump): Administer ADMELOG by continuous subcutaneous infusion using an insulin pump. (2.2)
- 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 individual'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 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. (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:* Carry out under close medical supervision and increase 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:* Severe, life-threatening, generalized allergic, including anaphylaxis can occur. 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 Affect Glucose Metabolism:* Adjustment of insulin dosage may be needed. (7.1, 7.2, 7.3)
- *Antiadrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent. (5.3, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

- *Pediatrics:* Safety and effectiveness not established in pediatric patients < 3 years of age with type 1 diabetes mellitus or in pediatric patients with type 2 diabetes mellitus. (8.4)

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

Revised: 12/2017

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 adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important 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.
- Do NOT mix ADMELOG with other insulins when administering using a continuous subcutaneous infusion pump.

2.2 Route of Administration

Subcutaneous Injection

- Administer the dose of ADMELOG within fifteen minutes before a meal or immediately after a meal.
- ADMELOG administered by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin.
- ADMELOG should be administered by subcutaneous injection in the abdominal wall, thigh, upper arm, or buttocks. Rotate injection site within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.

Continuous Subcutaneous Infusion (Insulin Pump)

- Administer ADMELOG by continuous subcutaneous infusion into the subcutaneous tissue of the abdominal wall. Rotate infusion sites within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- Follow healthcare provider recommendations when setting basal and mealtime infusion rate.
- Do NOT dilute or mix ADMELOG when administering by continuous subcutaneous infusion.
- Change ADMELOG in the pump reservoir at least every 7 days.
- Change the infusion sets and the infusion set insertion site at least every 3 days.
- Do NOT expose ADMELOG in the pump reservoir to temperatures greater than 98.6°F (37°C).
- Use ADMELOG in accordance with the insulin infusion pump systems instructions for use. See the insulin infusion pump system labeling to determine if ADMELOG can be used with the pump system.

Intravenous Administration

- Dilute ADMELOG to concentrations from 0.1 unit/mL to 1 unit/mL using 0.9% sodium chloride.

- Administer ADMELOG intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6) and How Supplied/Storage and Handling (16.4)]*.

2.3 Dosage Information

- Individualize and adjust the dosage of ADMELOG based on route of administration, the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dosage adjustments 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)]*.
- If changing patients 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)]*.

2.4 Dosage Adjustment Due to Drug Interactions

- Dosage adjustment may be needed when ADMELOG is coadministered with certain drugs *[see Drug Interactions (7)]*.
- Dosage adjustment may be needed when switching from another insulin to ADMELOG *[see Warnings and Precautions (5.2)]*.
- **Do NOT mix** ADMELOG with any other insulin.

3 DOSAGE FORMS AND STRENGTHS

Insulin lispro injection 100 units per mL (U-100) is available as:

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

4 CONTRAINDICATIONS

ADMELOG is contraindicated:

- during episodes of hypoglycemia.
- in patients who are hypersensitive to insulin lispro or to any of the excipients.

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 insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. These changes should be made cautiously and under close medical supervision and the frequency

of blood glucose monitoring should be increased. 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 insulin preparations, 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 coadministered 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 basal insulin products and other insulins, particularly rapid-acting insulins, 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 allergic reactions, including anaphylaxis, can occur with insulin products, 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 *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, 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 also discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic 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.

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 occurring 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) occurring in ≥5% of ADMELOG-treated patients (n=253) were observed.

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

	ADMELOG + Insulin Glargine (100 units/mL), % (n=252)
Nasopharyngitis	13.1%
Upper respiratory tract infection	6.0%

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)]*.

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. Rotate

insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration (2.2)]*.

Weight Gain

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

Peripheral Edema

Insulin, 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)

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 children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions for another insulin lispro product, 100 units/mL, occurred in 21% of patients. The most frequently reported infusion site adverse events 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 metacresol, which is an excipient in ADMELOG *[see Contraindications (4)]*.

6.2 Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with ADMELOG may develop anti-insulin antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, the incidence of antibodies to ADMELOG in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other products.

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 postapproval 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 postapproval use *[see Patient Counseling Information (17)]*.

7 DRUG INTERACTIONS

7.1 Drugs that May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with ADMELOG use may be increased when coadministered with antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide). Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is coadministered with these drugs.

7.2 Drugs that May Decrease the Blood Glucose Lowering Effect of ADMELOG

The glucose lowering effect of ADMELOG may be decreased when coadministered with corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is coadministered with these drugs.

7.3 Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of ADMELOG

The glucose lowering effect of ADMELOG may be increased or decreased when coadministered with beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when ADMELOG is coadministered with these drugs.

7.4 Drugs that May Blunt Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)]* may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are coadministered with ADMELOG.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with ADMELOG in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. 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, stillbirth, 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 embryofetal 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 embryofetal 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

There is no information regarding the presence of insulin lispro in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk.

