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 [rDNA origin] injection) solution for injection
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 10/2008

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

----------DOSAGE AND ADMINISTRATION----------
The dosage of APIDRA must be individualized (2.1)

Subcutaneous Injection	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Use in a regimen with an intermediate or long-acting insulin. (2.1, 2.2)
Continuous Subcutaneous Infusion Pump	APIDRA must not be mixed or diluted when used in an external insulin infusion pump. (2.3)
Intravenous Infusion	Infuse intravenously (0.05 Units/mL to 1 Units/mL APIDRA in 0.9% sodium chloride using polyvinyl chloride infusion bags) only under strict medical supervision with close monitoring of blood glucose and potassium. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
APIDRA 100 units/mL (U-100) is available as: (3)
- 10 mL vials
- 3 mL cartridge system for use in OptiClik ® (Insulin Delivery Device)

----------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----------
- Dose adjustment and monitoring: Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously and only under medical supervision.(5.1)
- Hypoglycemia: Most common adverse reaction of insulin therapy and may be life-threatening (5.2)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with any insulin, including APIDRA (5.3)
- Hypokalemia: All insulins, including APIDRA can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death (5.4)
- Renal or hepatic impairment: Like all insulins, may require a reduction in the APIDRA dose (5.5)
- Mixing: APIDRA for subcutaneous injection should not be mixed with insulins other than NPH insulin. Do not mix APIDRA with any insulin for intravenous administration or for use in a continuous infusion pump (5.6)
- Pump use: Change the APIDRA in the pump reservoir every 48 hours (5.7)
- Intravenous use: Frequently monitor for hypoglycemia and hypokalemia. (5.8)

----------ADVERSE REACTIONS----------
Adverse reactions commonly associated with APIDRA 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----------
- Certain drugs affect glucose metabolism and may necessitate insulin dose adjustment (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine). (7)

----------USE IN SPECIFIC POPULATIONS----------
- APIDRA has not been studied in children under 4 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage considerations
2.2 Subcutaneous administration
2.3 Continuous subcutaneous infusion (insulin pump)
2.4 Intravenous administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Dose adjustment and monitoring
5.2 Hypoglycemia
5.3 Hypersensitivity and allergic reactions
5.4 Hypokalemia
5.5 Renal or hepatic impairment
5.6 Mixing of insulins
5.7 Subcutaneous insulin infusion pumps
5.8 Intravenous administration
5.9 Drug interactions
6 ADVERSE REACTIONS
6.1 Clinical trial experience
6.2 Postmarketing experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing mothers
8.4 Pediatric use
8.5 Geriatric use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Clinical pharmacology in specific populations
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, mutagenesis, impairment of fertility
14 CLINICAL STUDIES
14.1 Type 1 Diabetes-Adults
14.2 Type 2 Diabetes-Adults
14.3 Type 1 Diabetes-Adults: Pre-and post-meal administration
14.4 Type 1 Diabetes-Pediatric patients
14.5 Type 1 Diabetes-Adults: Continuous subcutaneous insulin infusion
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How supplied
16.2 Storage
16.3 Preparation and handling
17 PATIENT COUNSELING INFORMATION
17.1 Instructions for all patients
17.2 For patients using continuous subcutaneous insulin pumps
*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage considerations

APIDRA is a recombinant insulin analog that is equipotent to human insulin (i.e. one unit of APIDRA has the same glucose-lowering effect as one unit of regular human insulin) when given intravenously. When given subcutaneously, APIDRA has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of APIDRA must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 Unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

2.2 Subcutaneous administration

APIDRA should be given within 15 minutes before a meal or within 20 minutes after starting a meal.

APIDRA given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin.

APIDRA should be administered by subcutaneous injection in the abdominal wall, thigh, or upper arm. Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*.

2.3 Continuous subcutaneous infusion (insulin pump)

APIDRA may be administered by continuous subcutaneous infusion in the abdominal wall. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*. 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.

Physicians and patients should carefully evaluate information on pump use in the APIDRA prescribing information, Patient Information Leaflet, and the pump manufacturer's manual. APIDRA-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to APIDRA usage, because APIDRA-specific information may differ from general pump manual instructions.

Based on *in vitro* studies which have shown loss of the preservative, metacresol and insulin degradation, APIDRA in the reservoir should be changed at least every 48 hours. APIDRA in clinical use should not be exposed to temperatures greater than 98.6°F (37°C). *[See Warnings and Precautions (5.7) and How Supplied/Storage and Handling (16.2)]*.

2.4 Intravenous administration

APIDRA can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and serum potassium to avoid hypoglycemia and hypokalemia. For intravenous use, APIDRA should be used at concentrations of 0.05 Units/mL to 1 Unit/mL insulin glulisine in infusion systems using polyvinyl chloride (PVC) bags. APIDRA has been shown to be stable only in normal saline solution (0.9% sodium chloride). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer insulin mixtures intravenously.

3 DOSAGE FORMS AND STRENGTHS

APIDRA 100 units per mL (U-100) is available as:

- 10 mL vials
- 3 mL cartridges for use in the OptiClik® Insulin Delivery Device

4 CONTRAINDICATIONS

APIDRA is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to APIDRA or to any of its excipients
  When used in patients with known hypersensitivity to APIDRA or its excipients, patients may develop localized or generalized hypersensitivity reactions *[See Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Dosage adjustment and monitoring

Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for APIDRA may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin therapy, including APIDRA. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with APIDRA.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers *[See Drug Interactions (7)]*, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring closer monitoring for hypoglycemia.

5.3 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including APIDRA *[See Adverse reactions (6.1)]*.

5.4 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). Monitor glucose and potassium frequently when APIDRA is administered intravenously.

5.5 Renal or hepatic impairment

Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment *[See Clinical Pharmacology (12.4)]*.

5.6 Mixing of insulins

APIDRA for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If APIDRA is mixed with NPH insulin, APIDRA should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix APIDRA with other insulins for intravenous administration or for use in a continuous subcutaneous infusion pump.

