CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-629

APPROVED LABELING

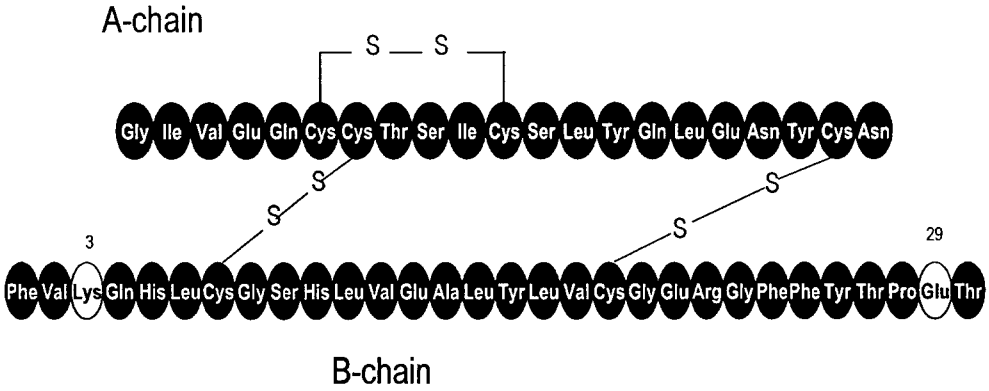
Rev. April 2004

APIDRA™
Insulin glulisine (rDNA origin) injection

Rx only

DESCRIPTION

APIDRA™ (insulin glulisine [rDNA origin]) is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. 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, it 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. It has the following structural formula:



APIDRA is a sterile, aqueous, clear, and colorless solution. Each milliliter of APIDRA (insulin glulisine injection) contains 100 IU (3.49 mg) insulin glulisine, 3.15 mg m-cresol, 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

The primary activity of insulins and insulin analogs, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit 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.

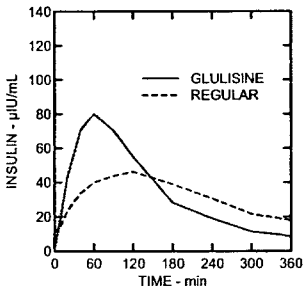
Pharmacokinetics

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 regular human insulin.

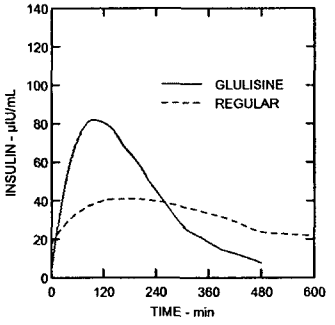
In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 IU/kg, the median time to maximum concentration (T_{max}) was 55 minutes (range 34 to 91 minutes) and the peak concentration (C_{max}) was 82 μIU/mL (range 42 to 134 μIU/mL) for insulin glulisine compared to a median T_{max} of 82 minutes (range 52 to 308 minutes) and a C_{max} of 46 μIU/mL (range 32 to 70 μIU/mL) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 98 minutes, range 55 to 149 minutes) than for regular human insulin (median: 161 minutes, range 133 to 193 minutes). (See Figure 1.)

Figure 1. Pharmacokinetic profile of insulin glulisine and regular human insulin in patients with type 1 diabetes after a dose of 0.15 IU/kg.



In a euglycaemic clamp study in patients with type 2 diabetes (n=24) with a body mass index (BMI) between 20 to 36 kg/m^2 after subcutaneous administration of 0.2 IU/kg, the median time to maximum concentration (Tmax) was 89 minutes (range 74 to 103 minutes) and the median peak concentration (Cmax) was 81μIU/mL (range 75 to 112 μIU/mL) for insulin glulisine compared to a median Tmax of 94 minutes (range 55 to140 minutes) and a median Cmax of 39 μIU/mL (range 30 to 56 μIU/mL) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 154 minutes, range 122 to 174 minutes) than for regular human insulin (median: 280 minutes, range 227 to 294 minutes).

Figure 2. Pharmacokinetic profile of insulin glulisine and regular human insulin in patients with type 2 diabetes after a dose of 0.2 IU/kg.



In a euglycaemic clamp study in obese, non-diabetic subjects (n=18) with a body mass index (BMI) between 30 to 40 kg/m^2 after subcutaneous administration of 0.3 IU/kg, the median time to maximum concentration (Tmax) was 76 minutes (range 51 to 118 minutes) and the median peak concentration (Cmax) was 199 µIU/mL (range 99 to 387 µIU/mL) for insulin glulisine compared to a median Tmax of 144 minutes (range 110 to 207 minutes) and a median Cmax of 79 µIU/mL (range 39 to 166 µIU/mL) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 141 minutes, range 105 to 210 minutes) than for regular human insulin (median: 226 minutes, ranging between 188 to 293 minutes).