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 have been established in pediatric patients with type 1 diabetes mellitus who are 3 years of age and older. Use of ADMELOG in these age groups is supported by evidence from adequate and well-controlled studies of ADMELOG and another insulin lispro product, 100 units/ml, in adults with additional data from adequate and well-controlled studies of pediatric patients using another insulin lispro product, 100 units/ml *[see Clinical Studies (14)]*.

The safety and effectiveness of ADMELOG have not been established in pediatric patients younger than 3 years of age with type 1 diabetes mellitus or in pediatric patients with type 2 diabetes mellitus.

The dosage of ADMELOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

8.5 Geriatric Use

Of the total number of subjects (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 had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age.

Of the total number of subjects (n=1,011) in clinical studies of patients treated with ADMELOG or another insulin lispro product, 100 units/mL, 26.5% (n=268) were 65 years of age or over. The majority of these 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)]*.

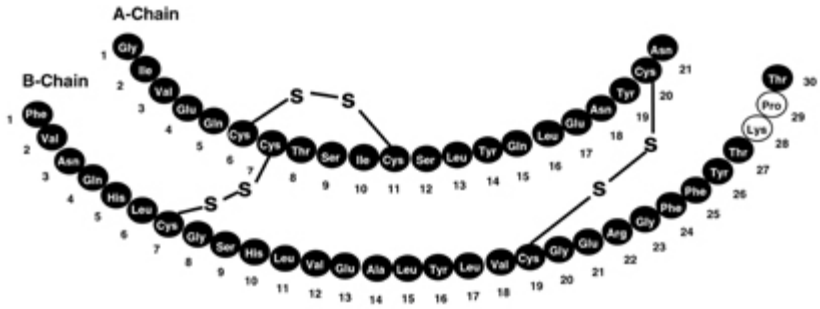
10 OVERDOSAGE

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 intramuscular/subcutaneous glucagon 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

ADMELOG (insulin lispro injection) is a rapid-acting human insulin analog used to lower blood glucose. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analog and has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

ADMELOG has the following primary structure:



ADMELOG is a sterile, aqueous, clear, and colorless solution. Each milliliter of ADMELOG contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, and Water for Injection. 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.

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

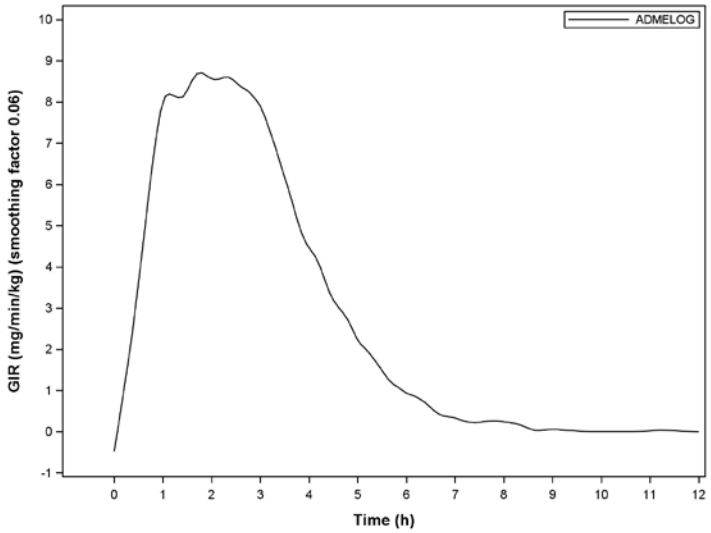
lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

Subcutaneous Administration

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 2.07 (0.78) 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)]*.

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 2. 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 2: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of Another Insulin Lispro Product, 100 units/mL

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
300	120 ± 27
360	122 ± 25

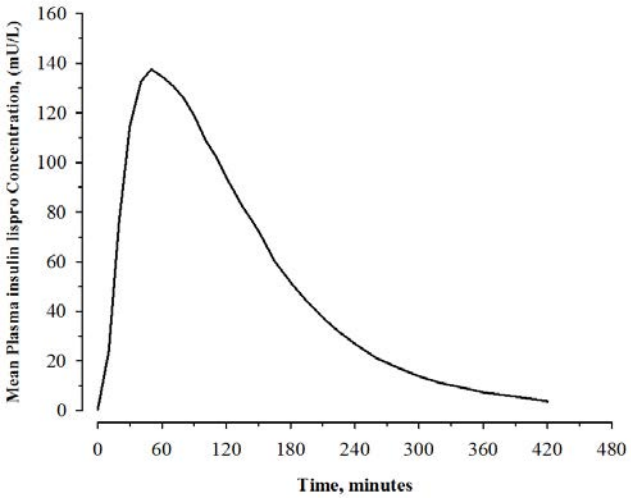
* Results shown as mean ± SD

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. Careful glucose monitoring and dose adjustments of insulin, including ADMELOG, may be necessary in patients with renal dysfunction.

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. Careful glucose monitoring and dose adjustments of insulin, including ADMELOG, may be necessary in patients with hepatic dysfunction.