APIDRA for intravenous administration should not be diluted with solutions other than 0.9% sodium chloride (normal saline). The efficacy and safety of mixing APIDRA with diluents or other insulins for use in external subcutaneous infusion pumps have not been established.

5.7 Subcutaneous insulin infusion pumps

When used in an external insulin pump for subcutaneous infusion, APIDRA should not be diluted or mixed with any other insulin. APIDRA in the reservoir should be changed at least every 48 hours. APIDRA should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. 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 Dosage and Administration (2.3), How Supplied/Storage and Handling (16), and Patient Counseling Information (17.2)]*.

5.8 Intravenous administration

When APIDRA is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

Do not mix APIDRA with other insulins for intravenous administration. APIDRA may be diluted only in normal saline solution.

5.9 Drug interactions

Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia *[See Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[See Warnings and Precautions (5.2)]*
- Hypokalemia *[See Warnings and Precautions (5.4)]*

6.1 Clinical trial 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: Treatment –emergent adverse events in pooled studies of adults with type 1 diabetes (adverse events with frequency ≥ 5%)

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

a Insulin lispro, regular human insulin, insulin aspart
b Only severe symptomatic hypoglycemia

Table 2: Treatment –emergent adverse events in pooled studies of adults with type 2 diabetes (adverse events with frequency ≥ 5%)

	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 children and adolescents with type 1 diabetes treated with APIDRA (n=277) or insulin lispro (n=295).

Table 3: Treatment –emergent adverse events in children and adolescents with type 1 diabetes (adverse reactions with frequency ≥ 5%)

	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 *[See Warnings and Precautions (5.2)]*. The rates and incidence of severe symptomatic hypoglycemia, defined as hypoglycemia requiring intervention from a third party, were comparable for all treatment regimens (see Table 4). In the phase 3 clinical trial, 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 <36mg/dL or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

- *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. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. *[See Dosage and Administration (2.2, 2.3)]*.

- *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.

- *Peripheral Edema*

Insulin, including APIDRA, 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 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 (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*

Local Allergy

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.

Systemic Allergy

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.

Localized reactions and generalized myalgias have been reported with the use of metacresol, which is an excipient of APIDRA.

Antibody Production
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. The clinical significance of these antibodies is not known.

APIDRA did not elicit a significant antibody response in a study of children and adolescents with type 1 diabetes.

6.2 Postmarketing experience
The following adverse reactions have been identified during post-approval 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 *[See Patient Counseling Information (17)]*.

7 DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may necessitate insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood glucose-lowering effect of insulins including APIDRA, and therefore increase the risk of hypoglycemia, include oral antidiabetic products, pramlintide, ACE

inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

Drugs that may reduce the blood-glucose-lowering effect of APIDRA include corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors, and atypical antipsychotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Reproduction and teratology studies have been performed 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 U/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison) and did not have any remarkable toxic effects on embryo-fetal development.

Insulin glulisine was given to female rabbits throughout pregnancy at subcutaneous doses up to 1.5 Units/kg/day (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison). Adverse effects on embryo-fetal development were only seen at maternal toxic dose levels inducing hypoglycemia. Increased incidence of post-implantation losses and skeletal defects were observed at a dose level of 1.5 Units/kg once daily (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison) that also caused mortality in dams. A slight increased incidence of post-implantation losses was seen at the next lower dose level of 0.5 Units/kg once daily (dose resulting in an exposure 0.2 times the average human dose, based on body surface area comparison) which was also associated with severe hypoglycemia but there were no defects at that dose. No effects were observed in rabbits at a dose of 0.25 Units/kg once daily (dose resulting in an exposure 0.1 times the average human dose, based on body surface area comparison). The effects of insulin glulisine did not differ from those observed with subcutaneous regular human insulin at the same doses and were attributed to secondary effects of maternal hypoglycemia.

There are no well-controlled clinical studies of the use of APIDRA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during

the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing mothers
It is unknown whether insulin glulisine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when APIDRA is administered to a nursing woman. Use of APIDRA is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric use
The safety and effectiveness of subcutaneous injections of APIDRA have been established in pediatric patients (age 4 to 17 years) with type 1 diabetes *[See Clinical Studies (14.4)]*. APIDRA has not been studied in pediatric patients with type 1 diabetes younger than 4 years of age and in pediatric patients with type 2 diabetes.

As in adults, the dosage of APIDRA must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

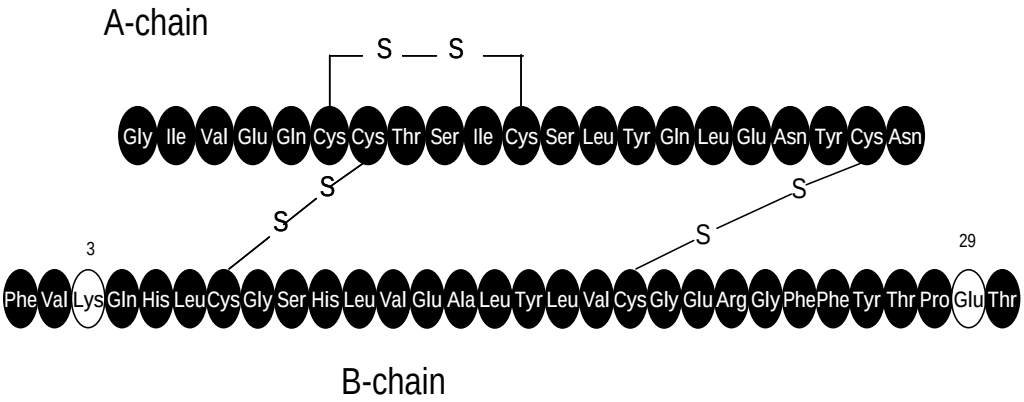
8.5 Geriatric use
In clinical trials (n=2408), APIDRA was administered to 147 patients ≥65 years of age and 27 patients ≥75 years of age. The majority of this small subset of elderly patients had type 2 diabetes. The change in HbA1c values and hypoglycemia frequencies did not differ by age. Nevertheless, caution should be exercised when APIDRA is administered to geriatric patients.

