APIDRA® (insulin glulisine [rDNA origin] injection) solution for injection
Initial U.S. Approval: 2004

APIDRA® (insulin glulisine [rDNA origin] injection) solution for injection

Recent Major Changes

Warnings and Precautions (5.1) 02/2015
Warnings and Precautions (5.11) 02/2014

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 SoloStar® prefilled pen

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Revised: 02/2015
APIDRA is contraindicated:

4 CONTRAINDICATIONS

The following insulin pumps external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Do not administer insulin mixtures intravenously. Monitor of blood glucose and serum potassium to avoid hypoglycemia and hypokalemia. For injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia.

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 insulins 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™, and Tender™)
• MiniMed® Models 506, 507, 507c and 508 with MiniMed catheters (Solo-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. Failure to follow APIDRA-specific instructions may lead to serious adverse events.

Patients administering APIDRA by continuous subcutaneous infusion must have an alternative insulin delivery system in case of pump system failure. 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 should not be exposed to temperatures greater than 88.6°F (37°C).

In clinical use, the insulin level in the APIDRA in the reservoir must be changed at least every 48 hours [See Warnings and Precautions (5.8) 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 hyperkalemia. 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 mLSoloStar prefilled pen

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 Never share an APIDRA SoloStar pen or syringe or needle between patients

APIDRA SoloStar pens must never be shared between patients, even if the needle is changed. Patients using APIDRA vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of bloodborne pathogens.

5.2 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 cardiovascular load may require adjustment of insulin dosages.

5.3 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. 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.

5.4 Hypersensitivity and allergic reactions

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

5.5 Hypokalemia

All insulin products, including APIDRA, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-sparing medications, patients taking medications sensitive to serum potassium concentrations). Monitor glucose and potassium frequently when APIDRA is administered intravenously.

5.6 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)].

5.7 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. The needle should not be left in the syringe longer than 30 minutes. Needles should be replaced after each use.

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 dilluents or other insulins for use in external subcutaneous infusion pumps have not been established.

5.8 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 must be changed at least every 48 hours. APIDRA should not be exposed to temperatures greater than 88.6°F (37°C).

Malfunction of the insulin pump or infusion set or handling errors or insulin degradation can rapidly lead to hyperglycemia, ketosis and diabetic ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis or diabetic ketoacidosis is necessary. Intramuscular injections 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. [See Dosage and Administration (2.3), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.3)].

5.9 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.

5.10 Drug interactions

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

5.11 Fluid retention and heart failure with concomitant use of PPAR-gamma agonists

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

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

• Hypoglycemia [See Warnings and Precautions (5.3)]
• Hypokalemia [See Warnings and Precautions (5.5)]

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%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>APIDRA, % (n=950)</th>
<th>All comparators, % (n=4411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>10.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Influenza</td>
<td>4.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Insulin aspro, regular human insulin, insulin aspart

Only severe symptomatic hypoglycemia
Localized reactions and generalized myalgias have been reported with the use of metacresol, which continued in 1 of 1833 patients due to a potential systemic allergic reaction. Medication errors have been reported in which other insulins, particularly long-acting insulins, have been accidentally administered instead of APIDRA.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>APIDRA, % (n=297)</th>
<th>Lispro, % (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Hypoglycemic seizure</td>
<td>6.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Severe symptomatic hypoglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

## Table 4: Severe Symptomatic Hypoglycemia

<table>
<thead>
<tr>
<th>Type 1 Diabetes Adults 26 weeks with insulin glargine</th>
<th>Type 1 Diabetes Adults 26 weeks with insulin glargine</th>
<th>Type 2 Diabetes Adults 26 weeks with NPH human insulin</th>
<th>Type 1 Diabetes Pediatrics 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event per month per patient</td>
<td>Event per month per patient</td>
<td>Event per month per patient</td>
<td>Event per month per patient</td>
</tr>
<tr>
<td>APIDRA Pre-meal</td>
<td>APIDRA Post-meal</td>
<td>APIDRA</td>
<td>APIDRA</td>
</tr>
<tr>
<td>ADI</td>
<td>ADI</td>
<td>ADI</td>
<td>ADI</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.05</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.8%</td>
<td>4.8%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.8% (16/339)</td>
<td>4.0% (13/333)</td>
<td>1.4% (6/416)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0% (4/395)</td>
<td>1.2% (5/420)</td>
<td>16.2% (45/277)</td>
</tr>
<tr>
<td>Percent of patients (n/total N)</td>
<td>8.4% (24/286)</td>
<td>8.4% (25/296)</td>
<td>10.1% (28/278)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Event</th>
<th>APIDRA (n=29)</th>
<th>Insulin aspart (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter occlusions/month</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>10.3% (3/29)</td>
<td>13.3% (4/30)</td>
</tr>
</tbody>
</table>

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 glargine (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, diisoprim, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxyfilline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

Drugs that may decrease the blood glucose-lowering effect of insulins including APIDRA, and therefore lower the blood-glucose-lowering effect of insulin.

