

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

APIDRA® (insulin glulisine injection), for subcutaneous or intravenous use
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for important administration instructions. (2.1,2.2)
- Individualize and adjust the dosage of APIDRA based on route of administration, individual's metabolic needs, blood glucose monitoring results, and glycemic control goal. (2.2)
- Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns, changes in renal or hepatic function or during acute illness. (2.2)
- **Subcutaneous Injection:** (2.2)
 - Inject within 15 minutes before a meal or within 20 minutes after starting a meal into the abdomen, thigh, or upper arm.
 - Rotate injection sites within the same region.
 - Should generally be used in regimens with an intermediate or long-acting insulin.
- **Continuous Subcutaneous Infusion (Insulin Pump):** (2.2)
 - Administer by continuous subcutaneous infusion in the abdominal wall.
 - Rotate infusion sites within the same region.
 - Do not dilute or mix insulins in external insulin pumps.
- **Intravenous Administration:** Administer only under medical supervision after diluting to concentrations from 0.05 to 1 unit/mL APIDRA in 0.9% sodium chloride injection, USP using polyvinyl chloride infusion bags. (2.2)

DOSAGE FORMS AND STRENGTHS

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

- 10 mL multiple-dose vial
- 3 mL single-patient-use SoloStar® prefilled pen

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to APIDRA or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- **Never share an APIDRA SoloStar pen between patients, even if the needle is changed.** (5.1)
- **Hypoglycemia 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. Increase frequency of glucose monitoring with changes to: insulin dosage, coadministered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness. (5.3)
- **Hypoglycemia Due to Medication Errors:** Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- **Hypokalemia:** May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. (5.5)
- **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue APIDRA, monitor and treat if indicated. (5.6)
- **Fluid Retention and Heart Failure Can Occur with Concomitant Use of Thiazolidinediones (TZDs):** Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation of TZD if heart failure occurs. (5.7)
- **Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:** Monitor glucose and administer APIDRA by subcutaneous injection if pump malfunction occurs. (5.8)

ADVERSE REACTIONS

Adverse reactions commonly associated with APIDRA include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, and weight gain. (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 Increase Hypoglycemia Risk or Increase or Decrease Blood Glucose Lowering Effect:** Adjustment of dosage may be needed; closely monitor blood glucose. (7)
- **Drugs that Blunt Hypoglycemia Signs and Symptoms** (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Increased frequency of glucose monitoring may be required. (7)

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APIDRA is indicated to improve glycemic control in adults and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin label before administration [see Warnings and Precautions (5.4)].

- Inspect visually for particulate matter and discoloration. Only use APIDRA if the solution appears clear and colorless.
- Train patients on proper use and injection technique before initiating APIDRA [see Warnings and Precautions (5.1)].
- Use APIDRA SoloStar prefilled pen with caution in patients with visual impairment who may rely on audible clicks to dial their dose.

- APIDRA may be administered by subcutaneous injection, by continuous subcutaneous infusion (insulin pump), or intravenously [see *Dosage and Administration* (2.2)].
- DO NOT administer APIDRA intramuscularly.

2.2 Dosing and Administration Instructions

General Dosing Instructions

- Individualize and adjust the dosage of APIDRA based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dose adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [see *Warnings and Precautions* (5.2, 5.3), *Drug Interactions* (7), *Use in Specific Populations* (8.6, 8.7)].

Subcutaneous Injection

- Inject APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Administer APIDRA by subcutaneous injection in the abdominal wall, thigh, or upper arm. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [see *Adverse Reactions* (6.1)].
- APIDRA given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin.
- The APIDRA SoloStar prefilled pen dials in 1-unit increments.
- Do not mix APIDRA for subcutaneous injection with insulin preparations other than NPH insulin. If APIDRA is mixed with NPH insulin, draw APIDRA into the syringe first and inject immediately after mixing.

Continuous Subcutaneous Infusion (Insulin Pump)

- Administer APIDRA by continuous subcutaneous infusion in the abdominal wall.
- Rotate infusion sites within the same region to reduce the risk of lipodystrophy [see *Adverse Reactions* (6.1)].
- Do not dilute or mix insulins in external insulin pumps.
- The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen.
- The following insulin pumps[†] have been used in APIDRA clinical trials conducted by sanofi-aventis, the manufacturer of APIDRA:
 - Disetronic[®] H-TRON[®] plus V100 and D-TRON[®] with Disetronic catheters (Rapid[™], Rapid C[™], Rapid D[™], and Tender[™])
 - MiniMed[®] Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR[™], and Quick-set[®]).
 - Before using a different insulin pump with APIDRA, read the pump label to make sure the pump has been evaluated with APIDRA.
- Use APIDRA in accordance with the insulin infusion pump systems instructions for use.
- Change APIDRA in the reservoir and the infusion sets at least every 48 hours.
- Do not expose APIDRA to temperatures greater than 98.6°F (37°C) [see *How Supplied/Storage and Handling* (16.2)].
- Patients administering APIDRA by continuous subcutaneous infusion must have an alternative insulin delivery system in case of pump system failure [see *Warnings and Precautions* (5.8)].

Intravenous Administration

- Administer APIDRA 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, 5.5)].
- Dilute APIDRA to concentrations from 0.05 unit/mL to 1 unit/mL insulin glulisine in infusion systems using polyvinyl chloride (PVC) infusion bags.
- APIDRA is stable at room temperature for 48 hours only in normal saline solution (0.9% Sodium Chloride Injection, USP).
- APIDRA is not compatible with Dextrose solution and Ringers solution.

3 DOSAGE FORMS AND STRENGTHS

APIDRA injection, 100 units per mL (U-100), is a clear and colorless solution available as:

- 10 mL multiple-dose vial
- 3 mL single-patient-use APIDRA SoloStar prefilled pen

4 CONTRAINDICATIONS

APIDRA is contraindicated:

- during episodes of hypoglycemia
- in patients with known hypersensitivity to APIDRA or to any of its excipients; systemic allergic reactions have occurred with APIDRA [see *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share an APIDRA SoloStar Pen or Syringe or Needle between Patients
APIDRA SoloStar pens must never be shared between patients, even if the needle is changed. Patients using APIDRA vials must never reuse or 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, insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments in concomitant oral antidiabetic treatment may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including APIDRA [see *Adverse Reactions* (6.1)]. Severe hypoglycemia can cause seizures, may lead to unconsciousness, 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). APIDRA, or any insulin, should not be used during episodes of hypoglycemia [see *Contraindications* (4)].