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 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.

The safety and effectiveness of 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.-approved insulin lispro, 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 subjects was 43 years, and 59.6% were male. The population was 82.1% White, 4.7% Black or African American and 5.3% 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, 60.6%, 37.5% and 2.0% 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 3).

Table 3: Type 1 Diabetes Mellitus – Adults – Mean Change in HbA1c (ADMELOG plus Insulin Glargine, 100 units/mL, versus Comparator plus Insulin Glargine, 100 units/mL)

Treatment Duration **Treatment in Combination with:**	**26 Weeks** **Insulin Glargine**	
	ADMELOG	**Comparator**
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. 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 subjects was 31 years (range 12 to 70 years), and 47% were male. The population was 97% White.

Table 4: Type 1 Diabetes Mellitus – 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)

Treatment Duration **Treatment in Combination with:**	**12 Months** **Human Insulin Extended Zinc**	
	Another Insulin Lispro Product	**Regular Human Insulin**
N	81	86
Baseline HbA1c (%)*	8.2 ± 1.4	8.3 ± 1.7
Change from baseline HbA1c (%)[a]	-0.1 ± 0.9	0.1 ± 1.1
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 5).

Table 5: Type 1 Diabetes Mellitus – 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 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 6).

Table 6: Type 1 Diabetes Mellitus – 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

Treatment duration	16 Weeks	
	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.-approved 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 subjects was 62.5 years, and 53.1% were male. The population was 88.3% White, 6.1% Black or African American and 17.8% 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, 51.4%, 48.2%, 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 7).

Table 7: Type 2 Diabetes Mellitus – Adults – Mean Change in HbA1c (%) (ADMELOG plus insulin glargine, 100 units/mL, versus comparator plus insulin glargine, 100 units/mL)

Treatment Duration **Treatment in Combination with:**	**26 Weeks** **Insulin Glargine**	
	ADMELOG	**Comparator**
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. 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 Caucasian (88%), and the numbers of men and women in each group were approximately equal. The mean age was 58.6 years (range 23.8 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 8).

Table 8: Type 2 Diabetes Mellitus – Adults – Mean Change in HbA1c (%) (another insulin lispro product, 100 units/mL, versus regular human insulin, 100 units/mL)

Treatment Duration		**3 Months**	
	Baseline	**Another Insulin Lispro Product + Basal**	**Regular Human Insulin + Basal**
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 per mL (U-100) is available as:

Dosage Unit	**Package Size**	**NDC#**
10 mL multiple-dose vials	Carton of 1	0024-5924-10
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. ADMELOG SoloStar 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.

16.2 Storage and Handling

Do not use after the expiration date.

Not in-use (unopened) ADMELOG should be stored in a refrigerator (36°F-46°F [2°C-8°C]), but not in the freezer. Do not use ADMELOG if it has been frozen.

In-use (opened) ADMELOG vials and ADMELOG SoloStar pens should be stored at room temperature (below 86°F [30°C]) and must be used within 28 days or be discarded, even if they still contain ADMELOG. Protect from direct heat and light.

See table below:

ADMELOG	**Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])**	**Not In-Use (Unopened) Refrigerated (36°F-46°F [2°C-8°C])**	**In-Use (Opened) Room Temperature (Below 86°F [30°C])**
10 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

Insulin in the reservoir should be discarded after 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

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.

16.3 Preparation and Handling

Diluted ADMELOG for Subcutaneous Injection

ADMELOG may be diluted with sterile 0.9% sodium chloride for subcutaneous injection. Diluting one part ADMELOG to one part 0.9% sodium chloride will yield a concentration one-half that of ADMELOG (equivalent to U-50).

16.4 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.

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)]*.

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)]*.

Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Pregnancy

Advise females of reproductive potential with diabetes to inform their doctor if they are pregnant or are contemplating pregnancy *[see Use in Specific Populations (8.1)]*.

Instructions for Patients Using Continuous Subcutaneous Insulin Pumps

Appropriately train patients using external pump infusion therapy on proper pump use.

Insulin pumps should be used in accordance with the pump's instructions for use. Before using ADMELOG in a pump system for continuous subcutaneous insulin infusion, read the pump user manual to make sure that ADMELOG can be used. ADMELOG is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual.

Instruct patients to replace insulin in the reservoir at least every 7 days to avoid insulin degradation, infusion set occlusion, loss of preservative efficacy; infusion sets and infusion set insertion sites should be changed at least every 3 days.

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 report infusion sites that are erythematous, pruritic, or thickened, and to select a new site because continued infusion may increase the skin reaction or alter the absorption of ADMELOG.

Inform patients that pump or infusion set malfunctions or insulin degradation can lead to rapid hyperglycemia and ketosis and to promptly identify and correct the cause of hyperglycemia or ketosis. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. Instruct patients to resume therapy with subcutaneous insulin injection and contact their healthcare professional if these problems cannot be promptly corrected *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)]*.