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 about 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%).

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 L 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.

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 IU/kg. (See Figure 3.)

Figure 3. Serial mean blood glucose collected up to 6 hours following 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 3A) and compared to regular human insulin (Regular - pre) given 2 minutes before a

meal (Figure 3B). 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 3C). On the x-axis zero (0) is the start of a 15-minute meal.

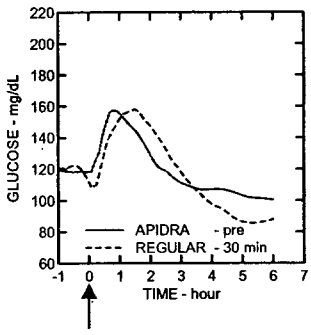


Figure 3A

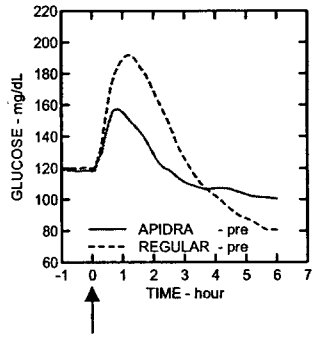


Figure 3B

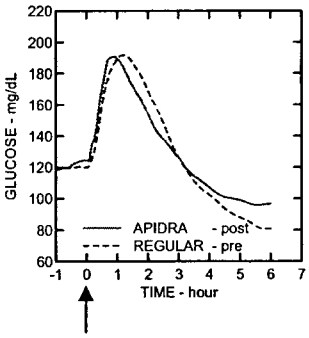


Figure 3C

Start of a 15-minute meal

The maximum blood glucose excursion (ΔGLU_{max}; baseline subtracted glucose concentration) for APIDRA injected 2 minutes before meal was 65 mg/dL compared to 64 mg/dL for regular human insulin injected 30 minutes before meal (see Figure 3A), and 84 mg.h/dL for regular human insulin injected 2 minutes before meal (see Figure 3B). The maximum blood glucose excursion for APIDRA injected 15 minutes after the start of a meal was 85 mg/dL compared to 84 mg.h/dL for regular human insulin injected 2 minutes before meal (see Figure 3C).

Special Populations

Pediatric Patients

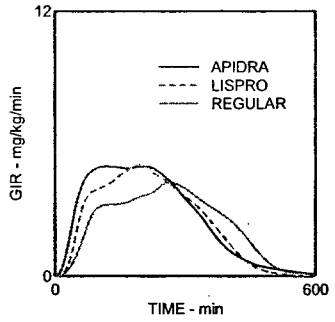
The pharmacokinetic and pharmacodynamic properties of APIDRA and regular human insulin were assessed in a study conducted in pediatric patients with type 1 diabetes (children [7 to 11 years, n = 10] and adolescents [12 to 16 years, n = 10]). The relative differences in pharmacokinetics and pharmacodynamics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

Gender
Information on the effect of gender on the pharmacokinetics of APIDRA is not available.

Race
A study was performed in 24 healthy Caucasians and Japanese to compare the pharmacokinetic and pharmacodynamic parameters 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(0-1hr) to AUC(0-clamp end) than that in Caucasians (21%) though the total exposures were similar. Similar findings were observed with insulin lispro and regular human insulin for the racial difference.

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

Figure 4. Glucose infusion rates (GIR) in a euglycemic clamp study after subcutaneous injection of 0.3 IU/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 covering a wide range of renal function (Cl_{Cr} >80mL/min; 30-50 mL/min; <30 mL/min), the subjects with moderate and severe renal impairment showed increased exposure of insulin glulisine by 29% to 40% and reduced clearance of insulin glulisine by 20 to 25% compared to normal subjects. Careful glucose monitoring and dose adjustments of insulin, including APIDRA, may be necessary in patients with renal dysfunction. (See PRECAUTIONS, Renal Impairment.)

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of APIDRA has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including APIDRA, may be necessary in patients with hepatic dysfunction. (See PRECAUTIONS, Hepatic Impairment.)

Pregnancy
The effect of pregnancy on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied. (See PRECAUTIONS, Pregnancy.)

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

CLINICAL STUDIES

The safety and efficacy of APIDRA was studied in adult patients with type 1 and type 2 diabetes (n =1833). The primary efficacy parameter was glycemic control, as measured by glycated hemoglobin (GHb), and expressed as hemoglobin A1c equivalents (HbA1c).