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. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of APIDRA 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 insulin products have been reported. To avoid medication errors between APIDRA and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypokalemia

All insulin products, including APIDRA, 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. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.6 Hypersensitivity and Allergic Reactions

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

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 APIDRA 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 APIDRA 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)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions* (5.3)]
- Hypokalemia [see *Warnings and Precautions* (5.5)]
- Hypersensitivity and Allergic Reactions [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. The frequencies of adverse drug reactions during APIDRA clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Adverse Reactions Occurring ≥5% in Pooled Studies of Adults with Type 1 Diabetes

	APIDRA, % (n=950)	All Comparators, % (n=641)
Nasopharyngitis	10.6	12.9
Hypoglycemia [†]	6.8	6.7
Upper respiratory tract infection	6.6	5.6
Influenza	4.0	5.0

*Insulin lispro, regular human insulin, insulin aspart

†Only severe symptomatic hypoglycemia

Table 2: Adverse Reactions Occurring $\geq 5\%$ in Pooled Studies of Adults with Type 2 Diabetes

	APIDRA, % (n=883)	Regular Human Insulin, % (n=883)
Upper respiratory tract infection	10.5	7.7
Nasopharyngitis	7.6	8.2
Edema peripheral	7.5	7.8
Influenza	6.2	4.2
Arthralgia	5.9	6.3
Hypertension	3.9	5.3

Pediatrics

Table 3 summarizes the adverse reactions occurring with frequency higher than 5% in a clinical study in pediatric patients with type 1 diabetes treated with APIDRA (n=277) or insulin lispro (n=295).

Table 3: Adverse Reactions Occurring $\geq 5\%$ in Pediatric Patients with Type 1 Diabetes

	APIDRA, % (n=277)	Lispro, % (n=295)
Nasopharyngitis	9.0	9.5
Upper respiratory tract infection	8.3	10.8
Headache	6.9	11.2
Hypoglycemic seizure	6.1	4.7

Severe Symptomatic Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including APIDRA. 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 APIDRA with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice. The rates and incidence of severe symptomatic hypoglycemia, defined as hypoglycemia requiring intervention from a third party are presented in Table 4. In the clinical trials, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to adults with type 1 diabetes (see Table 4) [see *Clinical Studies (14)*].

Table 4: Severe Symptomatic Hypoglycemia*

	Type 1 Diabetes Adults 12 weeks with insulin glargine			Type 1 Diabetes Adults 26 weeks with insulin glargine		Type 2 Diabetes Adults 26 weeks with NPH human insulin		Type 1 Diabetes Pediatrics 26 weeks	
	APIDRA Pre meal	APIDRA Post meal	Regular Human Insulin	APIDRA	Insulin Lispro	APIDRA	Regular Human Insulin	APIDRA	Insulin Lispro
Events per month per patient	0.05	0.05	0.13	0.02	0.02	0.00	0.00	0.09	0.08
Percent of patients (n/total N)	8.4% (24/286)	8.4% (25/296)	10.1% (28/278)	4.8% (16/339)	4.0% (13/333)	1.4% (6/416)	1.2% (5/420)	16.2% (45/277)	19.3% (57/295)

*Severe symptomatic hypoglycemia defined as a hypoglycemic event requiring the assistance of another person that met one of the following criteria: the event was associated with a whole blood referenced blood glucose < 36 mg/dL or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week randomized study in patients with type 1 diabetes (n=59), the rates of catheter occlusions and infusion site reactions were similar for APIDRA and insulin aspart-treated patients (see Table 5).

Table 5: Catheter Occlusions and Infusion Site Reactions.

	APIDRA (n=29)	Insulin Aspart (n=30)
Catheter occlusions/month	0.08	0.15
Infusion site reactions	10.3% (3/29)	13.3% (4/30)

Allergic Reactions

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

In controlled clinical trials up to 12 months duration, potential systemic allergic reactions were reported in 79 of 1833 patients (4.3%) who received APIDRA and 58 of 1524 patients (3.8%) who received the comparator short-acting insulins. During these trials, treatment with APIDRA was permanently discontinued in 1 of 1833 patients due to a potential systemic allergic reaction.

Injection Site Reactions

As with any insulin therapy, patients taking APIDRA may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions may require discontinuation of APIDRA. 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.

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 APIDRA, 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)*].

Peripheral Edema

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

Weight Gain

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. 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, comparison of the incidence of antibodies to APIDRA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a study in patients with type 1 diabetes (n=333), the concentrations of insulin antibodies that react with both human insulin and insulin glulisine (cross-reactive insulin antibodies) remained near baseline during the first 6 months of the study in the patients treated with APIDRA. A decrease in antibody concentration was observed during the following 6 months of the study. In a study in patients with type 2 diabetes (n=411), a similar increase in cross-reactive insulin antibody concentration was observed in the patients treated with APIDRA and in the patients treated with human insulin during the first 9 months of the study. Thereafter the concentration of antibodies decreased in the APIDRA patients and remained stable in the human insulin patients. There was no correlation between cross-reactive insulin antibody concentration and changes in HbA1c, insulin doses, or incidence of hypoglycemia. APIDRA did not elicit a significant antibody response in a study of children and adolescents with type 1 diabetes.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of APIDRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly long-acting insulins, have been accidentally administered instead of APIDRA.

7 DRUG INTERACTIONS

Table 6: Clinically Significant Drug Interactions with APIDRA

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 analog (e.g., octreotide), and sulfonamide antibiotics.

Table 6: Clinically Significant Drug Interactions with APIDRA (continued)

Drugs that May Increase the Risk of Hypoglycemia	
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when APIDRA is coadministered with these drugs.
Drugs that May Decrease the Blood Glucose Lowering Effect of APIDRA	
<i>Drugs:</i>	Atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, phenothiazine derivatives, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when APIDRA is coadministered with these drugs.
Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of APIDRA	
<i>Drugs:</i>	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when APIDRA is coadministered with these drugs.
Drugs that May Blunt Signs and Symptoms of Hypoglycemia	
<i>Drugs:</i>	Beta-blockers, clonidine, guanethidine, and reserpine.
<i>Intervention:</i>	Increased frequency of glucose monitoring may be required when APIDRA is coadministered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available pharmacovigilance data have not established an association with insulin glulisine use during pregnancy and major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see *Clinical Considerations*). Animal reproduction studies have been conducted with insulin glulisine in rats and rabbits using regular human insulin as a comparator. Insulin glulisine was given to female rats throughout pregnancy at subcutaneous doses up to 10 units/kg/day (2 times the average human dose, based on body surface area comparison) and to rabbits during organogenesis at subcutaneous doses up to 1.5 units/kg/day (0.5 times the average human dose, based on body surface area comparison). The effects did not differ from those observed with subcutaneous regular human insulin (see *Data*).

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20% to 25% in women with an 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% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

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

Data

Animal data

Insulin glulisine was given to pregnant female rabbits during gestation at doses up to 1.5 units/kg/day, resulting in an exposure 0.5 times the average human dose, based on body surface area. Adverse effects on embryo-fetal development, including postimplantation loss and skeletal defects, were observed at dose levels that caused maternal hypoglycemia and mortality.

Insulin glulisine given to pregnant female rats during gestation at doses up to 10 units/kg/day, resulting in an exposure 2 times the average human dose based on body surface area, resulted in maternal toxicity indicative of hypoglycemia but did not adversely affect embryo-fetal development. Postnatal development was not adversely effected following administration of insulin glulisine to pregnant female rats during gestation and throughout lactation at doses up to 8 units/kg/day.