Drugs that may reduce the blood-glucose-lowering effect of APIDRA include corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., ephedrine, 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, quinidine, and reserpine.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy Category C: Reproduction and teratology studies have been performed with insulin glargine in rats and rabbits using regular human insulin as a comparator. Insulin glargine was given to female rats throughout pregnancy 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). Insulin glargine 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 increase in incidences 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 rats 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 readjustments 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 [DNA 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 asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Chemically, insulin glulisine is 3\textsuperscript{2}P-lysine-29-glutamic acid-human insulin, has the empirical formula C\textsubscript{64}H\textsubscript{107}N\textsubscript{6}O\textsubscript{52}S\textsubscript{2} and a molecular weight of 5823 and has the following structural formula:

![Structural formula of insulin glulisine](image)

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 sodium hydroxide, and a molecular weight of 5823 and has the following structural formula:

![Structural formula of insulin glulisine](image)

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 sodium hydroxide, and a molecular weight of 5823 and has the following structural formula:

![Structural formula of insulin glulisine](image)

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 25 and 30 kg/m\textsuperscript{2}. The median time to maximum concentration (T\textsubscript{max}) was 60 minutes (range 40 to 120 minutes) and the peak concentration (C\textsubscript{max}) was 83 microUnits/mL (range 40 to 131 microUnits/mL) for insulin glulisine compared to a median T\textsubscript{max} of 120 minutes (range 60 to 239 minutes) and a C\textsubscript{max} of 50 microUnits/mL (range 35 to 71 microUnits/mL) for regular human insulin. (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.](image)

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 infusion at a rate of 0.8 milliUnits/kg for two hours. Infusion of the same dose of APIDRA or regular human insulin produced equivalent glucose disposal at steady state.

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 potent 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.)

![Pharmacodynamic profiles of insulin glulisine and regular human insulin in patients with type 1 diabetes after a subcutaneous dose of 0.2 Units/kg.](image)

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=52) the total insulin glulisine bioavailability was similar after subcutaneous injection of insulin glulisine and NPH insulin (precipitated in the syringe) and following separate simultaneous subcutaneous injections. There was 27% attenuation of the maximum concentration (C\textsubscript{max}) of APIDRA after premixing; however, the time to maximum concentration (T\textsubscript{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(0-1h) to AUC(0-24h) than Caucasians (21%) although the total exposures were similar. There were similar findings with insulin lispro and regular human insulin.

Obesity
Insulin glulisine and regular human insulin were administered subcutaneously at a dose of 0.3 Units/kg in a euglycemic clamp study in obese, non-diabetic subjects (n=18) with a body mass index (BMI) between 30 and 40 kg/m². The median time to maximum concentration (T(max)) was 85 minutes (range 49 to 150 minutes) and the median peak concentration (C(max)) was 192 microUnits/mL (range 88 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 (CLcr >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 (5.6)].

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. [See Warnings and Precautions (5.6)].

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 up to 10 Units/kg once daily (dose normalized to human dose, based on body surface area comparison). There was a non-dose dependent higher incidence of mammary gland tumors in female rats compared to males. 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 0.3 Units/kg once daily (dose normalized to human dose, based on body surface area comparison).

14 CLINICAL STUDIES

14.1 Type 1 Diabetes-Adults
A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in insulin-treated patients with type 1 diabetes to assess the safety and efficacy of APIDRA (n=435) given within 15 minutes before a meal compared to regular human insulin (n=441) administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period with regular human insulin and NPH human insulin. Eighty-five percent of patients were Caucasian and 11% were Black. The mean age was 58 years (range 26 to 84 years). The average body mass index (BMI) was 34.6 kg/m². At randomization, 58% of the patients were taking an oral antidiabetic agent. These patients were instructed to continue use of their oral antidiabetic agent at the same dose throughout the trial. The majority of patients (79%) mixed their short-acting insulin with NPH human insulin immediately prior to injection. The reductions from baseline in GHb were similar between the 2 treatment groups (see Table 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 6: Type 1 Diabetes Mellitus–Adult