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 [rDNA origin] 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 $C_{258}H_{384}N_{64}O_{78}S_{6}$ and a molecular weight of 5823 and has the following structural formula:



APIDRA is a sterile, aqueous, clear, and colorless solution. 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.

The glucose lowering activities of APIDRA and of regular human insulin are equipotent when administered by the intravenous route. After subcutaneous administration, the effect of APIDRA is more rapid in onset and of shorter duration compared to regular human insulin. *[See Pharmacodynamics (12.2)]*.

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. (Figure 1.)

The maximum blood glucose excursion (ΔGLU_{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 (Figure 1A) and compared to regular human insulin (Regular - pre) given 2 minutes before a meal (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 (Figure 1C). On the x-axis zero (0) is the start of a 15-minute meal.

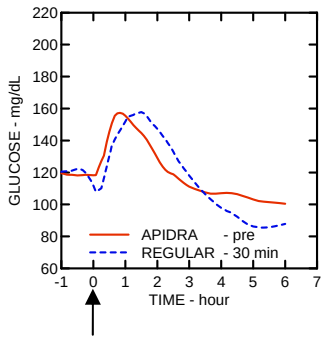


Figure 1A

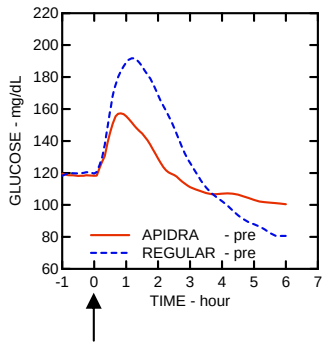


Figure 1B

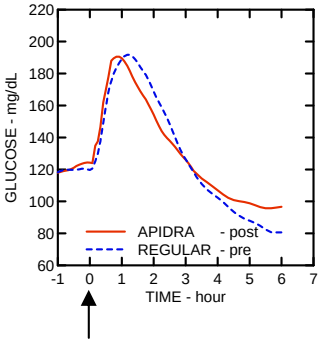


Figure 1C

Arrow ↑ indicates 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.

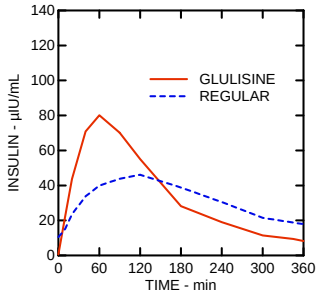
12.3 Pharmacokinetics

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.

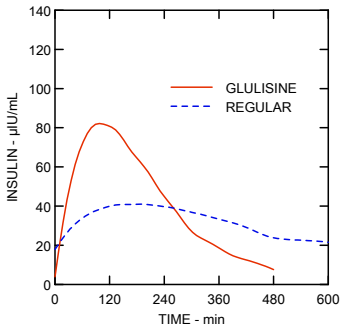
In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 Units/kg, the median time to maximum concentration (T_{max}) was 60 minutes (range 40 to 120 minutes) and the peak concentration (C_{max}) was 83 microUnits/mL (range 40 to 131 microUnits/mL) for insulin glulisine 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. (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 an euglycemic clamp study in patients with type 2 diabetes (n=24) and a body mass index (BMI) between 20 and 36 kg/m^2. 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. (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. No data are available on mixing APIDRA with insulin preparations other than NPH insulin. *[See Clinical Studies (14)]*.

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.

12.4 Clinical pharmacology in specific populations

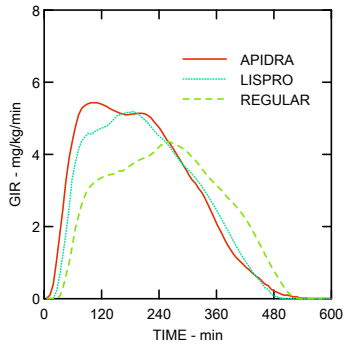
Pediatric patients
The pharmacokinetic and pharmacodynamic properties of APIDRA and regular human insulin were assessed in a study conducted in children 7 to 11 years old (n=10) and adolescents 12 to 16 years old (n=10) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics 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 $AUC_{(0\text{-}1h)}$ to $AUC_{(0\text{-clamp end})}$ 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/m^2. 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). (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 Warnings and Precautions (5.4)]*.

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 Warnings and Precautions (5.4)*].

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

Pregnancy
The effect of pregnancy 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
Standard 2-year carcinogenicity studies in animals have not been performed. In Sprague Dawley rats, a 12-month repeat dose toxicity study was conducted with insulin glulisine at subcutaneous doses of 2.5, 5, 20 or 50 Units/kg twice daily (dose resulting in an exposure 1, 2, 8, and 20 times the average human dose, based on body surface area comparison).

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. The relevance of these findings to humans is not known. 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 once daily (dose resulting in an exposure 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 children and adolescent 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 (Table 6).

Table 6: Type 1 Diabetes Mellitus–Adult

Treatment duration	26 weeks	
Treatment in combination with:	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/m^2. 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 7). 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 7.)

Table 7: Type 2 Diabetes Mellitus–Adult

Treatment duration	26 weeks	
Treatment in combination with:	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 8) 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 8.)

Table 8: Pre- and Post-Meal Administration in Type 1 Diabetes Mellitus–Adult

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
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
Body weight (kg)			
Baseline mean	79.2	80.3	78.9
Mean change from baseline	0.3	-0.3	0.3

*GHb reported as HbA_{1c} 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/m^2. Glycemic control (see Table 9) was comparable for the two treatment regimens.