The effects of insulin glulisine did not differ from those observed with regular human insulin used as a comparator in the same studies and administered at the same doses.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

APIDRA is indicated for glycemic control in pediatric patients with type 1 diabetes mellitus. Use of APIDRA for this indication is supported by evidence from a 26-week, randomized, open-label, active-controlled, non-inferiority study in pediatric patients older than 4 years of age with type 1 diabetes mellitus treated with APIDRA (n=271) [see *Clinical Studies* (14.4)].

In the clinical trials, pediatric patients with type 1 diabetes mellitus had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to adults with type 1 diabetes mellitus [see *Adverse Reactions* (6.1)]. The dosage of APIDRA must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In clinical trials, APIDRA was administered to 147 patients ≥65 years of age and 27 patients ≥75 years of age. The majority of this small subset of elderly patients had type 2 diabetes. The change in HbA1c values and hypoglycemia frequencies did not differ by age.

Nevertheless, caution should be exercised when APIDRA is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to reduce the risk of hypoglycemia [see *Warnings and Precautions* (5.3)].

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent APIDRA dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

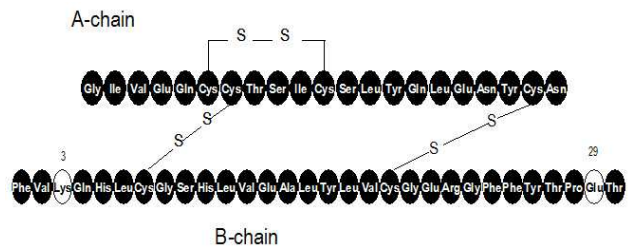
Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent APIDRA dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Excess insulin may cause hypoglycemia and, particularly when given intravenously, 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 of hypoglycemia 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

APIDRA[®] (insulin glulisine injection) is a rapid-acting human insulin analog used to lower blood glucose. Insulin glulisine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12). Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Chemically, insulin glulisine is 3^B-lysine-29^B-glutamic acid-human insulin, has the empirical formula C₂₅₈H₃₈₄N₆₄O₇₈S₆ and a molecular weight of 5823 and has the following structural formula:



APIDRA (insulin glulisine injection) is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous use. Each milliliter of APIDRA contains 100 units (3.49 mg) insulin glulisine, 3.15 mg metacresol, 6 mg tromethamine, 5 mg sodium chloride, 0.01 mg polysorbate 20, and water for injection. APIDRA has a pH of approximately 7.3. 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 glulisine. 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.

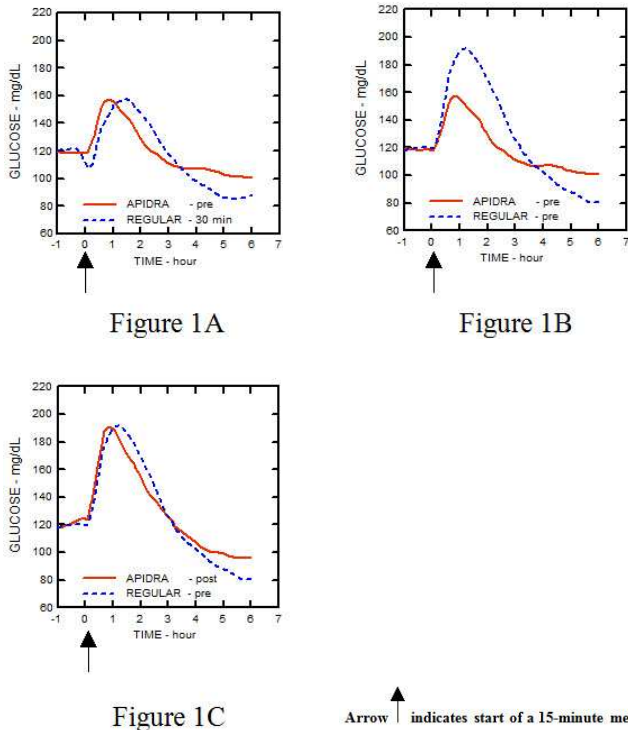
12.2 Pharmacodynamics

Studies in healthy volunteers and patients with diabetes demonstrated that APIDRA has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

In a study in patients with type 1 diabetes (n=20), the glucose-lowering profiles of APIDRA and regular human insulin were assessed at various times in relation to a standard meal at a dose of 0.15 units/kg (see Figure 1).

The maximum blood glucose excursion ($\Delta\text{GLU}_{\text{max}}$; baseline subtracted glucose concentration) for APIDRA injected 2 minutes before a meal was 65 mg/dL compared to 64 mg/dL for regular human insulin injected 30 minutes before a meal (see Figure 1A), and 84 mg/dL for regular human insulin injected 2 minutes before a meal (see Figure 1B). The maximum blood glucose excursion for APIDRA injected 15 minutes after the start of a meal was 85 mg/dL compared to 84 mg/dL for regular human insulin injected 2 minutes before a meal (see Figure 1C).

Figure 1: Serial mean blood glucose collected up to 6 hours following a single dose of APIDRA and regular human insulin. APIDRA given 2 minutes (APIDRA - pre) before the start of a meal compared to regular human insulin given 30 minutes (Regular - 30 min) before start of the meal (see Figure 1A) and compared to regular human insulin (Regular - pre) given 2 minutes before a meal (see Figure 1B). APIDRA given 15 minutes (APIDRA - post) after start of a meal compared to regular human insulin (Regular - pre) given 2 minutes before a meal (see Figure 1C). On the x-axis, zero (0) is the start of a 15-minute meal.



In a randomized, open-label, two-way crossover study, 16 healthy male subjects received an intravenous infusion of APIDRA or regular human insulin with saline diluent at a rate of 0.8 milliunits/kg/min for two hours. Infusion of the same dose of APIDRA or regular human insulin produced equivalent glucose disposal at steady state.

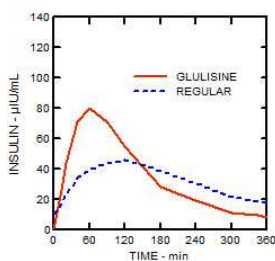
12.3 Pharmacokinetics

Absorption and Bioavailability

Pharmacokinetic profiles in healthy volunteers and patients with diabetes (type 1 or type 2) demonstrated that absorption of insulin glulisine was faster than that of regular human insulin.

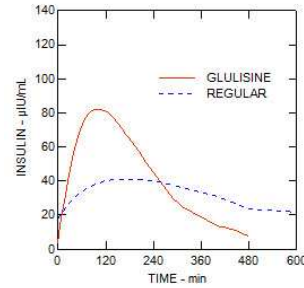
In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 units/kg, the median time to maximum concentration (T_{max}) was 60 minutes (range 40 to 120 minutes) and the peak concentration (C_{max}) was 83 microunits/mL (range 40 to 131 microunits/mL) for insulin glulisine compared to a median T_{max} of 120 minutes (range 60 to 239 minutes) and a C_{max} of 50 microunits/mL (range 35 to 71 microunits/mL) for regular human insulin (see Figure 2).

Figure 2: Pharmacokinetic Profiles of Insulin Glulisine and Regular Human Insulin in Patients with Type 1 Diabetes after a Dose of 0.15 units/kg.