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

*GHb reported as HbA1c equivalent

14.2 Type 2 Diabetes-Adults
A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in insulin-treated patients with type 2 diabetes to assess the safety and efficacy of APIDRA (n=435) given within 15 minutes before a meal compared to regular human insulin (n=441) administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period with regular human insulin and NPH human insulin. Eighty-five percent of patients were Caucasian and 11% were Black. The mean age was 58 years (range 26 to 84 years). The average body mass index (BMI) was 34.6 kg/m². At randomization, 58% of the patients were taking an oral antidiabetic agent. These patients were instructed to continue use of their oral antidiabetic agent at the same dose throughout the trial. The majority of patients (79%) mixed their short-acting insulin with NPH human insulin immediately prior to injection. The reductions from baseline in GHb were similar between the 2 treatment groups (see Table 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

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with:</th>
<th>26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NHPI human insulin</td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin (GHB)* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>404</td>
<td>403</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>7.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.5</td>
<td>-0.3</td>
</tr>
<tr>
<td>Treatment difference: APIDRA – Regular Human Insulin</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>95% CI for treatment difference</td>
<td>(-0.3; -0.1)</td>
<td></td>
</tr>
<tr>
<td>Basal insulin dose (Units/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Short-acting insulin dose (Units/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Mean number of short-acting insulin injections per day</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
14.3 Type 1 Diabetes-Adults: Pre- and post-meal administration

A 12-week, randomized, open-label, 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 7: Type 2 Diabetes Mellitus–Adult (continued)

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>26 weeks</th>
<th>NPH human insulin</th>
<th>APIDRA</th>
<th>Regular Human Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment in combination with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glycated hemoglobin (GHb)* (%)

Number of patients
Baseline mean
Adjusted mean change from baseline
Basal insulin dose (Units/day)
Adjusted mean change from baseline
Short-acting insulin dose (Units/day)
Baseline mean
Adjusted mean change from baseline
Mean number of short-acting insulin injections per day
Body weight (kg)
Baseline mean
Mean change from baseline

1GHb reported as HbA1c equivalent

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

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>12 weeks</th>
<th>12 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment in combination with:</td>
<td>insulin glargine</td>
<td>insulin glargine</td>
<td>insulin glargine</td>
</tr>
<tr>
<td></td>
<td>APIDRA pre meal</td>
<td>APIDRA post meal</td>
<td>Regular Human Insulin</td>
</tr>
</tbody>
</table>

Glycated hemoglobin (GHb)* (%)

Number of patients
Baseline mean
Adjusted mean change from baseline
Basal insulin dose (Units/day)
Adjusted mean change from baseline
Short-acting insulin dose (Units/day)
Baseline mean
Adjusted mean change from baseline
Mean number of short-acting insulin injections per day
Body weight (kg)
Baseline mean
Mean change from baseline

1GHb reported as HbA1c equivalent

14.4 Type 1 Diabetes-Pediatric patients

A 26-week, randomized, open-label, 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) 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 (91%). Fifty percent of the patients were male. The mean age was 12.5 years (range 4 to 17 years). Mean BMI was 20.6 kg/m². Glycemic control (see Table 9) was comparable for the two treatment regimens.

Table 9: Results from a 26-week study in pediatric patients with type 1 diabetes mellitus

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>APIDRA</th>
<th>Lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin</td>
<td>271</td>
<td>291</td>
</tr>
<tr>
<td>NPH or insulin glargine</td>
<td>NPH or insulin glargine</td>
<td></td>
</tr>
</tbody>
</table>
| Glycated hemoglobin (GHb)* (%)
Baseline mean | 8.2 | 8.2 |

1GHb reported as HbA1c equivalent

14.5 Type 1 Diabetes-Adults: Continuous subcutaneous insulin infusion

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

APIDRA 100 units per mL (U-100) is available as:
- 10 mL vials NDC 0088-2500-33
- 3 mL SoloStar prefilled pen, package of 5 NDC 0088-2502-05

Pen needles are not included in the packs.

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

16.2 Storage

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

Unopened Vial/SoloStar

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

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

Open (In-Use) Vial:

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

Open (In-Use) SoloStar prefilled pen:

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

Infusion sets:

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

Intravenous use:

Infusion bags 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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Never share an APIDRA SoloStar pen or syringe or needle between patients

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

17.2 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.

17.3 For patients using continuous subcutaneous insulin pumps

Patients using external pump infusion therapy should be trained appropriately. The following insulin pumps1 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 Tandem™)
- Minimed® Models 506, 507, 507c and 508 with Minimed catheters (Sol-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 must be replaced at least 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 86.6°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 handling errors or insulin degradation can lead to rapid hyperglycemia, and ketosis and diabetic ketoacidosis. 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 or diabetic ketoacidosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, handling errors 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. Patients administering APIDRA by continuous subcutaneous infusion must have an alternative insulin delivery system in case of pump system failure. [See Dosage and Administration (2.3), Warnings and Precautions (5.8), and How Supplied/Storage and Handling (16)].