Table 9: 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 HbA_{1c} 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 100 units per mL (U-100) is available as:

10 mL vials	NDC 0088-2500-33
3 mL cartridge system*, package of 5	NDC 0088-2500-52

* Cartridge systems are for use only in OptiClik® (Insulin Delivery Device)

16.2 Storage

Do not use after the expiration date.

Unopened Vial/Cartridge System

Unopened APIDRA vials and cartridge systems 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/cartridge systems 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) Cartridge System:
The opened (in-use) cartridge system inserted in OptiClik® should NOT be refrigerated but should be kept below 77°F (25°C) away from direct heat and light. The opened (in-use) cartridge system must be discarded after 28 days. Do not store OptiClik®, with or without cartridge system, in a refrigerator at any time.

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

Intravenous use:
Infusion bags prepared as indicated under DOSAGE AND ADMINISTRATION (2.4) are stable at room temperature for 48 hours.

16.3 Preparation and Handling
After dilution for intravenous use, the solution should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it has become cloudy or contains particles; use only if it is clear and colorless. APIDRA is not compatible with Dextrose solution and Ringers solution and, therefore, cannot be used with these solution fluids. The use of APIDRA with other solutions has not been studied and is, therefore, not recommended.

Cartridge system: If OptiClik® (the Insulin Delivery Device for APIDRA) malfunctions, APIDRA may be drawn from the cartridge system into a U-100 syringe and injected.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Instructions for all patients
Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia.
Patients must be instructed 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.
Refer patients to the APIDRA Patient Information Leaflet for additional information.

Women with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

Accidental mix-ups between APIDRA and other insulins, particularly long-acting insulins, have been reported. To avoid medication errors between APIDRA and other insulins, patients should be instructed to always check the insulin label before each injection.

17.2 For patients using continuous subcutaneous insulin pumps
Patients using external pump infusion therapy should be trained appropriately.

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.

To minimize insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), the infusion sets (reservoir, tubing, and catheter) and the APIDRA in the reservoir should be replaced every 48 hours and a new infusion site should be selected. 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. Insulin exposed to temperatures higher than 98.6°F (37°C) should be discarded. Infusion sites that are erythematous, pruritic, or thickened should be reported to the healthcare professional, and a new site selected because continued infusion may increase the skin reaction or alter the absorption of APIDRA.

Pump or infusion set malfunctions or insulin degradation can lead to rapid hyperglycemia and ketosis. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their healthcare professional. *[See Dosage and Administration (2.3), Warnings and Precautions (5.7), and How Supplied/Storage and Handling (16)]*.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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Patient Information
APIDRA® 10 mL vial (1000 units per vial) 100 units per mL (U-100)
(insulin glulisine [recombinant DNA origin] injection)

Read the "Patient Information" that comes with APIDRA (uh-PEE-druh) before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. If you have questions about APIDRA or about diabetes, talk with your healthcare provider.

What is the most important information I should know about APIDRA?

- **Do not change the insulin you use without talking to your healthcare provider.** Any change in insulin strength, manufacturer, type (regular, NPH, analog), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal-source insulin) may need a change in the dose you are using. This dose change may be needed right away or later on. Sometimes this dose change may happen during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.

- **You must test your blood sugar levels while using an insulin such as APIDRA.** Your healthcare provider will tell you how often you should test your blood sugar level, and what to do if it is high or low.

- **When used in a pump do not mix APIDRA with any other insulin or liquid.**

- **APIDRA** comes as U-100 insulin. It contains 10 milliliters (mL) of APIDRA. One milliliter (mL) of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

What is diabetes?

- Your body needs insulin to turn sugar (glucose) into energy. If your body does not make enough insulin, you need to take more insulin so you will not have too much sugar in your blood.

- Insulin injections are important in keeping your diabetes under control. But other factors can have an effect on your diabetes, such as the foods you eat, how often you check your blood sugars, and your exercise level.

What is APIDRA?

- APIDRA (insulin glulisine [recombinant DNA origin]) is a rapid-acting man-made insulin. APIDRA is used to treat patients with diabetes for the control of high blood sugar.

- APIDRA is a clear, colorless, sterile solution for injection under the skin (subcutaneously). APIDRA may also be given by infusion into one of your veins (intravenously) by healthcare providers only.

- You need a prescription to get APIDRA. Always be sure you receive the right insulin from the pharmacy.

Who should not take APIDRA?

Do not take APIDRA if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Apidra.
- **you are allergic to insulin glulisine** or any of the inactive ingredients in APIDRA. Check with your healthcare provider if you are not sure.

What should I tell my healthcare provider before taking APIDRA?

Tell your healthcare provider:

- **about all of your medical conditions, including liver or kidney problems.** Your dose may need to be adjusted.
- **if you are pregnant or plan to become pregnant.** It is not known if APIDRA may harm your unborn baby. It is very important to maintain control of your blood sugar levels during pregnancy. Your healthcare provider will decide which insulin is best for you during your pregnancy.
- **if you are breast-feeding or plan to breast-feed.** It is not known whether APIDRA passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- **about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. Your APIDRA dose may change if you take other medicines. For more information look under **Medicines**, under the heading "What can affect how much insulin I need?".

How should I use APIDRA?

See "**Instructions for Use"** including the sections **"How do I draw the insulin into the syringe?"** and **"How should I infuse APIDRA with an external subcutaneous insulin infusion pump?"** for additional information.

- Follow the instructions given by your healthcare provider about the type or types of insulin you are using. Do not make any changes with your insulin unless you have talked to your healthcare provider. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your healthcare provider about how to adjust your insulin dose.
- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Only use APIDRA that is clear and colorless. If your APIDRA is cloudy or colored, return it to your pharmacy for a replacement.

- Follow your healthcare provider's instructions for testing your blood sugar.
- Inject APIDRA under your skin (subcutaneously) in your upper arm, abdomen (stomach area), or thigh (upper leg). Never inject it into a vein or muscle.
- If you use a pump, infuse APIDRA through the skin of your abdomen.
- Change (rotate) injection sites within the same body area.