Insulin glulisine and regular human insulin were administered subcutaneously at a dose of 0.2 units/kg in a euglycemic clamp study in patients with type 2 diabetes (n=24) and a body mass index (BMI) between 20 and 36 kg/m². The median time to maximum concentration (T_{max}) was 100 minutes (range 40 to 120 minutes) and the median peak concentration (C_{max}) was 84 microunits/mL (range 53 to 165 microunits/mL) for insulin glulisine compared to a median T_{max} of 240 minutes (range 80 to 360 minutes) and a median C_{max} of 41 microunits/mL (range 33 to 61 microunits/mL) for regular human insulin (see Figure 3).

Figure 3: Pharmacokinetic Profiles of Insulin Glulisine and Regular Human Insulin in Patients with Type 2 Diabetes after a Subcutaneous Dose of 0.2 units/kg.



When APIDRA was injected subcutaneously into different areas of the body, the time-concentration profiles were similar. The absolute bioavailability of insulin glulisine after subcutaneous administration is approximately 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%).

In a clinical study in healthy volunteers (n=32) the total insulin glulisine bioavailability was similar after subcutaneous injection of insulin glulisine and NPH insulin (premixed in the syringe) and following separate simultaneous subcutaneous injections. There was 27% attenuation of the maximum concentration (C_{max}) of APIDRA after premixing; however, the time to maximum concentration (T_{max}) was not affected.

Distribution and Elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration are similar with volumes of distribution of 13 and 21 L and half-lives of 13 and 17 minutes, respectively. After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes.

Specific Populations

Pediatric patients

The pharmacokinetic and pharmacodynamic properties of APIDRA and regular human insulin were assessed in a study conducted in children 7 to 11 years old (n=10) and adolescents 12 to 16 years old (n=10) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics between APIDRA and regular human insulin in these patients with type 1 diabetes were similar to those in healthy adult subjects and adults with type 1 diabetes.

Race

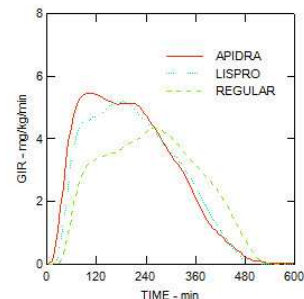
A study in 24 healthy Caucasians and Japanese subjects compared the pharmacokinetics and pharmacodynamics after subcutaneous injection of insulin glulisine, insulin lispro, and regular human insulin. With subcutaneous injection of insulin glulisine, Japanese subjects had a greater initial exposure (33%) for the ratio of $AUC_{(0-1h)}$ to $AUC_{(0-clamp\ end)}$ than Caucasians (21%) although the total exposures were similar. There were similar findings with insulin lispro and regular human insulin.

Obesity

Insulin glulisine and regular human insulin were administered subcutaneously at a dose of 0.3 units/kg in a euglycemic clamp study in obese, non-diabetic subjects (n=18) with a body mass index (BMI) between 30 and 40 kg/m². The median time to maximum concentration (T_{max}) was 85 minutes (range 49 to 150 minutes) and the median peak concentration (C_{max}) was 192 microunits/mL (range 98 to 380 microunits/mL) for insulin glulisine compared to a median T_{max} of 150 minutes (range 90 to 240 minutes) and a median C_{max} of 86 microunits/mL (range 43 to 175 microunits/mL) for regular human insulin.

The more rapid onset of action and shorter duration of activity of APIDRA and insulin lispro compared to regular human insulin were maintained in an obese non-diabetic population (n=18) (see Figure 4).

Figure 4: Glucose Infusion Rates (GIR) in a Euglycemic Clamp Study after Subcutaneous Injection of 0.3 units/kg of APIDRA, Insulin Lispro or Regular Human Insulin in an Obese Population.



Renal impairment

Studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study performed in 24 non-diabetic subjects with normal renal function ($Cl_{Cr} > 80$ mL/min), moderate renal impairment (30–50 mL/min), and severe renal impairment (<30 mL/min), the subjects with moderate and severe renal impairment had increased exposure to insulin glulisine by 29% to 40% and reduced clearance of insulin glulisine by 20% to 25% compared to subjects with normal renal function [see Use in Specific Populations (8.6)].

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure [see Use in Specific Populations (8.7)].

Gender

The effect of gender on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied.

Smoking

The effect of smoking on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed. In Sprague Dawley rats, a 12-month study was conducted with insulin glulisine at subcutaneous doses of 2.5, 5, 20 or 50 units/kg administered twice daily, resulting in an exposure 1, 2, 8, and 20 times the average human dose, based on body surface area.

There was a non-dose dependent higher incidence of mammary gland tumors in female rats administered insulin glulisine compared to untreated controls. The incidence of mammary tumors for insulin glulisine and regular human insulin was similar. Insulin glulisine was not mutagenic in the following tests: Ames test, *in vitro* mammalian chromosome aberration test in V79 Chinese hamster cells, and *in vivo* mammalian erythrocyte micronucleus test in rats.

In fertility studies in male and female rats at subcutaneous doses up to 10 units/kg/day (2 times the average human dose, based on body surface area comparison), no clear adverse effects on male and female fertility, or general reproductive performance of animals were observed.

14 CLINICAL STUDIES

The safety and efficacy of APIDRA was studied in adult patients with type 1 and type 2 diabetes (n=1833) and in pediatric patients (4 to 17 years) with type 1 diabetes (n=572). The primary efficacy parameter in these trials was glycemic control, assessed using glycated hemoglobin (GHb reported as HbA_{1c} equivalent).

14.1 Type 1 Diabetes-Adults

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in patients with type 1 diabetes to assess the safety and efficacy of APIDRA (n=339) compared to insulin lispro (n=333) when administered subcutaneously within 15 minutes before a meal. Insulin glargine was administered once daily in the evening as the basal insulin. There was a 4-week run-in period with insulin lispro and insulin glargine prior to randomization. Most patients were Caucasian (97%). Fifty eight percent of the patients were men. The mean age was 39 years (range 18 to 74 years). Glycemic control, the number of daily short-acting insulin injections and the total daily doses of APIDRA and insulin lispro were similar in the two treatment groups (see Table 7).