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Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

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 insulin used to control high blood sugar in adults and children with diabetes mellitus.
- It is not known if ADMELOG is safe and effective in children younger than 3 years of age or when used to treat children with type 2 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, planning to become pregnant, or are breastfeeding. It is not known if ADMELOG may harm your unborn or breastfeeding baby.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, or 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 amount of ADMELOG you use. **Do not** change the amount of ADMELOG 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 disposable 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 is a rapid-acting insulin. Take ADMELOG within **15 minutes** before eating or right after eating a meal.
- ADMELOG is injected under your skin (subcutaneously).
- Change (rotate) your injection site with each dose.
- **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, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood changes, hunger.
- **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, trouble breathing, a fast heartbeat, feel faint, or sweating.
- **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.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

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 no**t 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: glycerin, dibasic sodium phosphate, metacresol, zinc oxide (zinc ion), and Water for Injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Manufactured By**:** sanofi-aventis U.S. LLC, Bridgewater, NJ 08807 A SANOFI COMPANY

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

Approved: Dec 2017

Instructions for Use

ADMELOG® (ad-mah-log)
(insulin lispro injection) for subcutaneous use
10 mL Vial (100 Units/mL, U-100)

Read these Instructions for Use before you start taking ADMELOG and each time you get a new ADMELOG vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your ADMELOG syringes 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.

Supplies needed to give your injection

- an ADMELOG 10 mL vial
- a U-100 insulin syringe and needle
- 2 alcohol swabs
- 1 sharps container for throwing away used needles and syringes. See **"Disposing of used needles and syringes**" at the end of these instructions.

Preparing your ADMELOG dose

- Wash your hands with soap and water or with alcohol.
- Check the ADMELOG label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- Check the insulin to make sure it is clear and colorless. **Do not** use ADMELOG if it is colored or cloudy, or if you see particles in the solution.
- **Do not** use ADMELOG after the expiration date stamped on the label or 28 days after you first use it.
- **Always use a syringe that is marked for U-100 insulin**. If you use a syringe other than a U-100 insulin syringe, you may get the wrong dose of insulin.
- **Always use a new syringe or needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.**

Step 1:

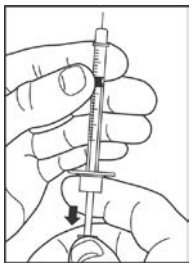
If you are using a new vial, remove the protective cap. **Do not** remove the stopper.

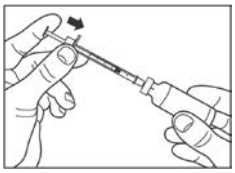
Step 2:

Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of ADMELOG before use.

Step 3:

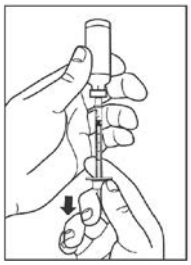
Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.





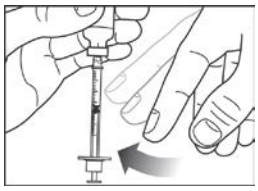
Step 4:

Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.



Step 5:

Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw insulin back in until you have the correct dose.



Step 6:

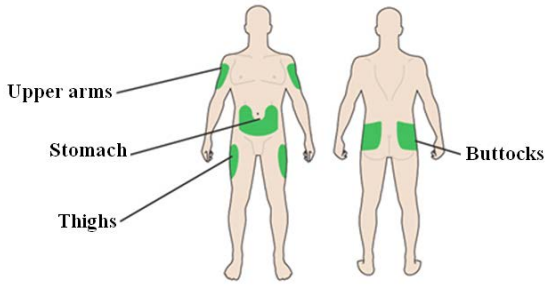
Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

Giving your ADMELOG **injection with a syringe**

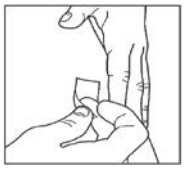
- Inject your insulin exactly as your healthcare provider has shown you.
- **ADMELOG starts acting fast,** so give your injection within 15 minutes before or right after you eat a meal.
- **Change (rotate) your injection site for each injection.**

Step 7:

- Choose your injection site: ADMELOG is injected under the skin (subcutaneously) of your upper arms, thighs, buttocks, or stomach area (abdomen).

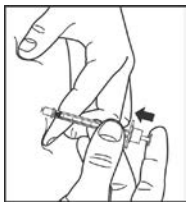


- Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before you inject your dose.



Step 8:

- Pinch the skin.
- Insert the needle in the way your healthcare provider showed you.
- Release the skin.
- Slowly push in the plunger of the syringe all the way, making sure you have injected all the insulin.
- Leave the needle in the skin for about **10** seconds.



Step 9:

- Pull the needle straight out of your skin.
- Gently press the injection site for several seconds. **Do not** rub the area.
- **Do not** recap the used needle. Recapping the needle can lead to a needle-stick injury.