Type 1 Diabetes:

A 26-week, randomized, open-label, active-control 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. Lantus® (insulin glargine)† was administered once daily in the evening as the basal insulin. There was a 4-week run-in period combining insulin lispro and Lantus followed by randomization. Most patients were Caucasian (97%). Fifty eight percent of the patients were male. The mean age was 38.5 years (range 18 to 74 years). Glycemic control (see Table 1) and the rates of hypoglycemia requiring intervention from a third party (see Adverse Reactions), were comparable for the two treatment regimens. The number of daily short-acting insulin injections and the total daily doses of APIDRA and insulin lispro were similar. (See Table 1.)

Table 1: Type 1 Diabetes Mellitus–Adult

Treatment duration	26 weeks	
Treatment in combination with:	Lantus®	
	APIDRA	Insulin Lispro
HbA1c (%)		
Number of patients	331	322
Baseline mean	7.60	7.58
Adj. mean change from baseline	-0.14	-0.14
APIDRA – Insulin Lispro	0.00	
95% CI for treatment difference	(-0.09; 0.10)	
Basal insulin dose (IU/day)		
Endstudy mean	24.16	26.43
Adj. mean change from baseline	0.12	1.82
Short-acting insulin dose (IU/day)		
Endstudy mean	29.03	30.12
Adj. mean change from baseline	-1.07	-0.81
Mean number of short-acting insulin injections per day	3.36	3.42

Type 2 Diabetes:

A 26-week, randomized, open-label, active-control 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 combining regular human insulin and NPH human insulin. Eighty-five percent of patients were Caucasian and 11% were Black. The mean age was 58.3 years (range 26 to 84 years). The average body mass index (BMI) was 34.55 kg/m^2. At randomization, 58% of the patients were on an oral antidiabetic agent and were instructed to continue use of their oral antidiabetic agent at the same dose. The majority of patients (79%) mixed their short-acting insulin with NPH human insulin immediately prior to injection. The reductions from baseline in HbA1c were similar between treatment groups (see Table 2). The rates of hypoglycemia, requiring intervention from a third party, were comparable for the two treatment regimens (see Adverse Reactions). 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 2.)

Table 2: Type 2 Diabetes Mellitus–Adult

Treatment duration	26 weeks	
Treatment in combination with:	NPH human insulin	
	APIDRA	Regular Human Insulin
HbA1C (%)		
Number of patients	404	403
Baseline mean	7.57	7.50
Adj. mean change from baseline	-0.46	-0.30
APIDRA – Regular Human Insulin	-0.16	
95% CI for treatment difference	(-0.26; -0.05)	
Basal insulin dose (IU/day)		
Endstudy mean	65.34	63.05
Adj. mean change from baseline	5.73	6.03
Short-acting insulin dose (IU/day)		
Endstudy mean	35.99	36.16
Adj. mean change from baseline	3.69	5.00
Mean number of short-acting insulin injections per day	2.27	2.24

Pre- and Post-Meal Administration (Type 1 Diabetes):

A 12-week, randomized, open-label, active-control 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. Lantus® was administered once daily at bedtime as the basal insulin. There was a 4-week run-in period combining regular human insulin and Lantus followed by randomization. Most patients were Caucasian (94%). The mean age was 40.3 years (range 18 to 73 years). Glycemic control (see Table 3) and the rates of hypoglycemia requiring intervention from a third party (see Adverse Reactions) were comparable for the treatment regimens. No changes from baseline between the treatments were seen in the total daily number of short-acting insulin injections. (See Table 3.)

Table 3: Type 1 Diabetes Mellitus–Adult

Treatment duration Treatment in combination with:	12 weeks Lantus® APIDRA pre meal	12 weeks Lantus® APIDRA post meal	12 weeks Lantus® Regular Human Insulin
HbA1c			
Number of patients	268	276	257
Baseline mean	7.73	7.70	7.64
Adj. mean change from baseline*	-0.26	-0.11	-0.13
Basal insulin dose (IU/day)			
Endstudy mean	29.49	28.77	28.46
Adj. mean change from baseline	0.99	0.24	0.65
Short-acting insulin dose (IU/day)			
Endstudy mean	28.44	28.06	29.23
Adj. mean change from baseline	-0.88	-0.47	1.75
Mean number of short-acting insulin injections per day	3.15	3.13	3.03

* Adj. mean change from baseline treatment difference (98.33% CI for treatment difference): APIDRA pre meal vs. Regular Human Insulin - 0.13 (-0.26; 0.01); APIDRA post meal vs. Regular Human Insulin 0.02 (-0.11; 0.16); APIDRA post meal vs. pre meal 0.15 (0.02; 0.29).

Continuous Subcutaneous Insulin Infusion (CSII) (Type 1 Diabetes):
To evaluate the use of APIDRA for administration using an external pump, a 12-week randomized, active control study (APIDRA versus insulin aspart) was conducted in patients with type 1 diabetes (APIDRA n= 29, insulin aspart n=30). All patients were Caucasian. The mean age was 45.8 (range 21-73 years). Glycemic control (mean HbA1c value at endpoint 6.98% with APIDRA and 7.18% with insulin aspart) and the rates of hypoglycemia requiring intervention from a third party were comparable for the two treatment regimens.