Table 7: Type 1 Diabetes Mellitus-Adult

Treatment duration Treatment in combination with:	26 weeks Insulin glargine	
	APIDRA	Insulin Lispro
Glycated hemoglobin (GHb) [†] (%) Number of patients	331	322
Baseline mean	7.6	7.6
Adjusted mean change from baseline	-0.1	-0.1
Treatment difference: APIDRA – Insulin Lispro	0.0	
95% CI for treatment difference	(-0.1; 0.1)	
Basal insulin dose (Units/day)		
Baseline mean	24	24
Adjusted mean change from baseline	0	2
Short-acting insulin dose (Units/day)		
Baseline mean	30	31
Adjusted mean change from baseline	-1	-1
Mean number of short-acting insulin injections per day	3	3
Body weight (kg)		
Baseline mean	73.9	74.1
Mean change from baseline	0.6	0.3

[†]GHb reported as HbA_{1c} equivalent

14.2 Type 2 Diabetes-Adults

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in insulin-treated patients with type 2 diabetes to assess the safety and efficacy of APIDRA (n=435) given within 15 minutes before a meal compared to regular human insulin (n=441) administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period with regular human insulin and NPH human insulin. Eighty-five percent of patients were Caucasian and 11% were Black. The mean age was 58 years (range 26 to 84 years). The average body mass index (BMI) was 34.6 kg/m². At randomization, 58% of the patients were taking an oral antidiabetic agent. These patients were instructed to continue use of their oral antidiabetic

agent at the same dose throughout the trial. The majority of patients (79%) mixed their short-acting insulin with NPH human insulin immediately prior to injection. The reductions from baseline in GHb were similar between the 2 treatment groups (see Table 8). No differences between APIDRA and regular human insulin groups were seen in the number of daily short-acting insulin injections or basal or short-acting insulin doses (see Table 8).

Table 8: Type 2 Diabetes Mellitus-Adult

Treatment duration Treatment in combination with:	26 weeks NPH human insulin	
	APIDRA	Regular Human Insulin
Glycated hemoglobin (GHb) [†] (%) Number of patients	404	403
Baseline mean	7.6	7.5
Adjusted mean change from baseline	-0.5	-0.3
Treatment difference: APIDRA – Regular Human Insulin	-0.2	
95% CI for treatment difference	(-0.3; -0.1)	
Basal insulin dose (Units/day)		
Baseline mean	59	57
Adjusted mean change from baseline	6	6
Short-acting insulin dose (Units/day)		
Baseline mean	32	31
Adjusted mean change from baseline	4	5
Mean number of short-acting insulin injections per day	2	2
Body weight (kg)		
Baseline mean	100.5	99.2
Mean change from baseline	1.8	2.0

[†]GHb reported as HbA_{1c} equivalent

14.3 Type 1 Diabetes-Adults: Pre and Post Meal Administration

A 12-week, randomized, open-label, active-controlled, non-inferiority study was conducted in patients with type 1 diabetes to assess the safety and efficacy of APIDRA administered at different times with respect to a meal. APIDRA was administered subcutaneously either within 15 minutes before a meal (n=286) or immediately after a meal (n=296) and regular human insulin (n=278) was administered subcutaneously 30 to 45 minutes prior to a meal. Insulin glargine was administered once daily at bedtime as the basal insulin. There was a 4-week run-in period with regular human insulin and insulin glargine followed by randomization. Most patients were Caucasian (94%). The mean age was 40 years (range 18 to 73 years). Glycemic control (see Table 9) was comparable for the 3 treatment regimens. No changes from baseline between the treatments were seen in the total daily number of short-acting insulin injections (see Table 9).

Table 9: Pre and Post Meal Administration in Type 1 Diabetes Mellitus - Adult

Treatment duration Treatment in combination with:	12 weeks insulin glargine	12 weeks insulin glargine	12 weeks insulin glargine
	APIDRA pre meal	APIDRA post meal	Regular Human Insulin
Glycated hemoglobin (GHb) [†] (%) Number of patients	268	276	257
Baseline mean	7.7	7.7	7.6
Adjusted mean change from baseline [†]	-0.3	-0.1	-0.1
Basal insulin dose (Units/day)			
Baseline mean	29	29	28
Adjusted mean change from baseline	1	0	1
Short-acting insulin dose (Units/day)			
Baseline mean	29	29	27
Adjusted mean change from baseline	-1	-1	2
Mean number of short-acting insulin injections per day	3	3	3

Table 9: Pre and Post Meal Administration in Type 1 Diabetes Mellitus - Adult (continued)

Treatment duration Treatment in combination with:	12 weeks insulin glargine APIDRA pre meal	12 weeks insulin glargine APIDRA post meal	12 weeks insulin glargine Regular Human Insulin
Body weight (kg)			
Baseline mean	79.2	80.3	78.9
Mean change from baseline	0.3	-0.3	0.3

*Ghb reported as HbA1c equivalent

†Adjusted mean change from baseline treatment difference (98.33% CI for treatment difference):

APIDRA pre meal vs Regular Human Insulin -0.1 (-0.3; 0.0)

APIDRA post meal vs Regular Human Insulin 0.0 (-0.1; 0.2)

APIDRA post meal vs pre meal 0.2 (0.0; 0.3)

14.4 Type 1 Diabetes-Pediatric Patients

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in children and adolescents older than 4 years of age with type 1 diabetes mellitus to assess the safety and efficacy of APIDRA (n=277) compared to insulin lispro (n=295) when administered subcutaneously within 15 minutes before a meal. Patients also received insulin glargine (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There was a 4-week run-in period with insulin lispro and insulin glargine or NPH prior to randomization. Most patients were Caucasian (91%). Fifty percent of the patients were male. The mean age was 12.5 years (range 4 to 17 years). Mean BMI was 20.6 kg/m². Glycemic control (see Table 10) was comparable for the two treatment regimens.

Table 10: Results from a 26-Week Study in Pediatric Patients with Type 1 Diabetes Mellitus

	APIDRA	Lispro
Number of patients	271	291
Basal Insulin	NPH or insulin glargine	NPH or insulin glargine
Glycated hemoglobin (Ghb)* (%)		
Baseline mean	8.2	8.2
Adjusted mean change from baseline	0.1	0.2
Treatment Difference: Mean (95% confidence interval)	-0.1 (-0.2, 0.1)	
Basal insulin dose (Units/kg/day)		
Baseline mean	0.5	0.5
Mean change from baseline	0.0	0.0
Short-acting insulin dose (Units/kg/day)		
Baseline mean	0.5	0.5
Mean change from baseline	0.0	0.0
Mean number of short-acting insulin injections per day	3	3
Baseline mean body weight (kg)	51.5	50.8
Mean weight change from baseline (kg)	2.2	2.2

*Ghb reported as HbA1c equivalent

14.5 Type 1 Diabetes-Adults: Continuous Subcutaneous Insulin Infusion

A 12-week randomized, active control study (APIDRA versus insulin aspart) conducted in adults with type 1 diabetes (APIDRA n=29, insulin aspart n=30) evaluated the use of APIDRA in an external continuous subcutaneous insulin pump. All patients were Caucasian. The mean age was 46 years (range 21 to 73 years). The mean Ghb increased from baseline to endpoint in both treatment groups (from 6.8% to 7.0% for APIDRA; from 7.1% to 7.2% for insulin aspart).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

APIDRA injection, 100 units per mL (U-100), is a clear and colorless solution available as:

10 mL multiple-dose vial NDC 0088-2500-33
 3 mL single-patient-use APIDRA SoloStar prefilled pen, package of 5 NDC 0088-2502-05

Pen needles are not included in the packs.

SoloStar is compatible with all pen needles from Becton Dickinson and Company, Ypsomed, and Owen Mumford.

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

16.2 Storage

Do not use after the expiration date (see carton and container).