What kind of syringe should I use?

- Always use a syringe that is marked for U-100 insulin. If you use a wrong syringe, you may get the wrong dose. You could get a blood sugar level that is too low or too high.

Mixing with APIDRA

- If you are mixing APIDRA with NPH human insulin, draw APIDRA into the syringe first. Inject the mixture right away. **Do not mix APIDRA with any other type of insulin than NPH.**
- **Do not mix APIDRA with any other insulin when used in a pump.**

Instructions for Use

How do I draw the insulin into the syringe?

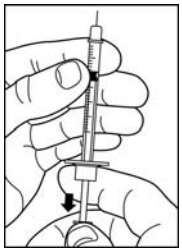
- **The syringe must be new and does not contain any other medicine.**
- **Do not mix APIDRA with any other type of insulin than NPH.** If you are mixing APIDRA with NPH human insulin, draw APIDRA into the syringe first. Inject the mixture right away.

Follow these steps:

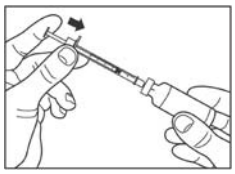
1. Wash your hands.
2. Check the insulin to make sure it is clear and colorless. Do not use the insulin after the expiration date stamped on the label, if it is colored or cloudy or if you see particles in the solution.
3. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.

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

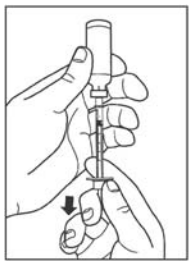
5. Use a new needle and syringe every time you give an injection. Use disposable syringes and needles only once. Throw them away properly. **Never** share needles and syringes.
6. Draw air into the syringe equal to your insulin dose.



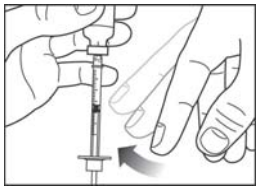
7. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.



8. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
9. 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.



10. 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. If you are mixing APIDRA with NPH insulin, check with your healthcare provider on how to mix.



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

For information on mixing insulins, see section "**Mixing with Apidra**".

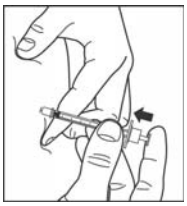
How do I inject APIDRA?

Inject APIDRA under your skin. Take APIDRA as prescribed by your healthcare provider.

Follow these steps:

1. Decide on an injection area - either upper arm, thigh or abdomen. Injection sites within an injection area must be different from one injection to the next.
2. Use alcohol or soap and water to clean the injection site. The injection site should be dry before you inject.

3. Pinch the skin. Stick the needle in the way your healthcare provider showed you. Release the skin.
4. 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.



Pull the needle straight out and gently press on the spot where you injected yourself for several seconds. **Do not rub the area.**

5. Follow your healthcare provider's instructions for throwing away the needle and syringe. Do not recap the used needle. The used needle and syringe should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

How should I infuse APIDRA with an external subcutaneous insulin infusion pump?

Do not mix APIDRA with any other insulin or liquid when used in a pump.

- APIDRA is recommended for use in the following pumps and infusion sets: 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™)[‡]. 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.

- If the pump or infusion set does not work right, you may not receive the right amount of insulin. Hypoglycemia (blood sugar that is too low), hyperglycemia (blood sugar that is too high), or ketosis (when fats instead of sugar are broken down for energy because of lack of insulin, chemicals called ketones appear in the blood) can happen. See instruction manual for your pump. You may have less time to identify and correct the problem than with regular insulin. This is because APIDRA starts working faster and does not work as long.

- If you start using APIDRA by pump infusion, you may need to adjust your insulin doses. Check with your healthcare provider.

- You must use insulin from a new vial of APIDRA if unexplained hyperglycemia happens, or if pump alarms do not respond to all of the following:
  - a repeat dose (injection or bolus) of APIDRA
  - a change in the infusion set, including the reservoir with APIDRA
  - a change in the infusion site.

  If these actions do not work, you may need to restart your injections with syringes and you must call your healthcare provider. Continue to check your blood sugar often.

The infusion set, reservoir with insulin, and infusion site should be changed:

- every 48 hours or less
- when unexpected hyperglycemia or ketosis occurs
- when alarms sound, as specified by your pump manual
- if the insulin has been exposed to temperatures over 98.6°F (37°C). If the insulin or pump could have absorbed radiant heat, for example from sunlight, that would heat the insulin to 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.
- Patients who get skin reactions at the infusion site may need to change infusion sites more often.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your healthcare provider in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your healthcare provider if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take,** including prescription and non-prescription

medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to all your healthcare providers and pharmacists anytime you get a new medicine or refill. Your healthcare provider will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need a different dose of insulin. Talk to your healthcare provider if you change your diet so that you know how to adjust your APIDRA and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way APIDRA works and affect your blood sugar levels. Talk to your healthcare provider about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your healthcare provider before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your healthcare provider about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of APIDRA on an unborn child or on a nursing baby are unknown. Therefore, tell your healthcare provider if you are planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What are the possible side effects of APIDRA and other insulins?

Insulins, including APIDRA, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar):

Hypoglycemia is often called an "insulin reaction" or "low blood sugar". It may happen when you do not have enough sugar in your blood. Common causes of hypoglycemia are illness, emotional or physical stress, too much insulin, too little food or missed meals, and too much exercise or activity.

Early warning signs of hypoglycemia may be different, less noticeable or not noticeable at all in some people. That is why it is important to check your blood sugar as you have been advised by your healthcare provider.

Hypoglycemia can happen with:

- **Taking too much insulin.** This can happen when too much insulin is injected. For pump users, it could happen if the pump dose is too high.

- **Not enough carbohydrate (sugar or starch) intake**. This can happen if a meal or snack is missed or delayed.