INDICATIONS AND USAGE
APIDRA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

APIDRA has a more rapid onset of action and a shorter duration of action than regular human insulin. APIDRA should normally be used in regimens that include a longer-acting insulin or basal insulin analog. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

APIDRA may also be infused subcutaneously by external insulin infusion pumps. (See WARNINGS, PRECAUTIONS, Usage in Pumps, Information for Patients, Mixing of Insulins, DOSAGE AND ADMINISTRATION, RECOMMENDED STORAGE.)

CONTRAINDICATIONS
APIDRA is contraindicated during episodes of hypoglycemia and in patients hypersensitive to APIDRA or one of its excipients.

WARNINGS

APIDRA differs from regular human insulin by its rapid onset of action and shorter duration of action. When used as a meal time insulin, the dose of APIDRA should be given within 15 minutes before or immediately after a meal.

Because of the short duration of action of APIDRA, patients with diabetes also require a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analogs), or species (animal, human) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

Glucose monitoring is recommended for all patients with diabetes.

Hypoglycemia is the most common adverse effect of insulin therapy, including APIDRA. The timing of hypoglycemia may differ among various insulin formulations.

Insulin Pumps: When used in an external insulin pump for subcutaneous infusion, APIDRA should not be diluted or mixed with any other insulin. 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. Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time. 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. Interim therapy with subcutaneous injection may be required. (See PRECAUTIONS, Usage in Pumps, Information for Patients, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

PRECAUTIONS

General

As with all insulin preparations, the time course of APIDRA action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Hypoglycemia
As with all insulin preparations, hypoglycemic reactions may be associated with the administration of APIDRA. 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 long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. (See PRECAUTIONS, Drug Interactions.)
Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment
The requirements for APIDRA may be reduced in patients with renal impairment. (See CLINICAL PHARMACOLOGY, Special Populations.)

Hepatic Impairment
Studies have not been performed in patients with hepatic impairment. APIDRA requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations.)

Allergy
Local Allergy
As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. 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
Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reactions, may be life threatening.

In controlled clinical trials up to 12 months, 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 cresol as an injectable excipient.

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption.

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 incidences of hypoglycemia.

Usage in Pumps

APIDRA has been studied 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™)‡.

Based on *in vitro* studies which have shown loss of m-cresol, and insulin degradation, APIDRA should not be used beyond 48 hours at 98.6°F (37°C) in infusion sets and reservoirs. APIDRA in clinical use should not be exposed to temperatures greater than 98.6°F (37°C). **APIDRA should not be mixed with other insulins or with a diluent when used in the pump.** (See WARNINGS, PRECAUTIONS, Information for Patients, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

Information for Patients

For all patients

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management.

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, or 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.

For patients using pumps

Patients using external pump infusion therapy should be trained appropriately. APIDRA has been studied 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).

To minimize insulin degradation, infusion set occlusion, and loss of the preservative (m-cresol), the infusion sets (reservoir, tubing, and catheter) and the APIDRA in the reservoir should be replaced every 48 hours or less 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 and/or alter the absorption of APIDRA.

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time. 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 WARNINGS, PRECAUTIONS, Usage in Pumps, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

Drug Interactions
A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diazoxide, 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 antipsychotic medications (e.g., olanzepine and clozapine).

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Mixing of Insulins
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 some attenuation (27%) of the maximum concentration (C_{max}) after premixing, however the time to maximum concentration (T_{max}) was not affected.

If APIDRA is mixed with NPH human insulin, APIDRA should be drawn into the syringe first. Injection should be made immediately after mixing.

No data are available on mixing APIDRA with insulin preparations other than NPH. (See CLINICAL STUDIES.) APIDRA should not be mixed with insulin preparations other than NPH.

Mixtures should not be administered intravenously.

The effects of mixing APIDRA with diluents or other insulins when used in external subcutaneous infusion pumps for insulin have not been studied. Therefore, APIDRA should not be mixed in these instances.

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 IU/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 IU/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.

Pregnancy - Teratogenic Effects - Pregnancy Category C
Reproduction and teratology studies have been performed with insulin glulisine in rats and rabbits using regular human insulin as a comparator.
The drug was given to female rats throughout pregnancy at subcutaneous doses up to 10 IU/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison). Insulin glulisine did not have any remarkable toxic effects on the embryo-fetal development in rats.

The drug was given to female rabbits throughout pregnancy at subcutaneous doses up to 1.5 IU/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 IU/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 IU/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 IU/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 insulin glulisine 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 such patients.