Unopened Vial/SoloStar

Unopened APIDRA vials and SoloStar should be stored in a refrigerator, 36°F–46°F (2°C–8°C). Protect from light. APIDRA should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen.

Unopened vials/SoloStar not stored in a refrigerator must be used within 28 days.

Open (In-Use) Vial

Opened vials, whether or not refrigerated, must be used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 77°F (25°C).

Open (In-Use) SoloStar Prefilled Pen

The opened (in-use) SoloStar should NOT be refrigerated but should be kept below 77°F (25°C) away from direct heat and light. The opened (in-use) SoloStar kept at room temperature must be discarded after 28 days.

Use in an External Insulin Pump

Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir must be discarded after 48 hours of use or after exposure to temperatures that exceed 98.6°F (37°C).

Intravenous Use

Infusion bags in normal saline solution (0.9% Sodium Chloride Injection, USP) are stable at room temperature for 48 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 APIDRA SoloStar Pen or Syringe or Needle between Patients

Advise patients that they must never share an APIDRA SoloStar pen with another person, even if the needle is changed. Advise patients using APIDRA vials not to reuse or share needles or syringes with another person. Sharing carries a risk for transmission of blood-borne pathogens [see *Warnings and Precautions* (5.1)].

Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of APIDRA 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 [see *Warnings and Precautions* (5.3)].

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.

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 APIDRA. Inform patients on the symptoms of hypersensitivity reactions and to seek medical attention if they occur [see *Warnings and Precautions* (5.6)].

Instructions For Patients Using Continuous Subcutaneous Insulin Pumps

Train patients using external pump infusion therapy appropriately.

Inform patients to replace the infusion sets (reservoir, tubing, and catheter) and the APIDRA in the reservoir at least every 48 hours and select a new infusion site. 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. Discard insulin exposed to temperatures higher than 98.6°F (37°C). Instruct patients to report infusion sites that are erythematous, pruritic, or thickened to their healthcare professional and select a new site.

Inform patients that pump or infusion set malfunctions or handling errors or insulin degradation can lead to rapid hyperglycemia, and ketosis and diabetic ketoacidosis. Instruct patients to resume therapy with subcutaneous insulin injection and contact their healthcare professional if pump problems cannot be promptly corrected [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.8), *How Supplied/Storage and Handling* (16.2)].

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 Bridgewater, NJ 08807
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PATIENT INFORMATION
APIDRA® (uh PEE druh)
(insulin glulisine injection) for subcutaneous use
100 units/mL (U-100)

Do not share your APIDRA SoloStar® pen or 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.

What is APIDRA?

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

- It is not known if APIDRA is safe or effective in children less than 4 years of age with type 1 diabetes.
- It is not known if APIDRA is safe or effective in children with type 2 diabetes.

Who should not use APIDRA?

Do not use APIDRA if you:

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

What should I tell my healthcare provider before using APIDRA?

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

- have liver or kidney problems.
- take other medicines, especially ones called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with APIDRA.
- are pregnant, planning to become pregnant, or are breastfeeding. It is not known if APIDRA may harm your unborn baby or breastfeeding baby.

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 APIDRA, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use APIDRA?

- APIDRA comes in a SoloStar disposable prefilled pen or in a vial.
- Read the detailed **Instructions for Use** that come with your APIDRA.
- Use APIDRA exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much APIDRA to use and when to use it.
- Know the amount of APIDRA you use. **Do not** change the amount of APIDRA you use unless your healthcare provider tells you to.
- Know the best time for you to take your insulin. This may change if you take a different type of insulin or if the way you give your insulin changes, for example, using an insulin pump instead of giving injections under the skin (subcutaneous injections).
- Check your insulin label each time you give your injection to make sure you have the correct insulin. This is especially important if you also take long-acting insulin.
- **Do not reuse needles.** Always use a new needle for each injection. Reuse of needles increase your risk of having blocked needles, which may cause you to get the wrong dose of APIDRA. Using a new needle for each injection lowers your risk of getting an infection.
- Apidra is a rapid-acting insulin. Take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Apidra is injected under your skin (subcutaneously) and by continuous infusion under your skin through an insulin pump.
- Change (rotate) injection sites within the area you chose with each dose. **Do not** use the exact spot for each injection.
- **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 APIDRA and all medicines out of the reach of children.

Your dose of APIDRA may need to change because of:

- a change in level of 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 APIDRA?

While using APIDRA do not:

- drive or operate heavy machinery until you know how APIDRA affects you.
- drink alcohol or use over-the-counter medicines that contain alcohol.

What are the possible side effects of APIDRA?

APIDRA 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, trouble concentrating or confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety; irritability or mood change, hunger
- **severe allergic reaction (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, shortness of breath, trouble breathing, fast pulse, sweating, or feeling faint
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with APIDRA 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 APIDRA. Your healthcare provider should monitor you closely while you are taking TZDs with APIDRA. 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 APIDRA may need to be changed 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 APIDRA include:

- low blood sugar (hypoglycemia), weight gain, itching, rash, swelling, allergic reactions including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy).

These are not all the possible side effects of APIDRA. 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 APIDRA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use APIDRA for a condition for which it was not prescribed. **Do not** give APIDRA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about APIDRA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about APIDRA that is written for health professionals.

What are the ingredients in APIDRA?

- **Active ingredient:** insulin glulisine
- **Inactive ingredients:** metacresol, tromethamine, sodium chloride, polysorbate 20, and water for injection. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

sanofi-aventis U.S. LLC Bridgewater, NJ 08807, A SANOFI COMPANY
 For more information, go to www.APIDRA.com or call 1-800-633-1610.

This Patient Information has been approved by the U.S. Food and Drug Administration.
 Approved: December 2018

INSTRUCTIONS FOR USE

APIDRA® 10 mL vial (100 Units/mL)

Do not share your 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.

This Instructions for Use has two parts:

Part 1 Use with a syringe

Part 2 Use with an external insulin infusion pump

Be sure to read, understand and follow these instructions before taking APIDRA.

Part 1 Use with a syringe

If you will give yourself subcutaneous injections of APIDRA:

- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Do not inject APIDRA if you are not going to eat within 15 minutes.
- Inject APIDRA into the skin of your upper arm, thigh, or stomach area. Do not inject APIDRA into a vein or into a muscle.
- Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. **Do not inject into the exact same spot for each injection.**
- Do not mix APIDRA with insulins other than NPH, for subcutaneous injections. If mixing APIDRA with NPH insulin, draw up APIDRA into the syringe first. Inject the mixture right away.
- Use the needles and syringes prescribed by your healthcare provider.
- **Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them.**
- **Do not reuse needles.**

Before every injection make sure you have the following items:

- Alcohol swabs
- Needle and syringe
- Insulin vial
- Puncture resistant container. See "How do I dispose of used needles and syringes?".

Drawing the insulin into a syringe

1. Use a new syringe each time you give an injection of APIDRA. **Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them.**

Preparing for an injection

2. Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin.
3. Look at the APIDRA in the vial. It should look clear. Do not use this vial of APIDRA if the solution is colored, or cloudy, or if you see particles in it.
4. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.