Giving your ADMELOG using an insulin pump

- Change your insertion site every 3 days.
- Change the insulin in the reservoir at least every 7 days, even if you have not used all of the insulin.
- **Do not** dilute or mix ADMELOG with any other type of insulin in your insulin pump.
- See your insulin pump manual for instructions or talk to your healthcare provider.

Disposing of used needles and syringes

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have a FDA-cleared sharps container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

How should I store ADMELOG?

Unopened (not in-use) ADMELOG vials

- Store unused ADMELOG vials in the refrigerator from 36°F to 46°F (2°C to 8°C).
- **Do not** freeze ADMELOG.
- Keep ADMELOG away from direct heat and light.
- If a vial has been frozen or overheated, throw it away.
- Unopened vials can be used until the expiration date on the carton and label if they have been stored in the refrigerator.
- Unopened vials should be thrown away after 28 days if they are stored at room temperature.

After ADMELOG vials have been opened (in-use)

- Store in-use (opened) ADMELOG vials in a refrigerator from 36°F to 46°F (2°C to 8°C) or at room temperature below 86°F (30°C) for up to **28 days**.
- **Do not** freeze ADMELOG.
- Keep ADMELOG out of direct heat and light.
- If a vial has been frozen, throw it away.
- The ADMELOG vial you are using should be thrown away after **28** days, even if it still has insulin left in it.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured By: sanofi-aventis U.S. LLC, Bridgewater, NJ 08807 A SANOFI COMPANY

ADMELOG is a registered trademark of sanofi-aventis U.S. LLC.

Approved: December 2017

Instructions for Use

ADMELOG® SoloStar® (ad-mah-log)
(insulin lispro injection) for subcutaneous use
3 mL disposable prefilled pen (100 Units/mL, U-100)

Read this first

Do not share your ADMELOG SoloStar pen 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.

ADMELOG SoloStar should not be used by people who are blind or have severe vision problems without the help of a person who has good eyesight and who is trained to use the ADMELOG SoloStar the right way.

ADMELOG SoloStar is a disposable prefilled pen used to inject ADMELOG. Each ADMELOG SoloStar has 300 units of insulin which can be used for multiple injections. You can select doses from 1 to 80 units in steps of 1 unit. The pen plunger moves with each dose. The plunger will only move to the end of the cartridge when 300 units of insulin have been given.

Important information

- **Do not** use your pen if it is damaged or if you are not sure that it is working properly.
- **Do not** use a syringe to remove insulin from your pen.
- **Do not reuse needles.** If you do, you might get the wrong dose of ADMELOG and/or increase the chance of getting an infection.
- Always perform a safety test (see **Step 3**).
- Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject

- Talk with your healthcare provider about how to inject before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get too much or too little insulin.

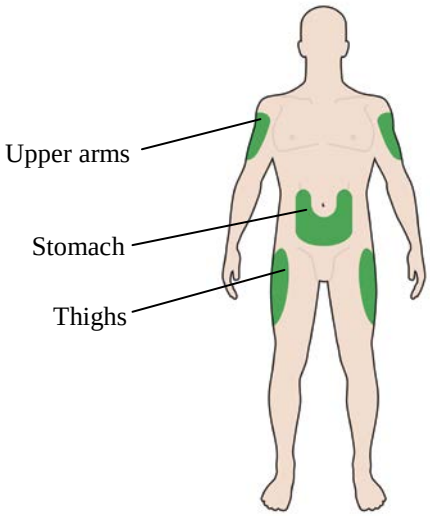
Need help?

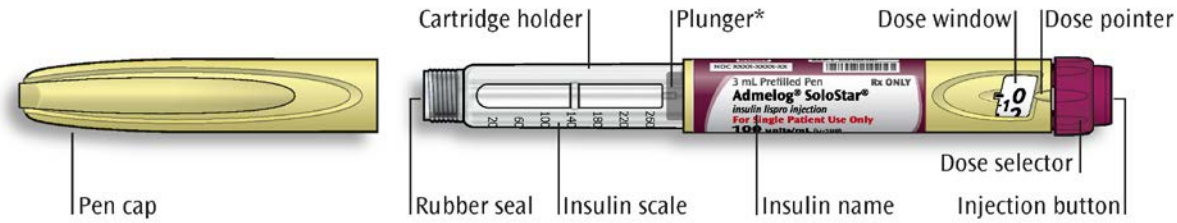
If you have any questions about your pen or about diabetes, ask your healthcare provider, or go to **www.Admelog.com** or call sanofi-aventis at **1-800-633-1610**.

Extra items you will need:

- a new sterile needle (see **Step 2**).
- an alcohol swab.
- a puncture-resistant container for used needles and pens. (See **“Throwing your pen away”**).

Places to inject





*You will not see the plunger until you have injected a few doses

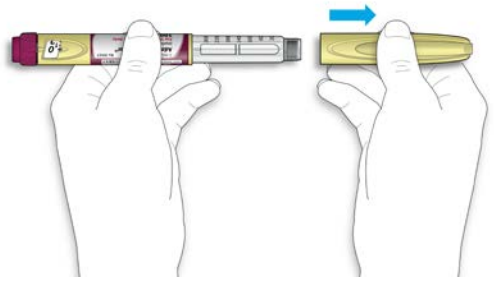
Step 1: Check your pen

Take a new pen out of the refrigerator at least **1** hour before you inject. Cold insulin is more painful to inject.