Nursing Mothers
It is unknown whether insulin glulisine is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when APIDRA is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in APIDRA dose, meal plan, or both.

Pediatric Use
Safety and effectiveness of APIDRA in pediatric patients have not been established.

Geriatric Use
In Phase III clinical trials (n=2408), APIDRA was administered to 147 patients ≥65 years of age and 27 patients ≥75 years of age. The majority of these were patients with type 2 diabetes. The change in A1C values and hypoglycemia frequencies did not differ by age, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
Overall, clinical studies comparing APIDRA with short-acting insulins did not demonstrate a difference in frequency of adverse events.

Adverse events commonly associated with human insulin therapy include the following:

Body as a whole: allergic reactions. (See PRECAUTIONS.)

Skin and appendages: injection site reaction, lipodystrophy, pruritus, rash. (See PRECAUTIONS.)

Other: hypoglycemia. (See WARNINGS and PRECAUTIONS.)

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).

Table 4: Severe Symptomatic Hypoglycemia

	Type 1 Diabetes Mellitus – Adult 12 weeks in combination with Lantus®*			Type 1 Diabetes Mellitus – Adult 26 weeks in combination with Lantus®**		Type 2 Diabetes Mellitus – Adult 26 weeks in combination with NPH human insulin**	
	Apidra Pre-meal	Apidra Post-meal	Regular Human Insulin	APIDRA	Insulin Lispro	APIDRA	Regular Human Insulin
Severe symptomatic Hypoglycemia (events/month/patient)	0.05	0.05	0.13	0.02	0.02	0.00	0.00
Severe symptomatic hypoglycemia Percent of patients (n/total N)	8.4% (24/286)	8.4% (25/296)	10.1% (28/278)	4.8% (16/335)	4.0% (13/326)	1.4% (6/416)	1.2% (5/420)

*Entire treatment phase (3 months) has been included.
**Last three months of treatment have been considered.

Continuous Subcutaneous Insulin Infusion (CSII) (Type 1 Diabetes): The rates of catheter occlusions and infusion site reactions were similar for APIDRA and insulin aspart (see Table 5).

Table 5: Catheter Occlusions and Infusion Site Reactions.

	Apidra	Insulin aspart
Catheter occlusions/month	0.08	0.15
Infusion site reactions	10.3% (3/29)	13.3% (4/30)

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both.
Mild/Moderate episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed.
Severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/ subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

APIDRA is a recombinant insulin analog that has been shown to be equipotent to human insulin. One unit of APIDRA has the same glucose-lowering effect as one unit of regular human insulin. After subcutaneous administration, it has a more rapid onset and shorter duration of action.

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

APIDRA is intended for subcutaneous administration and for use by external infusion pump.

The dosage of APIDRA should be individualized and determined based on the physician's advice in accordance with the needs of the patient. APIDRA should normally be used in regimens that include a longer-acting insulin or basal insulin analog.

APIDRA should be administered by subcutaneous injection in the abdominal wall, the thigh or the deltoid or by continuous subcutaneous infusion in the abdominal wall. As with all insulins, injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next.

As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables. Blood glucose monitoring is recommended for all patients with diabetes.

Preparation and Handling
Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. APIDRA must only be used if the solution is clear and colorless with no particles visible.

When it is used in a pump, Apidra should not be mixed with other insulins or with a diluent.

HOW SUPPLIED
APIDRA 100 units per mL (U-100) is available in the following package size:
10 mL vials NDC 0088-2500-33

Storage:
Unopened Vial:
Unopened APIDRA vials 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 vial if frozen.
Open (In Use) Vial:
Opened vials, whether or not refrigerated, must be used within 28 days. They must be discarded if not 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).

	Not in-use (unopened) Refrigerated	**Not in-use (unopened) Room Temperature, below 77°F (25°C)**	**In-use (opened) Room Temperature, below 77°F (25°C)**
10 mL Vial	Until expiration date	28 days	28 days, refrigerated/room temperature

Infusion sets:
Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir should be discarded after no more than 48 hours of use or after exposure to temperatures that exceed 98.6°F (37°C).

Rx only
Rev. April 2004

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Frankfurt, Germany

Manufactured for:
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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 condition 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 are using without talking to your healthcare provider. Any change in insulin strength, manufacturer, type (regular, NPH, analog), or species (animal, human) may need a change in the dose. This dose change may be needed right away or later on 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 and contains 100 units of APIDRA. One milliliter (mL) of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

What is APIDRA?
APIDRA is a rapid-acting man-made insulin that is like insulin made by your body. APIDRA is used to treat adults with diabetes for the control of high blood sugar. 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.
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 the way you live, your diet, careful checking of your blood sugar levels, exercise, and planned physical activity, all work with your insulin to help you control your diabetes.