5. Wipe the rubber stopper with an alcohol swab. You do not have to shake the vial of APIDRA before use.



6. Use the needles and syringes prescribed by your healthcare provider. APIDRA 10 mL vials come with 100 units of insulin in 1 mL of APIDRA.
7. Use a new needle and syringe for each injection. Use disposable syringes and needles only one time. **Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them. Do not reuse needles.**

8. Draw air into the syringe equal to the insulin dose prescribed by your healthcare provider.



9. Put the needle through the rubber stopper of the vial and push the plunger to inject the air into the vial.



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



12. Before you take the needle out of the vial, check the syringe for air bubbles. If you see bubbles in the syringe, hold the syringe straight up and tap the side of the syringe with your finger a few times to make any air bubbles float to the top. Gently push the air bubbles out with the plunger and draw insulin back into the syringe until you have the correct dose. If you are mixing APIDRA with NPH insulin, check with your healthcare provider on how to mix it the right way.



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

Giving the injection

Do the injection exactly as shown to you by your healthcare provider. Inject APIDRA under your skin.

14. Choose an injection area (for example upper arm, thigh or stomach area). Change injection sites within the area you choose. **Do not inject in the same spot.**
15. Clean the area with an alcohol swab. Let the injection site dry before you inject.



16. Pinch the skin. Insert the needle into the skin. Release the skin.
17. Inject the dose by slowly pushing in the plunger of the syringe all the way, making sure you have injected all the insulin. Keep the needle in the skin for at least 10 seconds.



Pull the needle out of your skin, gently press the injection site with a finger for several seconds. **Do not rub the area.**

18. Do not recap the needle. Recapping can lead to a needle stick injury and passing of infection. See "How do I dispose of used needles and syringes?"

If your injection is given by another person, this person must also be careful to prevent accidental needle stick injury and passing infections.

How do I dispose of used needles and syringes?

19. Check with your healthcare provider's office for instructions about the right way to dispose of used needles and syringes. There may be local or state laws about how to dispose of used needles and syringes. Do not dispose of used needles or syringes in household trash and do not recycle them.
20. Put used needles and syringes in a container specially made for throwing away syringes and needles (called a "sharps" container) or a hard plastic container with a screw-on cap or a metal container with a plastic lid labeled "Used Syringes". These containers should be sealed and disposed of the right way.

See "How should I store APIDRA?" in the Patient Information leaflet that comes With APIDRA for complete instructions on how to store APIDRA vials.

Part 2 Use with an external insulin pump:

Be sure to read, understand, and follow these instructions before using APIDRA with an external insulin infusion pump. Always read the instruction manual for your pump. These instructions may differ from the instructions that accompany your insulin infusion pump. When you use Apidra in the pump system, it is important that you always follow these Apidra specific instructions. Failure to follow the Apidra specific instructions may lead to serious adverse events.

If you will be using an insulin pump:

- APIDRA should be given into the stomach area.
- Change injection sites in the stomach area.
- **Do not mix APIDRA with other insulins and do not dilute APIDRA.**
- Use only insulin pumps that have been specially tested with APIDRA.
Follow your healthcare provider or pharmacist instructions for which insulin pumps may be used.
- Change the infusion set (reservoir, tubing, and catheter), and the APIDRA in the reservoir at least every 2 days (48 hours). Change all of these parts sooner if they have been exposed to temperatures higher than 98.6°F (37°C).

Important information about using APIDRA with an external insulin infusion pump

- **Do not mix APIDRA with any other insulin or liquid when used in a pump.**
- If your APIDRA infusion pump set is not working the right way or in case of handling errors, you may not get the right amount of insulin that can cause:
 - low blood sugar (hypoglycemia)
 - high blood sugar (hyperglycemia)
 - high amounts of sugar and ketones in your blood or urine
 - build-up of acid in your blood because your body is breaking down fat instead of sugar (diabetic ketoacidosis)
- You must have an alternative insulin delivery system in case of pump failure.
- When you start using APIDRA by infusion pump, your insulin dose may need to be adjusted. Check with your healthcare provider before making any changes to your insulin dose.

How to use APIDRA with an external insulin infusion pump?

- Check with your healthcare provider or pharmacist to see if your pump and infusion set can be used with APIDRA. See the instruction manual of your specific pump on proper use of insulin in a pump. Call your healthcare provider if you have questions about using the pump.
- Change the infusion set, reservoir with insulin, and injection site:
 - at least every 48 hours, change more often than every 48 hours if you have high blood sugar (hyperglycemia), or the pump alarm sounds.

- if the insulin has been in temperatures over 98.6°F (37°C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may affect the temperature.

If you get reactions at the injections infusion site you may need to change infusion sites more often.

If your APIDRA infusion pump is not working the right way, follow these steps:

- Use insulin from a new vial of APIDRA if infusion pump alarms do not respond to all of the following:
 - a repeat injection or bolus of APIDRA
 - a change in the infusion set and the reservoir
 - a change in the infusion injection site
- If the same problems happen again, do not use your infusion pump with APIDRA. You may need to restart insulin injections with syringes and needles.
 - Contact your healthcare provider right away.
 - See section I of the Instructions for Use ("Use with a syringe") for the steps for giving injections of APIDRA using syringes and needles.
 - Continue to check your blood sugar often.

How should I store APIDRA 10 mL vial?

- Keep in the refrigerator or below 77°F (25°C).
- Keep vials away from direct heat and light.
- Dispose of any opened vial after 28 days after the first use, even if there is insulin left in the vial.

Rev. February 2015

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APIDRA® SoloStar®

(insulin glulisine injection) for subcutaneous use
3 mL SoloStar prefilled pen

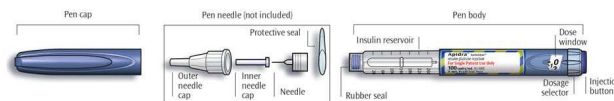
Instructions for Use

Be sure that you read, understand, and follow these instructions before you use your APIDRA SoloStar. Talk with your healthcare provider about the right way to use your APIDRA SoloStar before you use it for the first time. Keep this leaflet in case you need to look at it again later.

Do not share your APIDRA 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.

People who are blind or have vision problems should not use APIDRA SoloStar prefilled pen without help from a person trained to use APIDRA SoloStar prefilled pen.

APIDRA SoloStar is a disposable prefilled pen used to inject APIDRA. Each APIDRA SoloStar has 300 units of insulin which can be used for many doses. You can select a dose 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.



If you will give yourself subcutaneous injections of APIDRA:

- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Do not inject APIDRA if you are not going to eat within 15 minutes.
- Inject APIDRA into the skin of your upper arm, thigh, or stomach area. Do not inject APIDRA into a vein or into a muscle.
- Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. **Do not inject into the exact same spot for each injection.**

Important information for use of APIDRA SoloStar:

- **Do not share your APIDRA 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.
- **Do not reuse needles.** Use a new needle for each injection.

