PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

APIDRA®

insulin glulisine injection (rDNA origin)

Solution for injection 100 U/mL

ATC code: A10AB

Antidiabetic Agent

Short-acting Recombinant Human Insulin Analogue

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION 4.4 Administration	05/2021
7 WARNING AND PRECAUTIONS	05/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APIDRA [insulin glulisine injection (rDNA origin)] is a recombinant human insulin analogue indicated for:

- the treatment of adult patients with diabetes mellitus where treatment with insulin is required.
- the treatment of pediatric patients with type 1 diabetes mellitus who require a short acting insulin. There is insufficient clinical data on the use of APIDRA in children below the age of 6 years (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

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 analogue to maintain adequate glucose control (see 4 DOSAGE AND ADMINISTRATION). APIDRA can be used with oral hypoglycemic agents.

1.1 Pediatrics

Pediatrics (<6 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APIDRA in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS).

APIDRA has not been studied in pediatric patients younger than 4 years of age. There is insufficient clinical data on the use of APIDRA in children below the age of 6 years.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

APIDRA (insulin glulisine injection) is contraindicated during episodes of hypoglycemia (see 5 OVERDOSAGE) and in patients sensitive to insulin glulisine or any of the excipients they contain, including any non-medicinal ingredient or component of the container (for a complete list of excipients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin therapy, including APIDRA (7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision.
- 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 within 20 minutes after starting a meal (see 10 CLINICAL PHARMACOLOGY).
- APIDRA given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin. APIDRA can also be used alone in insulin infusion pump therapy to maintain adequate glucose control.
- APIDRA can be mixed with NPH human insulin (except when administered with pump (see 4 DOSAGE AND ADMINISTRATION, Continuous Subcutaneous Insulin Infusion pump)).
- This insulin product shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge (see 4 DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The dosage of APIDRA should be individualized and determined based on the physician's advice in accordance with the needs of the patient.

APIDRA (insulin glulisine injection [rDNA origin]) is a recombinant human insulin analogue 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 a shorter duration of action (see 10 CLINICAL PHARMACOLOGY).

APIDRA should be given by injection within 15 minutes before or within 20 minutes after starting a meal. APIDRA should normally be used in regimens that include a longer-acting insulin or basal insulin analogue (see 10 CLINICAL PHARMACOLOGY).

APIDRA is intended for subcutaneous administration by injection and for use as a continuous subcutaneous insulin infusion (CSII) in pump systems suitable for insulin infusion.

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.

4.4 Administration

Preparation and Handling:

APIDRA must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency. To minimize local irritation at the injection site, it is recommended to allow the insulin to reach room temperature before injection.

The instructions for using the APIDRA in a pump or with an injection pen must be followed carefully.

APIDRA should be administered by subcutaneous injection in the abdominal wall, the thigh, the buttock or the deltoid or by continuous subcutaneous infusion (CSII) in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh, buttock or deltoid) must be rotated from one injection to the next so that the same site is not used more than approximately once a month to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

Patient must be instructed to not re-use needles. INJECTION PENS, CARTRIDGES, NEEDLES, AND SYRINGES MUST NOT BE SHARED. To prevent the possible transmission of disease, never share an injection pen or cartridge between patients, even if the needle on the injection pen is changed.

An empty vial, cartridge, or SoloSTAR® must never be reused and must be properly discarded.

Vials

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of the dose.

Mixing of Insulins

APIDRA can be mixed with NPH human insulin (except when administered with pump (see 6 DOSAGE AND ADMINISTRATION, Continuous Subcutaneous Insulin Infusion pump)).

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 human insulin.

Mixtures should not be administered intravenously.

Cartridges or SoloSTAR

APIDRA cartridges or APIDRA SoloSTAR are not designed to allow any other insulin to be mixed in the cartridge.

Continuous Subcutaneous Insulin Infusion pump

APIDRA may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion. Patients using CSII must be comprehensively instructed on the use of the system pump.

The infusion set and reservoir used with APIDRA must be changed at least every 48 hours using aseptic technique. It is important that patients follow these instructions even if they differ from the general pump manual instructions. Failure to follow these instructions may lead to serious adverse events.

When used with an insulin infusion pump, APIDRA should not be mixed with any other insulin or diluted with any other solution.

Patients administering APIDRA by CSII must have an alternative insulin delivery system available in case of pump system failure (see 7 WARNINGS AND PRECAUTIONS, Insulin pumps).

5 OVERDOSAGE

Symptoms:

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy exposure or both.

Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Nocturnal hypoglycemia is common in people taking insulin and symptoms can include restlessness, making unusual noises, attempting to get out of bed or accidentally rolling out of bed, sleepwalking, nightmares and sweating. Patients may wake with a headache in the morning if their blood sugar was low during the night.

Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal. In some cases, the first sign of hypoglycemia may be confusion or loss of consciousness (hypoglycemia unawareness). Severe hypoglycemia, resulting in seizures, is more likely to occur at nighttime (nocturnal hypoglycemia) than during the day.

Management:

Mild/moderate episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in dosage of the medicinal product, meal patterns, or physical activity may be needed. It is therefore recommended that patients with diabetes carry sugar-containing products.

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution for injection 100 U/mL	hydrochloric acid, m-cresol, polysorbate 20, sodium chloride, sodium hydroxide (for pH adjustment), trometamol, ~~and~~ water for injection

The vials, cartridges, and SoloSTAR contain a sterile solution of insulin glulisine for use as an injection.

APIDRA [Insulin glulisine injection (rDNA origin)] consists of insulin glulisine dissolved in a clear aqueous solution.

Each milliliter of APIDRA contains insulin glulisine 100 units. APIDRA has a pH of approximately 7.3 and is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide.

APIDRA [insulin glulisine injection (rDNA origin)] 100 units per mL is available in the following package sizes:

- 10-mL vials
- 3-mL cartridges package of 5, for use with AllStar PRO and JuniorSTAR
- 3-mL APIDRA SoloSTAR (pre-filled disposable pen), package of 5

Pens to be used with APIDRA cartridge

The APIDRA cartridge should only be used with the following pens:

- JuniorSTAR® which delivers APIDRA in 0.5 unit dose increments
- AllStar PRO® which delivers APIDRA in 1 unit dose increments

This cartridge should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

Hypokalemia is among the potential clinical adverse effects associated with the use of all insulin therapies, particularly when given intravenously (e.g. treatment of diabetic ketoacidosis). This potential clinical adverse effect may be more relevant in patients who are on potassium lowering drugs, losing potassium through other means (e.g. diarrhea) or treated for diabetic ketoacidosis.

As with other insulins, additional caution should be exercised in patients with a long history of diabetes on insulin who might be prone to develop hypoglycemia and in patients with a previous history of cardiac ischemic disorders who might be prone to develop cardiac adverse events.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin

requirements. Additionally, drugs, losing potassium through other means (e.g. diarrhea) or treated for diabetic ketoacidosis.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of TZD with insulin is not indicated for the treatment of Type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph 7 WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including APIDRA, is contemplated.

To avoid transmission of disease, cartridge or a prefilled syringe/pen shoud not be used by more than one person.

Accidental mix-ups between insulin glulisine and other insulins, particularly long-acting insulins, have been reported. To avoid medication errors between insulin glulisine and other insulins, patients should be instructed to always check the insulin label before each injection (see 8 ADVERSE REACTIONS).

Driving and Operating Machinery

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

Endocrine and Metabolism

Hypoglycemia:
As with all insulin preparations, hypoglycemic reactions may be associated with the administration of APIDRA. Hypoglycemia is the most common adverse effect of insulin therapy, including APIDRA (see 8 ADVERSE REACTIONS). Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see 5 OVERDOSAGE). Use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). Early warning symptoms of hypoglycemia may be different, be less pronounced or absent, under certain conditions, as for example if glycemic control is markedly improved, if hypoglycemia is developing gradually, in elderly patients, in patients with a long history of diabetes, in patients with diabetic nerve disease, in patients using some medications such as beta-blockers, or intensified diabetes control (see 9 DRUG INTERACTIONS). Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an intramuscular/subcutaneous injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when treatment regimen is changed.

As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma or death (see 8 ADVERSE REACTIONS).

Hypoglycemic reactions following treatment with insulin products such as APIDRA are mostly mild and

easily managed. Changes in insulin therapy or changes in lifestyle (i.e. diet, omission of a meal, exercise/ physical activity) may require a change in dosage to avoid hypoglycemia. Glucose monitoring is recommended for all patients with diabetes.

Diabetic patients should be instructed to carry a few lumps of sugar, candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur (see PATIENT MEDICATION INFORMATION).

Hyperglycemia:
The use of too low insulin dosages or discontinuation of treatment, especially in Type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Uncorrected hyperglycemic reactions can cause loss of consciousness, coma, or death.

Other

The presence of diseases such as Acromegaly, Cushing's Syndrome, Hyperthyroidism, and Pheochromocytoma can complicate the control of Diabetes Mellitus.

Hepatic/Biliary/Pancreatic/Renal

The pharmacokinetic properties of APIDRA were generally maintained in subjects with renal impairment. Studies have not been performed in patients with hepatic impairment. As with all insulins, APIDRA requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions). Careful glucose monitoring and dose adjustments of insulin or insulin analogues including APIDRA may be necessary in patients with hepatic or renal dysfunction.

Immune

Injection Site and Local Allergic Reactions:
Injection site reactions that may occur with insulin therapy include redness, pain, itching at the injection site, hives, swelling, and inflammation. Most minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions.