- **Vomiting or diarrhea** that decreases the amount of sugar absorbed by your body.

- **Intake of alcohol.**

- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**

- **Medical conditions that can affect your blood sugar levels or insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.

- **Too much glucose use by the body.** This can happen if you exercise too much or have a fever.

- **Injecting insulin the wrong way or in the wrong injection area.**

Hypoglycemia can be mild to severe. Its onset may be rapid. Some patients have few or no warning symptoms, including:

- patients with diabetes for a long time
- patients with diabetic neuropathy (nerve problems)
- patients using certain medicines for high blood pressure or heart problems.

Hypoglycemia may reduce your ability to drive a car or use mechanical equipment and you may risk injury to yourself or others.

Severe hypoglycemia can be dangerous and can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.**
Symptoms of hypoglycemia may include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision
- slurred speech
- palpitations (fast heart beat)
- sweating
- tremor (shaking)
- unsteady gait (walking).

If you have hypoglycemia often or it is hard for you to know if you have the symptoms of hypoglycemia, talk to your healthcare provider.

Mild to moderate hypoglycemia is treated by eating or drinking carbohydrates such as fruit juice, raisins, sugar candies, milk, or glucose tablets. Talk to your healthcare provider about the amount of carbohydrates you should eat to treat mild to moderate hypoglycemia.

Severe hypoglycemia may require the help of another person or emergency medical people. A person with hypoglycemia who is unable to take foods or liquids with sugar by mouth, or is unconscious needs medical help fast and will need treatment with a glucagon injection or glucose given intravenously (IV). Without medical help right away, serious reactions or even death could happen.

Hyperglycemia (high blood sugar):

Hyperglycemia happens when you have too much sugar in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin than prescribed, or it can mean your diabetes is getting worse.

Hyperglycemia can happen with:

- **Insufficient (too little) insulin.** This can happen from:
  - injecting too little or no insulin
  - incorrect storage (freezing, excessive heat)
  - use after the expiration date.

  For pump users, this can also be caused when the bolus dose of APIDRA infusion or the basal infusion is set too low or the pump is delivering too little insulin.

- **Too much carbohydrate intake**. This can happen if you eat larger meals, eat more often or increase the amount of carbohydrate in your meals.

- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**

- **Medical conditions that affect insulin**. These medical conditions include fevers, infections, heart attacks, and stress.

- **Injecting insulin the wrong way or in the wrong injection area.**

Testing your blood or urine often will let you know if you have hyperglycemia. If your tests are often high, tell your healthcare provider so your dose of insulin can be changed.

Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA) or very high glucose levels (hyperosmolar coma) and result in unconsciousness and death.**

Although diabetic ketoacidosis occurs most often in patients with type 1 diabetes, it can also happen in patients with type 2 diabetes who become very sick. Because some patients get few symptoms of hyperglycemia, it is important to check your blood/urine sugar and ketones regularly.

Symptoms of hyperglycemia include:
- confusion or drowsiness
- increased thirst
- decreased appetite, nausea, or vomiting
- rapid heart rate
- increased urination and dehydration (too little fluid in your body).

Symptoms of DKA also include:
- fruity smelling breath
- fast, deep breathing
- stomach area (abdominal) pain.

Severe or continuing hyperglycemia or DKA needs evaluation and treatment right away by your healthcare provider.

Other possible side effects of APIDRA include:

Serious allergic reactions:
Some times severe, life-threatening allergic reactions can happen with insulin. If you think you are having a severe allergic reaction, get medical help right away. Signs of insulin allergy include:
- rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- fast pulse
- sweating
- low blood pressure.

Reactions at the injection site:
Injecting insulin can cause the following reactions on the skin at the injection site:
- little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction).

You can reduce the chance of getting an injection site reaction if you change (rotate) the injection site each time. An injection site reaction should clear up in a few days or a few weeks. If injection site reactions do not go away or keep happening call your healthcare provider.

These are not all the side effects of APIDRA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-332-1088.

How should I store APIDRA?

Unopened APIDRA:

- Do not use APIDRA after the expiration date stamped on the label.
- Store all unopened APIDRA in a refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not allow it to freeze. Do not use APIDRA if it has been frozen.
- Keep APIDRA out of direct heat and light.
- Do not use APIDRA if it has been overheated.
- Do not use APIDRA if it is cloudy, colored, or if you see particles.

Opened APIDRA:

Vial:

- Store in a refrigerator or below 77°F (25°C) and away from direct heat and light.
- Throw the vial away 28 days after the first use even if it still contains APIDRA.

Insulin pump infusion sets:

- Change the infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir at least every 48 hours. Change all these parts sooner if they have been exposed to temperatures higher than 98.6°F (37°C).
- Do not use a vial of APIDRA after the expiration date stamped on the label.
- Do not use APIDRA if it is colored, cloudy or if you see particles.

General Information about APIDRA

- Use APIDRA only to treat your diabetes. **Do not** give or share APIDRA with another person, even if they have diabetes also. It may harm them.

- The active ingredient in APIDRA is insulin glulisine. The concentration of insulin glulisine is 100 units per milliliter (mL) or U-100. APIDRA also contains metacresol, tromethamine, sodium chloride, polysorbate 20, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.

- This 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 for information about APIDRA that is written for healthcare providers. For more information about APIDRA call 1-800-633-1610 or go to website www.apidra.com.

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1701 N. Beauregard Street, Alexandria, Virginia 22311, 1-800-DIABETES (1-800-342-2383). You may also visit the ADA website at www.diabetes.org.

Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdrf.org.
To get more information about diabetes, check with your healthcare provider or diabetes educator or visit www.DiabetesWatch.com.

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sanofi-aventis U.S. LLC
Bridgewater NJ 08807

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Patient Information
APIDRA® 3 mL cartridge system (300 units per cartridge system)
100 units per mL (U-100)
(insulin glulisine [recombinant DNA origin] injection)

Read the "Patient Information" that comes with APIDRA (uh-PEE-druh) before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. If you have questions about APIDRA or about diabetes, talk with your healthcare provider.