1A Check the name and expiration date on the label of your pen.

- Make sure you have the correct insulin.
- **Do not** use your pen after the expiration date.

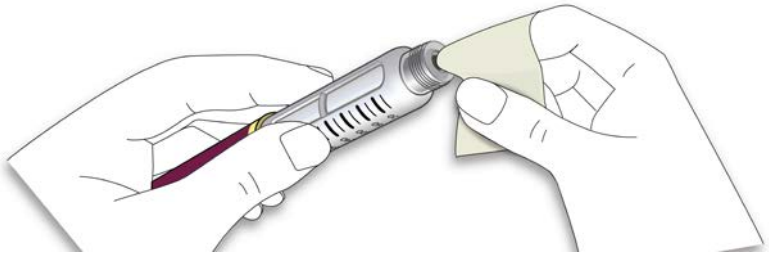
1B Pull off the pen cap.



1C Check that the insulin is clear.

- **Do not** use the pen if the insulin looks cloudy, colored or contains particles.

1D Wipe the rubber seal with an alcohol swab.



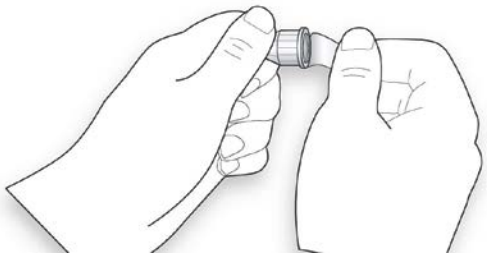
If you have other injector pens:

- Making sure you have the correct medicine is especially important if you have other injector pens.

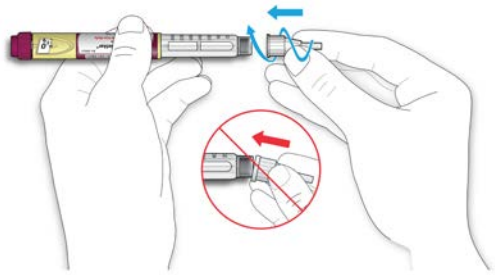
Step 2: Attach a new needle

- **Do not** reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination, and infection.
- Only use needles* that are compatible for use with ADMELOG SoloStar, e.g. needles from BD (such as BD Ultra-Fine®), Ypsomed (such as Clickfine®), Owen Mumford (such as Unifine® Pentips®).

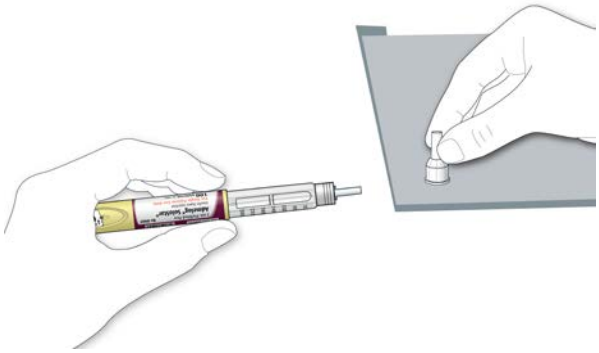
2A Take a new needle and peel off the protective seal.



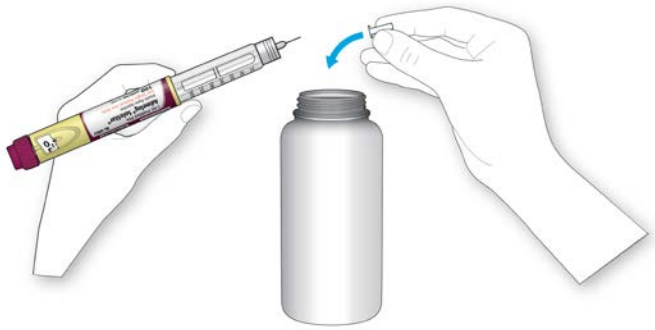
2B Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten.



2C Pull off the outer needle cap. Keep this for later.



2D Pull off the inner needle cap and throw away.



Handling needles:

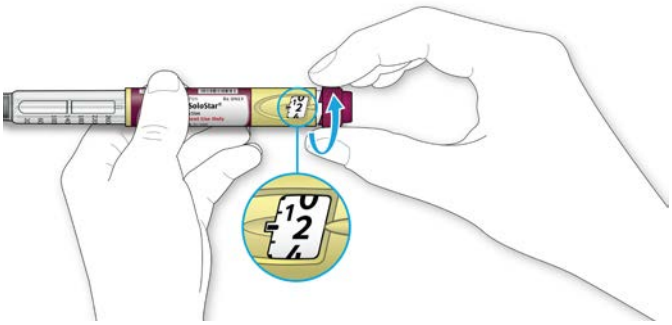
- Take care when handling needles to prevent needle-stick injury and cross-infection.