Lipodystrophy and Cutaneous Amyloidosis:

Subcutaneous (SC) administration of insulin products can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) or localized cutaneous amyloidosis (skin lumps).

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered (see 8 ADVERSE REACTIONS).

Systemic allergic reactions:
Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glulisine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm,

hypotension, anaphylactic reaction or shock and may be life threatening (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Patients who have demonstrated an allergic reaction to other insulin products may demonstrate an allergic reaction to APIDRA.

Antibody Production:
Insulin administration may cause insulin antibodies to form. Insulin antibodies are frequently cross-reactive. In clinical studies, cross-reactive antibodies were observed in both insulin glulisine and comparator (insulin lispro, regular human insulin) treatment groups with similar percents of increased and decreased titers. There was no correlation between cross-reactive insulin antibody concentration and changes in A1c, insulin doses, or incidence of hypoglycemia and the clinical significance of these antibodies is not clear. In theory, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycemia or hypoglycemia but has not been found on review of APIDRA clinical trials.

Intercurrent conditions:
Insulin requirements may be altered during illness, emotional disturbances or stress.

Insulin pumps
Patients using external pump infusion therapy should be trained appropriately. Physicians and patients should carefully evaluate information on pump use in the APIDRA product monograph, package insert, and the pump manufacturer's manual (see 4 DOSAGE AND ADMINISTRATION, Continuous Subcutaneous Insulin Infusion Pump).

When used in an external insulin pump for subcutaneous infusion, APIDRA should not be mixed with any other insulin or diluted with any other solution. The infusion set and reservoir used with APIDRA must be changed at least every 48 hours using aseptic technique. It is important that patients follow these instructions even if they differ from the general pump manual instructions. Failure to follow the instruction above, pump or infusion set malfunctions, handling errors or insulin degradation can lead to hyperglycemia, ketosis and diabetic ketoacidosis in a short time. This is especially pertinent for rapid-acting insulin analogues that are more rapidly absorbed and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis or diabetic ketoacidosis is necessary. Interim subcutaneous injection with APIDRA may be required. Patients using continuous subcutaneous insulin infusion (CSII) pump therapy must be trained to administer insulin by injection and have alternate insulin delivery system available in case of pump failure (see 4 DOSAGE AND ADMINISTRATION, Continuous Subcutaneous Insulin Infusion Pump, PATIENT MEDICATION INFORMATION - APIDRA® VIALS, Vials, Continuous Subcutaneous Insulin Infusion Pump, 11 STORAGE, STABILITY AND DISPOSAL).

Transferring Patients from Other Insulins

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

7.1 Special Populations

7.1.1 Pregnant Women

There are no well-controlled clinical studies of the use of APIDRA in pregnant women. Animal reproduction studies have not revealed any differences between APIDRA and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see 16 No microbiological information is required for this drug product.

NON-CLINICAL TOXICOLOGY, Reproduction toxicity).

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control before conception and during pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Careful monitoring of glucose control is essential. Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy.

7.1.2 Breast-feeding

It is unknown whether APIDRA is excreted in human milk. Many drugs including human insulin, are excreted in human milk. There are no adequate and well-controlled studies in nursing women. For this reason, caution should be exercised when APIDRA is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet (see 16 No microbiological information is required for this drug product.

NON-CLINICAL TOXICOLOGY, Reproduction toxicity).

7.1.3 Pediatrics

Pediatrics (below 6 years of age): The safety and effectiveness of APIDRA have been investigated in pediatric patients (age 4 to 17 years) with Type 1 diabetes [9(1.6%) below 6 years, 32 (5.6%) between 6 and 8 years, 149 (26%) between 8 and 12 years, and 382 (67%) above 12 years old]. APIDRA has not been studied in pediatric patients younger than 4 years of age. There is insufficient clinical data on the use of APIDRA in children below the age of 6 years.

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

7.1.4 Geriatrics

Hypoglycemia may be difficult to recognize in the elderly (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including APIDRA may be necessary (see 7 WARNINGS AND PRECAUTIONS, Renal/ Hepatic/ Biliary/ Pancreatic section).

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 glycated hemoglobin (A1c) values and hypoglycemia frequencies did not differ by age, but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

The adverse events observed were those known in this pharmacological class and consequently common to insulins.

Body as a whole – Allergic Reaction(s):

Local Allergy
As with other insulin therapy, local allergy in patient may occur as redness, itching, swelling, or hemorrhage. 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. Please see 7 WARNINGS AND PRECAUTIONS, Immune section.

Systemic Allergy
Less common, but potentially more serious, is generalized allergy to insulin (including insulin glulisine), 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.

Localized reactions and generalized myalgias have been reported with the use of m-cresol as an injectable excipient.

Hypoglycemia:

Hypoglycemia, a frequent adverse reaction to insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma or death.