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 you are allergic to insulin glulisine or any of the inactive ingredients in APIDRA. See the end of this leaflet for a list of the inactive ingredients.

Before starting APIDRA, tell your healthcare provider
- **about all you medical problems including if you:**

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **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 during your pregnancy.
- **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.

How should I use APIDRA?
See the end of this leaflet for the "**Instructions for Use**" including the sections "**How do I draw the insulin into the syringe?**" and **How do I use APIDRA with an external subcutaneous insulin infusion pump?**"

- 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 the 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 the 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.**

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. They 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 professional about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

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

Hypoglycemia (low blood glucose):
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:

- **The wrong insulin dose.** 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.
- you are vomiting or have diarrhea that decreases the amount of sugar absorbed by your body.
- you drink 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 can be 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. Someone with hypoglycemia who cannot take foods or liquids with sugar by mouth 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 occurs 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:

- **The wrong insulin dose.** 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 medicine can be changed.

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

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:
- a rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- a 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:
- a 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.

Tell your healthcare provider if you have any side effects that bother you.

These are not all the side effects of APIDRA. Ask your healthcare provider or pharmacist for more information.

How should I store APIDRA?
- **Unopened vial:**
  Store new unopened APIDRA vials in the refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not freeze APIDRA. Keep APIDRA out of direct heat and light. If a vial freezes or overheats, throw it away.
- **Open (In Use) vial:**

Once a vial is opened, you can keep it in the refrigerator or as cool as possible (below 77°F [25°C]), but the opened vial 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). For example, do not leave it in a car on a summer day.

	Not in-use (unopened) Refrigerated	**Not in-use (unopened) Room Temperature below 77°F (25°C)**	**In-use (opened) Room temperature, below 77°F (25°C)**
10 mL Vial	Until expiration date	28 days	28 days, refrigerated/room temperature

- **Insulin pump infusion sets:** Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir should be thrown away:
  - after no more than 48 hours of use or
  - after exposure 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 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.

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 or pharmacist for information about APIDRA that is written for health professionals. For more information about APIDRA call 1-800-633-1610 or go to website www.aventis-us.com.

What are the ingredients in APIDRA?
Active Ingredient: insulin glulisine
Inactive Ingredients: m-cresol, trometamoline, sodium chloride, polysorbate 20, and water for injection.

Instructions for Use

How do I draw the insulin into the syringe?
- **The syringe must be new and 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 it after the expiration date or if it is cloudy or if you see particles.
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 take a dose. 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. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.
7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
8. 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.
9. 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 professional on how to mix.
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject APIDRA?
Inject APIDRA under your skin. Take APIDRA as prescribed by your healthcare provider.

You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, do not use it. Contact your healthcare provider. Use a new vial.

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 skin where you are going to inject. 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 syringe. 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™)‡. Refer to 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 dose of insulin. Hypoglycemia, hyperglycemia or ketosis can happen. Problems should be identified and corrected as quickly as possible, see instruction manual for your pump. Because APIDRA starts working faster and does not work as long, you may have less time to identify and correct the problem than with regular insulin.

- 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.

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, **DIABETES 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 professional or diabetes educator or visit www.DiabetesWatch.com.

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Aventis Pharmaceuticals Inc.

Kansas City, MO 64137 USA
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Apidra™
insulin glulisine
(rDNA origin) injection
100 units/mL (U-100)

Apidra™ ℞ ONLY
insulin glulisine
(rDNA origin) injection

Each mL of APIDRA™ contains 100 IU (3.49mg) insulin glulisine, 3.15mg m-cresol, 6mg trometamine, 5mg sodium chloride, 0.01mg polysorbate 20, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide.

Dosage and Administration: See package insert for dosage information. As with any drug, if you are pregnant or nursing a baby, seek professional advice when using this product. Any change of insulin should be made cautiously and only under medical supervision.

WARNING: Keep out of reach of children.

Store refrigerated at 36–46°F (2–8°C). Do not freeze. Discard vial if frozen. Protect from light. Use within 28 days after opening.