Step 3: Do a safety test

Always do a safety test before each injection to:

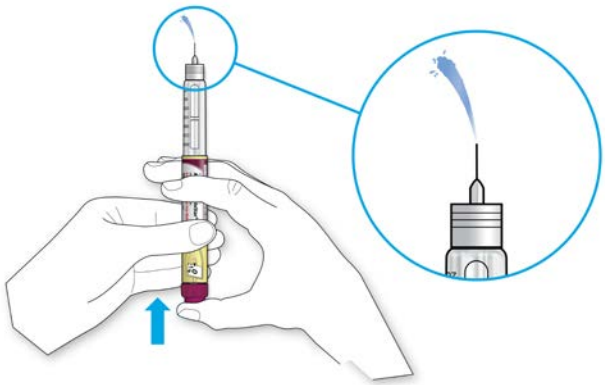
- Check your pen and the needle to make sure they are working properly.
- Make sure that you get the correct insulin dose.

3A Select 2 units by turning the dose selector until the dose pointer is at the 2 mark.



3B Press the injection button all the way in.

- When insulin comes out of the needle tip, your pen is working correctly.



If no insulin appears:

- You may need to repeat this step up to 3 times before seeing insulin.
- If no insulin comes out after the third time, the needle may be blocked. If this happens:
  - change the needle (see **Step 6** and **Step 2**),
  - then repeat the safety test (**Step 3**).
- **Do not** use your pen if there is still no insulin coming out of the needle tip. Use a new pen.
- **Do not** use a syringe to remove insulin from your pen.

If you see air bubbles:

- You may see air bubbles in the insulin. This is normal, they will not harm you.

Step 4: Select the dose

Do not select a dose or press the injection button without a needle attached. This may damage your pen.

4A Make sure a needle is attached and the dose is set to '0'.

4B Turn the dose selector until the dose pointer lines up with your dose.

- If you turn past your dose, you can turn back down.
- If there are not enough units left in your pen for your dose, the dose selector will stop at the number of units left.
- If you cannot select your full prescribed dose, use a new pen or inject the remaining units and use a new pen to complete your dose.

How to read the dose window

Even numbers are shown in line with dose pointer.

20 units selected

Odd numbers are shown as a line between even numbers.

21 units selected

Units of insulin in your pen:

- Your pen contains a total of **300** units of insulin. You can select doses from **1** to **80** units in steps of **1** unit. Each pen contains more than 1 dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale.

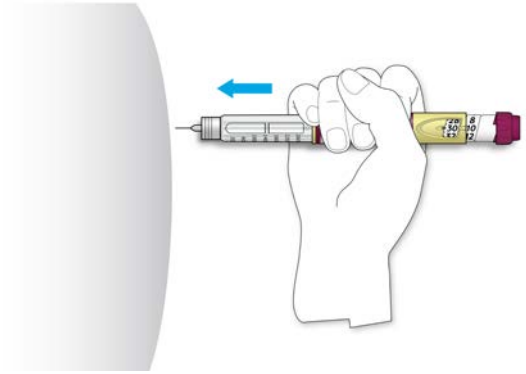
Step 5: Inject your dose

If you find it hard to press the injection button in, **do not** force it as this may break your pen. See the section below for help.

5A Choose a place to inject as shown in the picture above.

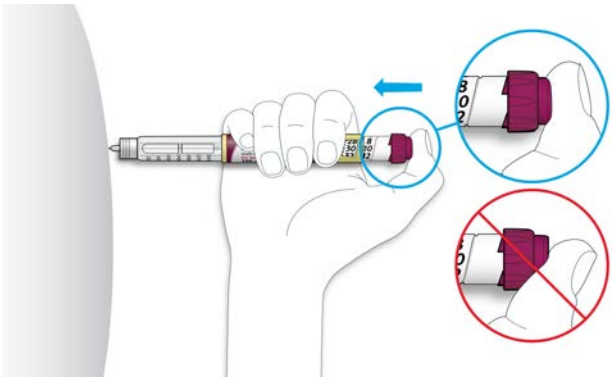
5B Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



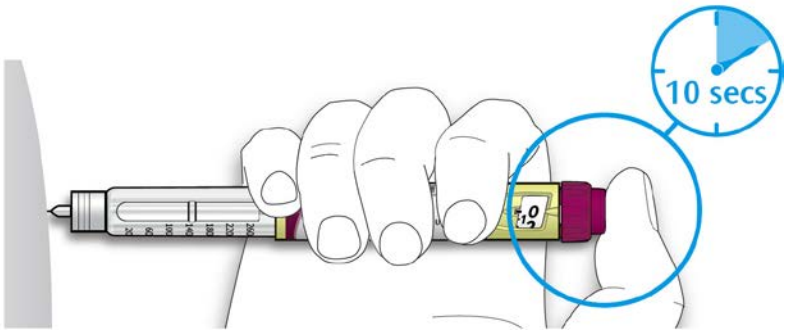
5C Place your thumb on the injection button. Then press all the way in and hold.