The risk of all categories of symptomatic hypoglycemia did not differ between APIDRA and short-acting insulin comparators in subjects with type 1 or type 2 diabetes (see 7 WARNINGS AND PRECAUTIONS).

Table 2: Number of subjects with at least one episode of symptomatic hypoglycemia in studies in adults with Type 1 and Type 2 diabetes

	Type 1 diabetes				Type 2 diabetes			
	Glulisine		Comparator[a]		Glulisine		Comparator[b]	
	n/N	%	n/N	%	n/N	%	n/N	%
Subcutaneous injection	783/921	85.0	516/611	84.5	562/883	63.6	578/883	65.5
Continuous[c] subcutaneous infusion	26/29	89.7	24/30	80.0	-	-	-	-

n = number of subjects with at least 1 episode of hypoglycemia; N = total number of evaluable ITT subjects.
[a]: insulin lispro, regular human insulin; [b]: regular human insulin; [c]: insulin aspart

Table 3: Number (percentage) of pediatric subjects with Type 1 diabetes with all symptomatic hypoglycemia

	Glulisine			Lispro		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
Screening / run-in phase	198/277	(71.5)	1269	213/295	(72.2)	1144
Month 1	195/277	(70.4)	1212	184/295	(62.4)	973
Month 2	125/274	(45.6)	781	125/295	(42.4)	756
Month 3	158/270	(58.5)	864	168/292	(57.5)	870
Month 4 - treatment end	199/268	(74.3)	2686	199/291	(68.4)	2747
Entire treatment phase	230/277	(83.0)	5543	238/295	(80.7)	5346

n = number of subjects reporting at least one episode of symptomatic hypoglycemia; N = number of randomized and treated subjects evaluable.

In pediatric subjects with type 1 diabetes, the overall incidence of symptomatic hypoglycaemia was comparable between the treatment groups (83% for insulin glulisine vs. 81% for insulin lispro). However, there was a significant difference between treatment groups during the first month of treatment in the frequency (70.4% in the insulin glulisine group, 62.4% in the insulin lispro group, p=0.0330) and in the monthly rate (4.77 vs. 3.59 respectively, p=0.0094) of symptomatic hypoglycemia. For nocturnal symptomatic hypoglycemia, a difference was noted between the two treatment groups in the frequency and monthly rate per subject, with a higher frequency (39.7% vs. 30.5%) and more events (0.25 vs. 0.19) reported in the insulin glulisine group. The difference was especially notable in the first month of treatment (frequency (19.9% vs. 11.2%) and events (0.41 vs. 0.23)), when all subjects had been randomized following a 4-week of run-in period with individualized dose adjustment of insulin lispro. The incidence of severe symptomatic hypoglycemia and the incidence of severe nocturnal symptomatic hypoglycemia were comparable between the treatment groups.

Skin and subcutaneous tissue disorders:

As with other insulin therapy, lipodystrophy (including lipohypertrophy, and lipoatrophy) may occur at the injection site and delay insulin absorption.

Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions.

Weight gain:

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 4: Common (≥1%) Adverse Drug Reactions in pooled adult Type 1 and 2 studies

Adverse Event System Organ Class/ Preferred Term	Insulin Glulisine (All studies) n=1833 (% of subjects)	Lispro n= 333 (% of subjects)	Regular Insulin n=1161 (% of subjects)	Aspart n= 30 (% of subjects)
General Disorders and Administration Site Condition				
Injection site hypertrophy	9 (0.5)	7 (2.1)	- (-)	- (-)
Metabolism and Nutrition Disorders				
Hypoglycemia NOS*	83 (4.5)	22 (6.6)	33 (2.8)	2 (6.7)
Hypoglycemic seizure	16 (0.9)	7 (2.1)	9 (0.8)	- (-)
Hypoglycemic unawareness	1 (0.1)	4 (1.2)	- (-)	2 (6.7)
Nervous System Disorders				
Hypoglycemic coma	49 (2.7)	13 (3.9)	19 (1.6)	- (-)

*Not otherwise specified

During clinical studies, there were no clinically noteworthy differences between insulin glulisine and comparator short-acting insulins in the overall incidences of adverse events. The adverse events observed were those known in this pharmacological class and consequently common to insulins.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Table 5 summarizes the adverse reactions occurring with frequency higher than 1% in a clinical study in children and adolescents with type 1 diabetes treated with insulin glulisine (n=277) or insulin lispro.