Apidra™
insulin glulisine
(rDNA origin)
injection
100 units/mL
(U-100)
One 10mL Vial

150581 A

U.S Patent 6,221,633

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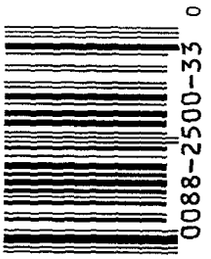

NDC 0088-2500-33

Apidra™
insulin glulisine
(rDNA origin)
injection
100 units/mL
(U-100)

FOR SUBCUTANEOUS USE ONLY

USE ONLY IF SOLUTION IS CLEAR AND COLORLESS WITH NO PARTICLES VISIBLE

One 10mL Vial

Aventis

NDC 0088-2500-33

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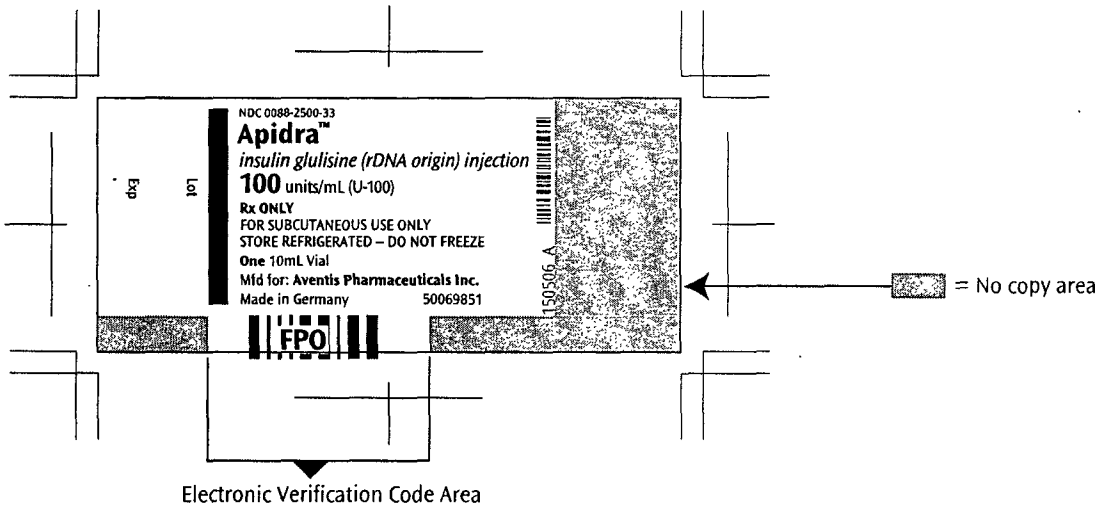
One 10mL Vial

Aventis


NDC 0088-2500-33
Apidra™
insulin glulisine (rDNA origin) injection
100 units/mL (U-100)
Rx ONLY
FOR SUBCUTANEOUS USE ONLY
STORE REFRIGERATED – DO NOT FREEZE
One 10mL Vial
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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 condition 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 are using without talking to your healthcare provider. Any change in insulin strength, manufacturer, type (regular, NPH, analog), or species (animal, human) may need a change in the dose. This dose change may be needed right away or later on 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 and contains 100 units of APIDRA. One milliliter (mL) of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

What is APIDRA?
APIDRA is a rapid-acting man-made insulin that is like insulin made by your body. APIDRA is used to treat adults with diabetes for the control of high blood sugar. 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.
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 the way you live, your diet, careful checking of your blood sugar levels, exercise, and planned physical activity, all work with your insulin to help you control your diabetes.

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 you are allergic to insulin glulisine or any of the inactive ingredients in APIDRA. See the end of this leaflet for a list of the inactive ingredients.

Before starting APIDRA, tell your healthcare provider
- **about all you medical problems including if you:**

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **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 during your pregnancy.
- **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.

How should I use APIDRA?
See the end of this leaflet for the **"Instructions for Use"** including the sections **"How do I draw the insulin into the syringe?"** and **How do I use APIDRA with an external subcutaneous insulin infusion pump?"**

- 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 the 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 the 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.**

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. They 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 professional about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

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

Hypoglycemia (low blood glucose):
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:

- **The wrong insulin dose.** 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.
- you are vomiting or have diarrhea that decreases the amount of sugar absorbed by your body.
- you drink 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 can be 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. Someone with hypoglycemia who cannot take foods or liquids with sugar by mouth 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 occurs 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:

- **The wrong insulin dose.** 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 medicine can be changed.

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

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:
- a rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- a 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:
- a 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.

Tell your healthcare provider if you have any side effects that bother you.

These are not all the side effects of APIDRA. Ask your healthcare provider or pharmacist for more information.

How should I store APIDRA?
- **Unopened vial:**
  Store new unopened APIDRA vials in the refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not freeze APIDRA. Keep APIDRA out of direct heat and light. If a vial freezes or overheats, throw it away.
- **Open (In Use) vial**:

Once a vial is opened, you can keep it in the refrigerator or as cool as possible (below 77°F [25°C]), but the opened vial 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). For example, do not leave it in a car on a summer day.

	Not in-use (unopened) Refrigerated	**Not in-use (unopened) Room Temperature below 77°F (25°C)**	**In-use (opened) Room temperature, below 77°F (25°C)**
10 mL Vial	Until expiration date	28 days	28 days, refrigerated/room temperature

- **Insulin pump infusion sets:** Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir should be thrown away:
  - after no more than 48 hours of use or
  - after exposure 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 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.