What is the most important information I should know about APIDRA?

- **Do not change the insulin you use without talking to your healthcare provider.** Any change in insulin strength, manufacturer, type (for example: regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal-source insulin) may need a change in the dose you are using. This dose change may be needed right away or later on. Sometimes this dose change may happen during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.

- **You must test your blood sugar levels while using an insulin, such as APIDRA.** Your healthcare provider will tell you how often you should test your blood sugar level, and what to do if it is high or low.

- **APIDRA** comes as U-100 insulin. It contains 3 milliliters (mL) of APIDRA. One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

What is Diabetes?

- Your body needs insulin to turn sugar (glucose) into energy. If your body does not make enough insulin, you need to take more insulin so you will not have too much sugar in your blood.

- Insulin injections are important in keeping your diabetes under control. But other factors can have an effect on your diabetes, such as the foods you eat, how often you check your blood sugars, and your exercise level.

What is APIDRA?

- APIDRA (insulin glulisine [recombinant DNA origin]) is a rapid-acting man-made insulin. APIDRA is used to treat patients with diabetes for the control of high blood sugar.

- APIDRA is a clear, colorless, sterile solution for injection under the skin (subcutaneously). APIDRA may also be given by infusion into one of your veins (intravenously) by healthcare providers only.

- APIDRA starts working faster than regular insulin and does not work as long. APIDRA is used with a longer-acting insulin or by itself as insulin pump therapy to maintain proper blood sugar control.

- You need a prescription to get APIDRA. Always be sure you receive the right insulin from the pharmacy.

Who should NOT take APIDRA?

Do not take APIDRA if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Apidra.
- **you are allergic to insulin glulisine** or any of the inactive ingredients in APIDRA. Check with your healthcare provider if you are not sure.

What should I tell my healthcare provider before taking APIDRA?

Tell your healthcare provider:

- **about all of your medical conditions, including liver or kidney problems.** Your dose may need to be adjusted.
- **if you are pregnant or plan to become pregnant.** It is not known if APIDRA may harm your unborn baby. It is very important to maintain control of your blood sugar levels during pregnancy. Your healthcare provider will decide which insulin is best for you during your pregnancy.
- **if you are breast-feeding or plan to breast-feed.** It is not known whether APIDRA passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- **about all the medicines you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Your APIDRA dose may change if you take other medicines. For more information look under **Medicines**, under the heading "What can affect how much insulin I need?".

How should I use APIDRA?

See the "**Instructions for OptiClik® Use"** section for additional information**.**

- Follow the instructions given by your healthcare provider about the type or types of insulin you are using. Do not make any changes with your insulin unless you have talked to your healthcare provider. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your healthcare provider about how to adjust your insulin dose.
- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal. Only use APIDRA that is clear and colorless. If your APIDRA is cloudy or colored, return it to your pharmacy for a replacement.
- Follow your healthcare provider's instructions for testing your blood sugar.
- Inject APIDRA under your skin (subcutaneously) in your upper arm, abdomen (stomach area), or thigh (upper leg). Never inject it into a vein or muscle.

- Change (rotate) injection sites within the same body area.

What kind of insulin Pen should I use with APIDRA cartridge system?

- Always use OptiClik® device distributed by sanofi-aventis U.S. LLC with your APIDRA cartridge system. If you use any other device than OptiClik® insulin Pen with APIDRA cartridge system, you may get the wrong dose of insulin causing serious problems for you, such as a blood sugar level that is too low or too high. Always use a new needle each time you give APIDRA injection.

- **NEEDLES AND INSULIN PEN MUST NOT BE SHARED.**

- Disposable needle should be used only once. Used needle should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

Instructions for OptiClik® Use

It is important to read, understand, and follow the step-by-step instructions in the "OptiClik® Instruction Leaflet" before using OptiClik® insulin Pen. Failure to follow the instructions may result in getting too much or too little insulin. If you have lost your leaflet or have a question, go to www.opticlik.com or call 1-800-633-1610.

OptiClik® insulin Pen is for use with BD Ultra-Fine needles.

The following general notes should be taken into consideration before injecting APIDRA:

- Always wash your hands before handling the cartridge system and/or the OptiClik® insulin Pen.
- Always attach a new needle before use.
- Always perform the safety test before use.
- Check the insulin solution in the cartridge system to make sure it is clear, colorless, and free of particles. If it is not, throw it away.
- Decide on an injection area - either upper arm, thigh, or abdomen. Do not use the same injection site as your last injection.
- After injecting APIDRA, leave the needle in the skin for an additional 10 seconds. Then pull the needle straight out. Gently press on the spot where you injected yourself for a few seconds. **Do not rub the area.**
- Do not drop the OptiClik® insulin Pen.

If your blood glucose reading is high or low, tell your healthcare provider so the dose can be adjusted.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your healthcare provider in advance so you will be ready when this

happens. Be sure to test your blood sugar more often and call your healthcare provider if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to all your healthcare providers and pharmacists anytime you get a new medicine or refill. Your healthcare provider will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need a different dose of insulin. Talk to your healthcare provider if you change your diet so that you know how to adjust your APIDRA and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way APIDRA works and affect your blood sugar levels. Talk to your healthcare provider about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your healthcare provider before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your healthcare provider about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of APIDRA on an unborn child or on a nursing baby are unknown. Therefore, tell your healthcare provider if you are planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What are the possible side effects of APIDRA and other insulins?

Insulins, including APIDRA, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar):
Hypoglycemia is often called an "insulin reaction" or "low blood sugar". It may happen when you do not have enough sugar in your blood. Common causes of hypoglycemia are illness, emotional or physical stress, too much insulin, too little food or missed meals, and too much exercise or activity.
Early warning signs of hypoglycemia may be different, less noticeable or not noticeable at all in some people. That is why it is important to check your blood sugar as you have been advised by your healthcare provider.