Table 5: Common (≥1%) Adverse Drug Reactions in children and adolescents with Type 1 diabetes

Adverse Event System Organ Class/ Preferred Term	Insulin Glulisine n=277 (% of subjects)	Lispro n= 295 (% of subjects)
General Disorders and Administration Site Condition		
Injection site hypertrophy	3 (1.1)	1 (0.3)
Metabolism and Nutrition Disorders		
Hypoglycemia NOS*	6 (2.2)	7 (2.4)
Hypoglycemic seizure	17 (6.1)	14 (4.7)
Nervous System Disorders		
Hypoglycemic coma	1 (0.4)	3 (1.0)

*Not otherwise specified

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

Gastrointestinal disorders: nausea

General disorders administration site conditions: fatigue, injection site reaction NOS*, peripheral oedema, asthenia, increased fat tissue, injection site stinging

Infections and infestations: cellulitis

Injury, poisoning and procedural (complications): overdose NOS*

Metabolism and nutrition disorders: hyperglycemia NOS*

Nervous system disorders: paraesthesia

Skin and subcutaneous tissue disorders: acquired lipodystrophy

*Not otherwise specified

8.5 Post-Market Adverse Reactions

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

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Patients should be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using APIDRA to obtain optimal glycemic control

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

The following are examples of potential drug-drug interactions that may occur with APIDRA treatment:

Table 6: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Oral antidiabetic agents ACE inhibitors Disopyramide Fibrates Fluoxetine MAO inhibitors Pentoxifylline Propoxyphene Salicylates Sulfonamide antibiotics	Theoretical	May enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycemia	May require close monitoring of blood glucose level and dose adjustment (reduction) of APIDRA
Corticosteroids Danazol Diazoxide Diuretics Glucagon Isoniazid Estrogens and progestogens (e.g. in oral contraceptives) Phenothiazine derivatives Somatropin Sympathomimetic agents (e.g. epinephrine, salbutamol, terbutaline) Protease inhibitors Atypical antipsychotic medications (e.g. olanzapine and clozapine)	Theoretical	May reduce the blood-glucose-lowering effect.	May require close monitoring of blood glucose level and dose adjustment (increase or decrease) of APIDRA
Somatostatin analogs Thyroid hormones	Theoretical	May enhance or decrease the insulin requirements	May require close monitoring of blood glucose level and dose adjustment (increase or decrease) of APIDRA
Alcohol Beta-blockers Clonidine Lithium salts	Theoretical	May either potentiate or weaken the blood-glucose-lowering effect of insulin	May require close monitoring of blood glucose level and dose adjustment (increase or decrease) of APIDRA
Pentamidine	Theoretical	May cause hypoglycemia, which may sometimes be followed by hyperglycemia	May require close monitoring of blood glucose level and dose adjustment (increase or decrease) of APIDRA
Sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine	Theoretical	The signs of hypoglycemia may be reduced or absent	May require close monitoring of blood glucose level and dosage adjustment (increase or decrease) of APIDRA

Other: To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herb have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The primary activity of insulins and insulin analogues, 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.

10.2 Pharmacodynamics

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. APIDRA has a rapid onset of action and a short duration of about 4 hours. This has been demonstrated in studies in healthy volunteers and patients with diabetes.

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 U/kg (see Figure 1).

Figure 1: Glucose-lowering effect over 6 hours.

APIDRA given 2 minutes (glulisine-pre) before the start of a meal compared to regular human insulin given 30 minutes (Regular - 30 min) before start of the meal (Figure 1A) and compared to regular human insulin (Regular - pre) given 2 minutes before a meal (Figure 1B). APIDRA given 15 minutes (glulisine-post) after start of a meal compared to regular human insulin (Regular - pre) given 2 minutes before a meal (Figure 1C). On the x-axis zero (0) is the start of a 15-minute meal.

Figure 1A

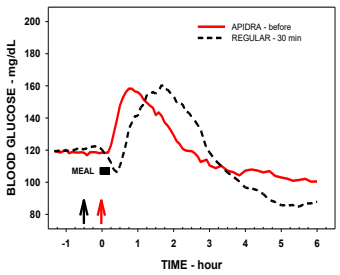


Figure 1B

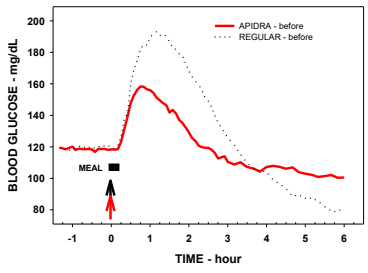
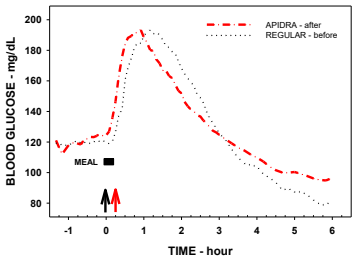


Figure 1C



Legend:

↑ = Injection time Regular Human Insulin
↑ = Injection time Apidra

10.3 Pharmacokinetics

APIDRA exhibits dose-proportionality in insulin exposure and less than dose-proportional increases in effect, as common to short and rapid acting insulins.