- **Do not** press at an angle. Your thumb could block the dose selector from turning.



5D Keep the injection button held in and when you see "0" in the dose window, slowly count to 10.

- This will make sure you get your full dose.



5E After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin.

If you find it hard to press the button in:

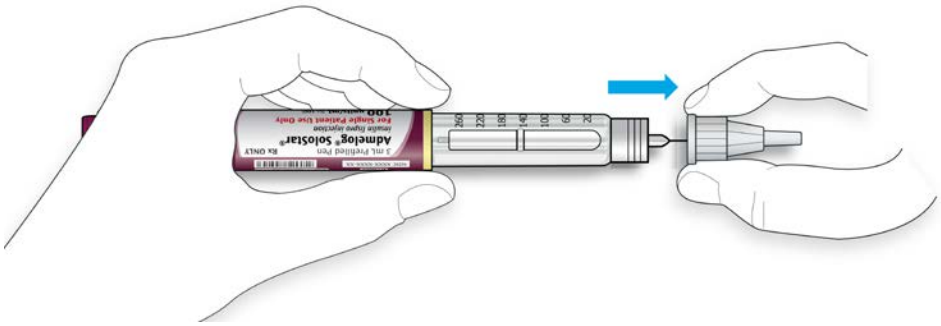
- Change the needle (see **Step 6** and **Step 2**) then do a safety test (see **Step 3**).
- If you still find it hard to press in, get a new pen.
- **Do not** use a syringe to remove insulin from your pen.

Step 6: Remove the needle

- Take care when handling needles to prevent needle-stick injury and cross-infection.
- **Do not** put the inner needle cap back on.

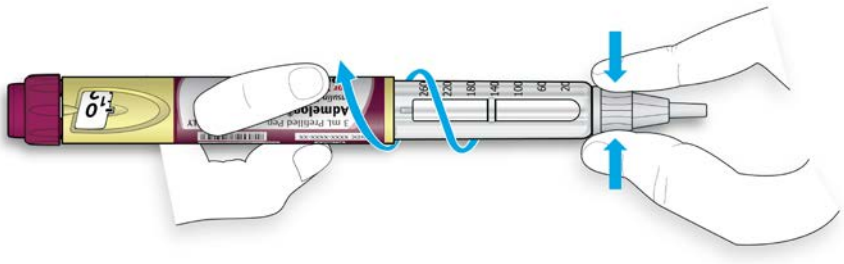
6A Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap. Then push firmly on.

- The needle can puncture the cap if it is recapped at an angle.



6B Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.

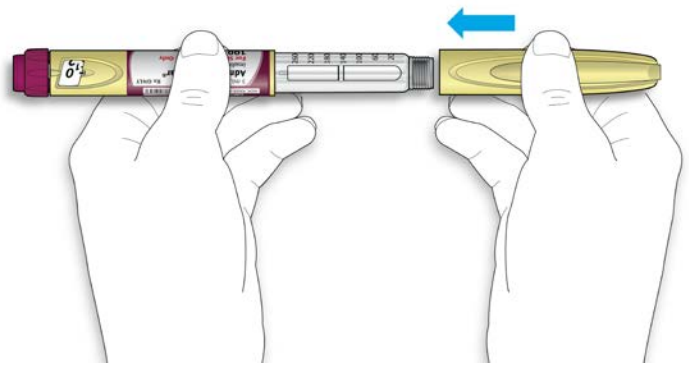
- Try again if the needle does not come off the first time.



6C Throw away the used needle in a puncture-resistant container (see "**Throwing your pen away"** at the end of this Instructions for Use).

6D Put your pen cap back on.

- Do not put the pen back in the refrigerator.



How to store your pen

Before first use

- Keep new pens in the refrigerator between **36°F to 46°F (2°C to 8°C)**.
- **Do not** freeze. **Do not** use ADMELOG if it has been frozen.

After first use

- Keep your pen at room temperature **below 86°F (30°C)**.
- Keep your pen away from heat or light.
- Store your pen with the pen cap on.
- **Do not** put your pen back in the refrigerator.
- **Do not** store your pen with the needle attached.
- **Keep out of the reach of children.**
- Only use your pen for **up to 28 days** after its first use. Throw away the ADMELOG SoloStar pen you are using after 28 day, even if it still has insulin left in it.

How to care for your pen

Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- If you think that your pen may be damaged, **do not** try to fix it. Use a new one.

Protect your pen from dust and dirt

- You can clean the outside of your pen by wiping it with a damp cloth (water only). **Do not** soak, wash or lubricate your pen. This may damage it.

Throwing your pen away

- Put the used ADMELOG SoloStar pen in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the ADMELOG SoloStar pen in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and

- properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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Manfufactured by:
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Approved: December 2017