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 or pharmacist for information about APIDRA that is written for health professionals. For more information about APIDRA call 1-800-633-1610 or go to website www.aventis-us.com.

What are the ingredients in APIDRA?
Active Ingredient: insulin glulisine
Inactive Ingredients: m-cresol, trometamoline, sodium chloride, polysorbate 20, and water for injection.

Instructions for Use

How do I draw the insulin into the syringe?
- **The syringe must be new and 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 it after the expiration date or if it is cloudy or if you see particles.
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 take a dose. 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. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.
7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
8. 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.
9. 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 professional on how to mix.
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject APIDRA?
Inject APIDRA under your skin. Take APIDRA as prescribed by your healthcare provider.

You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, do not use it. Contact your healthcare provider. Use a new vial.

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 skin where you are going to inject. 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 syringe. 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™)‡. Refer to 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 dose of insulin. Hypoglycemia, hyperglycemia or ketosis can happen. Problems should be identified and corrected as quickly as possible, see instruction manual for your pump. Because APIDRA starts working faster and does not work as long, you may have less time to identify and correct the problem than with regular insulin.

- 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.

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, **DIABETES 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 professional or diabetes educator or visit www.DiabetesWatch.com.

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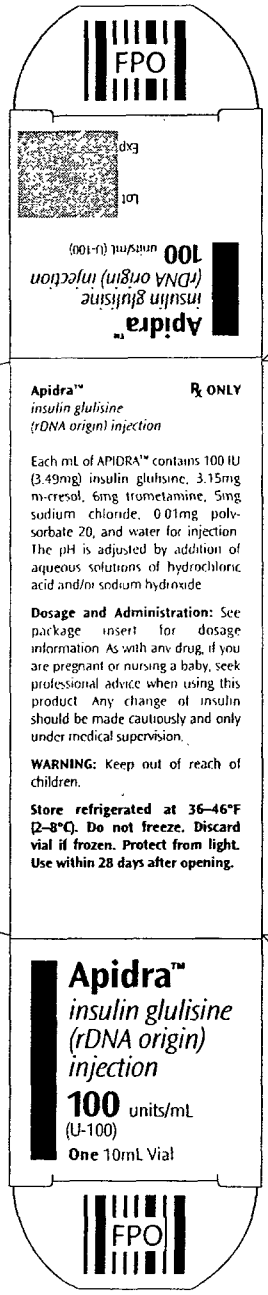
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insulin glulisine
(rDNA origin) injection
100 units/mL (U-100)
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Apidra™ ℞ ONLY
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(rDNA origin) injection
Each mL of APIDRA™ contains 100 IU (3.49mg) insulin glulisine, 3.15mg m-cresol, 6mg trometamine, 5mg sodium chloride, 0.01mg polysorbate 20, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide.
Dosage and Administration: See package insert for dosage information. As with any drug, if you are pregnant or nursing a baby, seek professional advice when using this product. Any change of insulin should be made cautiously and only under medical supervision.
WARNING: Keep out of reach of children.
Store refrigerated at 36–46°F (2–8°C). Do not freeze. Discard vial if frozen. Protect from light. Use within 28 days after opening.
Apidra™
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U.S. Patent 6,221,633
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D-65926 Frankfurt am Main
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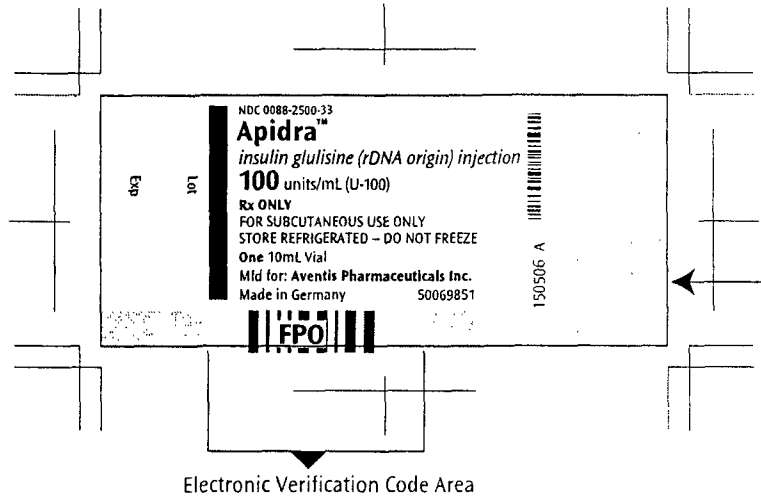

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Electronic Verification Code Area

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Robert Meyer
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