Table 7: Pharmacokinetic and Pharmacodynamic Results in Type 1 Diabetes Mellitus subjects treated with s.c insulin glulisine

Pharmacokinetic Parameters			
Dose	0.075 U/kg	0.15 U/kg	0.3 U/kg
AUC_{0-2h} ($\mu U.min.mL^{-1}$)	**3792** 3855 ± 677	**6676** 6832 ± 1461	**12992** 13237 ± 2599
AUC_{0-end} ($\mu U.min.mL^{-1}$)	**5341** 5372 ± 589	**11196** 11284 ± 1456	**24891** 25076 ± 3209
C_{max} ($\mu U.mL^{-1}$)	**42** 43 ± 9	**72** 73 ± 16	**140** 142 ± 25
MRT (min)	**115** 122 ± 50	**121** 125 ± 34	**134** 136 ± 28
T_{max} Min (*)	47 34 - 99	57 44 - 93	72 50 - 112
$T_{10\%-AUC}$ Min (*)	26 18 – 53	31 24 - 52	39 28 - 64
$T_{90\%-AUC}$ Min (*)	149 116 – 260	205 141 - 295	242 169 - 345
$T_{1/2}$ (min)	64 ± 33	55 ± 17	56 ± 17
Volume of Distribution (mL/kg)	1075 ± 362	986 ± 274	930 ± 216
Glucose Infusion Rate – Pharmacodynamic Parameters			
GIR-AUC (0-2h) (mg/kg)	314 ± 156	491 ± 167	536 ± 153
GIR-AUC (0-end) (mg/kg)	499 ± 233	1090 ± 271	1476 ± 300

Values in bold font represent the geometric means, all others are based on the mean & standard deviation, unless denoted with (*) to indicate the median, minimum & maximum range.

The table below compares pharmacokinetic and pharmacodynamic parameters for APIDRA (s.c.) from a study in patients with Type I diabetes (n=18) with historical data for Huminsulin® Normal 100 (s.c.) from a study in healthy adult subjects (n = 24; see Table 8).

Table 8: Pharmacokinetic and Pharmacodynamic Results for s.c Apidra® and Huminsulin® Normal 100

	APIDRA (N=18)[2]	**Huminsulin Normal 100**[1] (N=24)[3]
Dose	0.3 U/kg	0.3 IU/kg
Pharmacokinetic Parameters		
$AUC_{0\text{-end}}$ (µU.min.mL-1)	25076 ± 3209	17417 ± 2348
C_{max} (µU.mL-1)	142 ± 25	56 ± 16
MRT (min)	136 ± 28	229 ± 41
T_{max} Min (*)	72 50 – 112	120 60 - 240
$T_{10\%\text{- AUC}}$ Min (*)	39 28 – 64	58 45 - 81
$T_{90\%\text{- AUC}}$ Min (*)	242 169 – 345	448 321-590
$T_{1/2}$ (min)	56 ± 17	64 ± 28[4]
Volume of Distribution (mL/kg)	930 ± 216	2375 ± 963
Glucose Infusion Rate – Pharmacodynamic Parameter		
GIR-AUC (0-end) (mg/kg)	1476 ± 300	3032 ± 743

Values represent mean and standard deviation, unless denoted with (*) to indicate the median, minimum & maximum range.

[1] Historical data and different radioimmunoassay from Apidra study

[2] Type 1 Diabetes patients

[3] Healthy adult subjects.

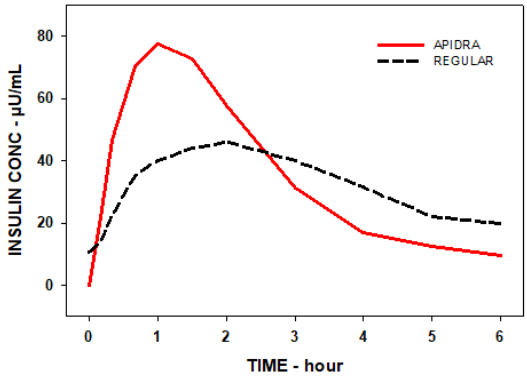
[4] N=23

Absorption

Pharmacokinetic profiles in healthy volunteers and diabetes patients (Type 1 or 2) demonstrated that absorption of insulin glulisine was up to twice as fast with a peak concentration approximately up to twice as high compared to regular human insulin.

In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 U/kg, the median time to maximum concentration (Tmax) was 55 minutes (range 34 to 91 minutes) and the peak concentration (Cmax) was 82 µU/mL (range 42 to 134 µU/mL) for insulin glulisine compared to a median Tmax of 82 minutes (range 52 to 308 minutes) and a Cmax of 46 µIU/mL (range 32 to 70µIU/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 2).

Figure 2 : Pharmacokinetic profile of insulin glulisine and regular human insulin in patients with Type 1 diabetes after a dose of 0.15 U/kg.