- APIDRA SoloStar may be used with pen needles from Becton Dickinson and Company, Ypsomed, and Owen Mumford. Contact your healthcare provider for further information.
- Do a safety test before each injection (see step 3).
- Do not select a dose or press the injection button without a needle attached.
- If your injection is given by another person, this person must be careful to avoid accidental needle stick injury and prevent passing (transmission of) infection.
- Do not use APIDRA SoloStar if it is damaged or if you are not sure that it is working correctly.
- Always carry an extra APIDRA SoloStar prefilled pen in case your APIDRA SoloStar is lost or damaged.

Step 1. Preparing for an Injection

Make sure you have the following items:

- APIDRA SoloStar
 - Pen needles
 - Alcohol swab
 - Puncture-resistant container. See "How do I dispose of used needles and APIDRA SoloStar?"
- Check the label on your APIDRA SoloStar to make sure you have the right insulin. The APIDRA SoloStar is blue. It has a dark blue injection button with a raised ring on the top.
 - Check the expiration date, located on the carton or the label of your APIDRA SoloStar, to make sure the date has not passed. Do not use an APIDRA SoloStar if the date has passed.
 - Take off the pen cap.
 - Look at the insulin in your APIDRA SoloStar. Check to make sure that the insulin looks clear. Do not use this APIDRA SoloStar if the insulin is cloudy, colored, or has particles in it.

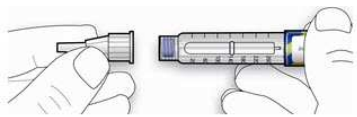
Step 2. Attaching the Needle

Do not reuse needles. Always use a new sterile needle for each injection to help prevent you from getting a serious infection (contamination) and potential needle blocks.

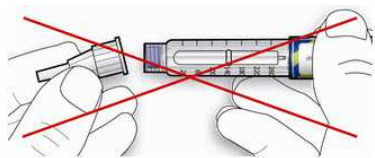
Read the pen needle "Instructions for Use" before you use them.

Please note: Pen needles may look different. The pen needles shown are for illustrative purposes only.

- Wipe the Rubber Seal with alcohol.
- Remove the protective seal from the new pen needle.
- Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If you do not keep the needle straight while you attach it this can damage the rubber seal and cause leakage of insulin or break the needle.



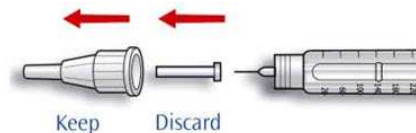
Step 3. Doing a Safety Test

Do a safety test before each injection to make sure that you get the correct dose of APIDRA. The safety test:

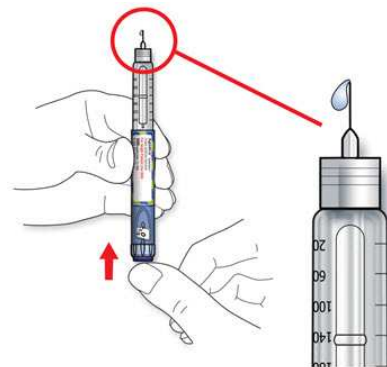
- makes sure that the pen and needle work properly
 - removes air bubbles
- Select a dose of 2 units by turning the dosage selector.



- Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and dispose of it.



- Hold the pen with the needle pointing upwards.
- Tap the insulin reservoir so that any air bubbles rise up towards the needle.
- Press the injection button all the way in. Check if insulin comes out of the needle tip.



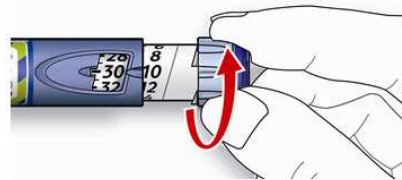
You may have to do the safety test more than one time before you see the insulin.

- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your APIDRA SoloStar may be damaged. Do not use this APIDRA SoloStar.

Step 4. Selecting your Dose

Select the APIDRA dose prescribed by your healthcare provider. You can select the insulin dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose larger than 80 units, you should give it as two or more injections.

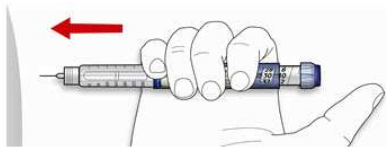
- Check that the dose window shows "0" after the safety test.
- Select your needed dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



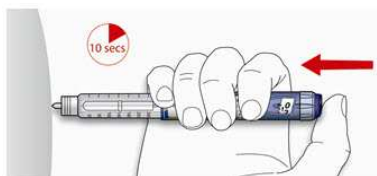
- Do not push the injection button while turning, insulin will come out.
- You cannot turn the dosage selector passed the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject the amount of insulin that is still in the pen and finish your dose with a new APIDRA SoloStar or you can use a new APIDRA SoloStar for your full dose.

Step 5. Giving the Injection

- A. Give the injection exactly as shown to you by your healthcare provider.
- B. Insert the needle into your skin.



- C. Inject the dose by pressing the injection button in all the way. Only push the injection button when you are ready to inject. The number in the dose window will return to "0" as you inject.



- D. Keep the injection button pressed all the way in. Slowly count to 10 before you take the needle out of your skin. This will make sure that the full dose has been given.

Step 6. Removing and Disposing of the Pen Needle

Always remove the pen needle after each injection and store your APIDRA SoloStar without a needle attached. This helps prevent:

- Contamination and infection
 - Air from getting into the insulin reservoir and leakage of insulin. This will help to make sure you inject the right dose of insulin.
- A. Follow the instructions from your healthcare provider when removing and disposing of the needle. For example "scoop" the outer needle cap back on the needle and use it to unscrew the used needle from the pen. To lessen the risk of accidental needle stick injury and passing infection:
 - do not recap needles with your fingers.
 - never replace the inner needle cap.

If your injection is given by another person, this person must also be careful when removing and disposing of the needles to prevent accidental needle stick injury and passing infection.

- B. Dispose of the needle the right way into your special puncture-resistant container (See "How Do I Dispose of used needles and APIDRA SoloStar?").
- C. Always put the pen cap back on the pen, then store the APIDRA SoloStar until your next injection.

How do I dispose of used needles and APIDRA SoloStar?

- Check with your healthcare provider for instructions about the right way to dispose of used needles and APIDRA SoloStar.
- Put used needles and used empty APIDRA SoloStar 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 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: <https://fda.gov/safesharpsdisposal>.

How should I store APIDRA SoloStar?

- Do not refrigerate APIDRA SoloStar after first use.
- Keep at room temperature below 77°F (25°C).
- Throw away (dispose of) any opened APIDRA SoloStar 28 days after first use.

Maintenance

- Protect your APIDRA SoloStar from dust and dirt.
- You can clean the outside of your APIDRA SoloStar by wiping it with a damp cloth.
- Do not soak, wash, or lubricate the pen as this may damage it.
- Handle your APIDRA SoloStar with care. Avoid situations where your APIDRA SoloStar might be damaged. If you are concerned that your APIDRA SoloStar may be damaged, use a new one.

If you have any questions about APIDRA SoloStar or about diabetes, ask your healthcare provider, go to www.apidra.com, or call sanofi-aventis U.S. at 1-800-633-1610.

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Rx Only