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

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Patient Information

APIDRA® (oh PEE dru)
(insulin glulisine [recombinant DNA origin] injection)
solution for injection

Read the Patient Information that comes with APIDRA before you start taking 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.

Do not share your APIDRA SoloStar pen or syringes with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is APIDRA?

APIDRA is a man-made insulin used to control high blood sugar in adults and children with diabetes mellitus. It is not known if APIDRA is safe or effective in:

- children under age 4 with type 1 diabetes
- children with type 2 diabetes

Who Should NOT take APIDRA?

Do not take APIDRA:

- when your blood sugar is too low (hypoglycemia). See the section, “What are the possible side effects of APIDRA?”
- if you are allergic to any of the ingredients in APIDRA. See the end of this leaflet for a complete list of ingredients.
- if you are taking APIDRA and then give other people your insulin. Y our healthcare provider should show you how to inject APIDRA before you start taking it.

Your healthcare provider will prescribe the best type of APIDRA for you. APIDRA is available in:

- 3 mL SoloStar® prefilled pen
- 10 mL vials

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

Check your blood sugar level before each use of APIDRA. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Check the label to make sure you have the correct insulin type. This is especially important if you also take long-acting insulin.

APIDRA should look clear and colorless. Do not use APIDRA if it looks cloudy, colored, or has particles in it. Talk with your pharmacist or healthcare provider if you have any questions.

If you take too much APIDRA, your blood sugar may fall low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away.

- Do not share your APIDRA SoloStar pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.
- Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them.
- Do not reuse needles.

Your dose of APIDRA may need to be changed because of:

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise
- travel

Check your blood sugar and stay on the diet and exercise plan as prescribed by your healthcare provider.

What should I consider while taking APIDRA?

Alcohol may affect your blood sugar when you take APIDRA
Driving and operating machinery. You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you have:

- low blood sugar (hypoglycemia)
- decreased or no warning signs of low blood sugar

What are the possible side effects of APIDRA?

APIDRA can cause serious side effects, including:

- Low blood sugar (hypoglycemia). Symptoms of low blood sugar may include:
  - feeling anxious, or irritable, mood changes
  - trouble concentrating or feeling confused
  - tingling in your hands, feet, lips, or tongue
  - feeling dizzy, light-headed, or drowsy
  - nightmares or trouble sleeping
  - headache
  - blurred vision
  - slurred speech
  - a fast heart beat
  - sweating
  - shakiness
  - walking unsteady

Very low blood sugar (hypoglycemia) can cause unconsciousness (passing out), seizures, and death. Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking APIDRA. Know your symptoms of low blood sugar. Follow your healthcare provider’s instructions for treating your low blood sugar.

Talk to your healthcare provider if low blood sugar is a problem for you. Your dose of APIDRA may need to be changed.

- Serious allergic reactions.
  - Get medical help right away if you have any of these symptoms of a severe allergic reaction:
    - a rash all over your body
    - shortness of breath
    - trouble breathing (wheezing)
    - fast pulse
    - sweating
    - feel faint (due to low blood pressure)
  - low potassium in your blood. Your doctor will check you for this.

Common side effects include:

- Reactions at the injection site (local allergic reaction). You may get redness, swelling and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider.

- Skin thickening or pits at the injection site. Do not inject insulin into skin where this has happened. Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. Do not inject into the exact same spot for each injection.

- Weight gain

Heart Failure. Taking certain diabetes pills called thiazolidinediones or “TZDs” with APIDRA may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with APIDRA.
Your healthcare provider should monitor you closely while you are taking TZDs with APIDRA. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:

- shortness of breath
- swelling of your ankles or feet
- sudden weight gain

During treatment with TZDs and APIDRA, the TZD dose may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the possible side effects of APIDRA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-332-1088.

How should I store APIDRA?

- See the Patient Instructions for Use that come with your APIDRA for specific storage instructions.

Unopened APIDRA:

- Do not use APIDRA after the expiration date stamped on the label.
- Keep all unopened APIDRA in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze. Do not use APIDRA if it has been frozen.
- Keep APIDRA away from direct heat and light.

Unopened vials and SoloStar that were not kept in a refrigerator must be used within 28 days after opening.

General Information about APIDRA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use APIDRA for a condition for which it was not prescribed. Do not give APIDRA to other people, even if they have the same symptoms you have. It may harm them.

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 www.apidra.com.

What are the ingredients in APIDRA?

Active ingredient: insulin glulisine

Inactive ingredients: metacresol, tromethamine, sodium chloride, polysorbate 20, water for injection, hydrochloric acid or sodium hydroxide

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.jdrf.org.

To get more information about diabetes, check with your healthcare provider or diabetes educator or visit www.DiabetesWatch.com.

For more information about APIDRA call 1-800-633-1610 or visit www.apidra.com.