When APIDRA was injected subcutaneously into different areas of the body, the time-concentration profiles were similar with a slightly faster absorption when administered in the abdomen compared to the deltoid or thigh (see 4 DOSAGE AND ADMINISTRATION.) The absolute bioavailability of insulin glulisine after subcutaneous administration is about 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%). The T_{max} for the abdomen was 44 min (range 27-69 min); 58 min for the deltoid (range 30-85 min), and 66 min for the thigh (range 35-108 min).

Distribution & Elimination

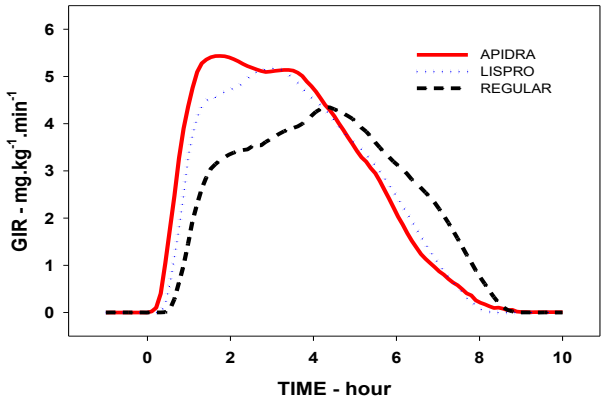
The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration are similar with volumes of distribution of 13 L and 21 L and half lives of 13 and 17 minutes, respectively. After subcutaneous administration, insulin glulisine is eliminated more rapidly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

Special Populations and Conditions

- **Pediatrics** The pharmacokinetic and pharmacodynamic properties of insulin glulisine and regular human insulin were assessed in a study conducted in pediatric patients with Type 1 diabetes (children [7 – 11 years, n = 10] and adolescents [12 – 16 years, n = 10]). The relative differences in pharmacokinetics and pharmacodynamics between insulin glulisine 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.
- **Sex** Information on the effect of sex on the pharmacokinetics of insulin glulisine is not available. However, in Phase III clinical trials in adults (n=2408), subgroup analyses based on sex did not show differences in safety and efficacy between insulin glulisine and other short-acting insulin formulations.
- **Pregnancy and Breast-feeding** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glulisine has not been studied. It is unknown whether APIDRA is excreted in human milk.
- **Race** Information on the effect of race on the pharmacokinetics of insulin glulisine is not available.
- **Hepatic Insufficiency** The effect of hepatic impairment on the pharmacokinetics of insulin glulisine has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure (see 7 WARNINGS AND PRECAUTIONS).

- **Renal Insufficiency** 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 (CrCl>80mL/min; 30-50mL/min; <30mL/min), the pharmacokinetic properties of insulin glulisine were generally maintained (see 7 WARNINGS AND PRECAUTIONS).
- **Obesity** The more rapid onset of action and shorter duration of activity of insulin glulisine and insulin lispro compared to regular human insulin were maintained in an obese non-diabetic population (n=18). The rapid onset of action was better maintained with insulin glulisine than with insulin lispro (see Figure 3).

Figure 3: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 U/kg of APIDRA (glulisine), insulin lispro or regular human insulin in an obese population.



11 STORAGE, STABILITY AND DISPOSAL

Vials

Unopened Vial:
Unopened APIDRA vials should be stored in a refrigerator, between 2°C to 8°C. Keep APIDRA away from direct heat and light. APIDRA should not be stored in the freezer and should not be allowed to freeze. If APIDRA freezes or overheats, discard it.

Opened (In Use) Vial: The opened vial can be kept refrigerated or unrefrigerated (15 to 25°C) for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C. Opened APIDRA vials, whether or not refrigerated, must be discarded after 28 days even if they contain insulin. Opened APIDRA vials should not be stored in the freezer and should not be allowed to freeze. If a vial freezes or overheats, discard it.

Cartridges

Unopened Cartridge:
Unopened APIDRA cartridges should be stored in a refrigerator, between 2°C to 8°C. Keep APIDRA away from direct heat and light. APIDRA should not be stored in the freezer and should not be allowed to freeze. If APIDRA freezes or overheats, discard it.

Opened (In Use) Cartridge:
The opened cartridge in use must be kept unrefrigerated (15 to 25°C) for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C. If the cartridge overheats or if there is any remaining insulin after 28 days, discard it. The opened cartridge in use must never be removed from and reinserted into the injection pen.

SoloSTAR

Unopened SoloSTAR:
Unopened APIDRA SoloSTAR should be stored in a refrigerator, between 2°C to 8°C. Keep APIDRA away from direct heat and light. APIDRA should not be stored in the freezer and should not be allowed to freeze. If APIDRA freezes or overheats, discard it.

Opened (In Use) SoloSTAR:
Opened APIDRA SoloSTAR in use must be kept unrefrigerated (15 to 25°C) for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C. If the APIDRA SoloSTAR overheats or if there is any remaining insulin after 28 days, discard it.