Hypoglycemia can happen with:

- **Taking too much insulin.** This can happen when too much insulin is injected. For pump users it could happen if the pump dose is too high.
- **Not enough carbohydrate (sugar or starch) intake**. This can happen if: a meal or snack is missed or delayed.
- **Vomiting or diarrhea** that decreases the amount of sugar absorbed by your body.
- **Intake of alcohol.**
- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**
- **Medical conditions that can affect your blood sugar levels or insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Too much glucose use by the body.** This can happen if you exercise too much or have a fever.
- **Injecting insulin the wrong way or in the wrong injection area.**

Hypoglycemia can be mild to severe. Its onset may be rapid. Some patients have few or no warning symptoms, including:

- patients with diabetes for a long time
- patients with diabetic neuropathy (nerve problems)
- or patients using certain medicines for high blood pressure or heart problems.

Hypoglycemia may reduce your ability to drive a car or use mechanical equipment and you may risk injury to yourself or others.

Severe hypoglycemia can be dangerous and can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.**
Symptoms of hypoglycemia may include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision
- slurred speech
- palpitations (fast heart beat)

- sweating
- tremor (shaking)
- unsteady gait (walking).

If you have hypoglycemia often or it is hard for you to know if you have the symptoms of hypoglycemia, talk to your healthcare provider.

Mild to moderate hypoglycemia is treated by eating or drinking carbohydrates such as fruit juice, raisins, sugar candies, milk or glucose tablets. Talk to your healthcare provider about the amount of carbohydrates you should eat to treat mild to moderate hypoglycemia.

Severe hypoglycemia may require the help of another person or emergency medical people. A person with hypoglycemia who is unable to take foods or liquids with sugar by mouth, or is unconscious needs medical help fast and will need treatment with a glucagon injection or glucose given intravenously (IV). Without medical help right away, serious reactions or even death could happen.

Hyperglycemia (high blood glucose):
Hyperglycemia happens when you have too much sugar in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin than prescribed, or it can mean your diabetes is getting worse.

Hyperglycemia can happen with:

- **Insufficient (too little) insulin.** This can happen from:
  - injecting too little or no insulin
  - incorrect storage (freezing, excessive heat)
  - use after the expiration date.

  For pump users this can also be caused when the bolus dose of APIDRA infusion or the basal infusion is set too low or the pump is delivering too little insulin.

- **Too much carbohydrate intake**. This can happen if you eat larger meals, eat more often or increase the amount of carbohydrate in your meals.

- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**

- **Medical conditions that affect insulin**. These medical conditions include fevers, infections, heart attacks, and stress.

- **Injecting insulin the wrong way or in the wrong injection area.**

Testing your blood or urine often will let you know if you have hyperglycemia. If your tests are often high, tell your healthcare provider so your dose of insulin can be changed.

Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA) or very high glucose levels (hyperosmolar coma) and result in unconsciousness and death.**

Although diabetic ketoacidosis occurs most often in patients with type 1 diabetes, it can also happen in patients with type 2 diabetes who become very sick. Because some patients get few symptoms of hyperglycemia, it is important to check your blood sugar regularly.

Symptoms of hyperglycemia include:
- confusion or drowsiness
- increased thirst
- decreased appetite, nausea, or vomiting
- rapid heart rate
- increased urination and dehydration (too little fluid in your body).

Symptoms of DKA also include:
- fruity smelling breath
- fast, deep breathing
- stomach area (abdominal) pain.

Severe or continuing hyperglycemia or DKA needs evaluation and treatment right away by your healthcare provider.

Other possible side effects of APIDRA include:

Serious allergic reactions:
Some times severe, life-threatening allergic reactions can happen with insulin. If you think you are having a severe allergic reaction, get medical help right away. Signs of insulin allergy include:
- rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- fast pulse
- sweating
- low blood pressure.

Reactions at the injection site:
Injecting insulin can cause the following reactions on the skin at the injection site:
- little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction).

You can reduce the chance of getting an injection site reaction if you change (rotate) the injection site each time. An injection site reaction should clear up in a few days or a few weeks. If injection site reactions do not go away or keep happening, call your healthcare provider.

These are not all the side effects of APIDRA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-332-1088.

How should I store APIDRA?

Unopened APIDRA:

- Do not use APIDRA after the expiration date stamped on the label.
- Store all unopened APIDRA in a refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not allow it to freeze. Do not use APIDRA if it has been frozen.
- Keep APIDRA out of direct heat and light.
- Do not use APIDRA if it has been overheated.
- Do not use APIDRA if it is cloudy, colored, or if you see particles.

Opened APIDRA:

Cartridge:

- Store the opened cartridge system below 77°F (25°C) and away from direct heat and light.
- Throw away the cartridge system 28 days after the first use even if it still contains APIDRA.
- Do not store an opened cartridge system or OptiClik® insulin Pen in a refrigerator.
- Do not use APIDRA if it is cloudy, colored, or if you see particles.

General Information about APIDRA

- Use APIDRA only to treat your diabetes. **Do not** give or share APIDRA with another person, even if they have diabetes also. It may harm them.

- The active ingredient in APIDRA is insulin glulisine. The concentration of insulin glulisine is 100 units per milliliter (mL), or U-100. APIDRA also contains metacresol, tromethamine, sodium chloride, polysorbate 20, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.

- This 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 for information about APIDRA that is written for healthcare providers. For more information about APIDRA call 1-800-633-1610 or go to website www.apidra.com.

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association,

(ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383). You may also visit the ADA website at www.diabetes.org.
Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdf.org.
To get more information about diabetes, check with your healthcare provider or diabetes educator or visit www.DiabetesWatch.com.

Additional information about APIDRA or OptiClik® can be obtained by calling 1-800-633-1610 or by visiting www.apidra.com or www.opticlik.com.

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