Opened APIDRA SoloSTAR should not be stored in the freezer and should not be allowed to freeze. If APIDRA SoloSTAR freezes discard it.

As with all medications and devices, keep out of reach of children.

Infusion sets:
Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir must be discarded after no more than 2 days of use or after exposure to temperatures that exceed 37°C.

12 SPECIAL HANDLING INSTRUCTIONS

See PATIENT MEDICATION INFORMATION and refer patients to the APIDRA Information for the Patient circular for APIDRA VIAL, APIDRA CARTRIDGE, and APIDRA SoloSTAR for additional information. Refer patients to the "Instructions for Use" for AllStar PRO and JuniorSTAR or to the User Manual for APIDRA SoloSTAR for additional information on use of the pens.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

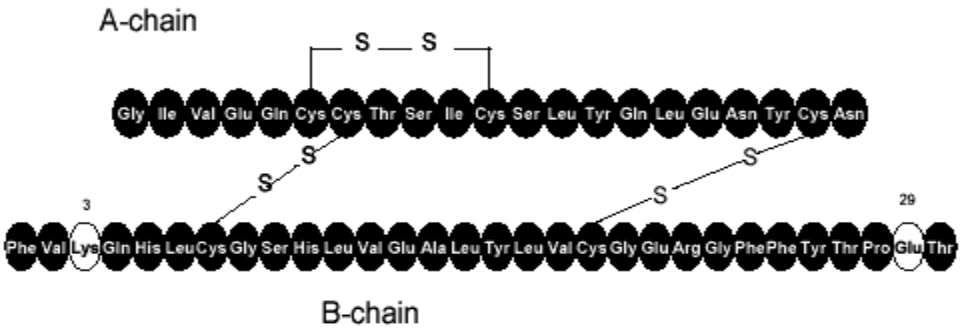
Drug Substance

Proper name: insulin glulisine (rDNA origin)

Chemical name: 3^{B}-lysine-29^{B} -glutamic acid-human insulin

Molecular formula and molecular mass: $C_{258}H_{384}N_{64}O_{78}S_6$ & 5823

Structural formula:



14 CLINICAL TRIALS

14.1 Efficacy and safety studies

Trial Design and Study Demographics

The safety and efficacy of APIDRA (insulin glulisine) was studied in adult patients with Type 1 and Type 2 diabetes (n = 2408) and in children and adolescent patients (4 to 17 years) with type 1 diabetes (n=572). The primary efficacy parameter was glycemic control, as measured by glycated hemoglobin (A1c).

Type 1 Diabetes:

A 26-week, randomized, open-label, active-control study (n = 672) was conducted in patients with Type 1 diabetes to assess the safety and efficacy of APIDRA compared to insulin lispro when administered subcutaneously within 15 minutes before a meal. Insulin glargine (LANTUS®) was administered once daily in the evening as the basal insulin in both groups. Before start of the study there was a 4-week run-in period combining insulin lispro and insulin glargine followed by randomization. Glycemic control and the rates of hypoglycemia requiring intervention from a third party were comparable for the two treatment regimens. The number of daily insulin injections and the total daily doses of APIDRA and insulin lispro were similar. The decrease in A1c was observed in patients treated with APIDRA without an increase in the basal insulin dose (see **Error! Reference source not found.**).

Table 9: Type 1 Diabetes Mellitus–Adult

Treatment duration	**26 weeks**	
Treatment in combination with following basal insulin:	**LANTUS (insulin glargine)**	
	APIDRA	**Insulin lispro**
Number of subjects treated	**339**	**333**
A1c (%)		
Endstudy mean	7.46	7.45
Adjusted 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 (U/day)		
Endstudy mean	24.16	26.43
Adjusted mean change from baseline	0.12	1.82
Short-acting insulin dose (U/day)		
Endstudy mean	29.03	30.12
Adjusted mean change from baseline	-1.07	-0.81
Severe hypoglycemia*		
Number of subjects (%)	16/335 (4.8)	13/326(4.0)
Rate (events/month/patient)	0.02	0.02
Mean number of short-acting insulin injections per day	3.36	3.42

* Events requiring assistance from third party during the last 3 months of the study
CI = Confidence Interval

Type 1 Diabetes-Pediatric:

A 26-week phase III open-label, active controlled study (n=572) evaluated the efficacy and safety of APIDRA in children and adolescents with type I diabetes mellitus, in comparison with insulin lispro when administered subcutaneously within 15 minutes before a meal. LANTUS (insulin glargine) was administered once daily in the evening or NPH twice daily in the morning and in the evening as basal insulin. The study consisted of a 4-week run-in phase during which patients received NPH or insulin glargine combined with insulin lispro, followed by a 26-week treatment-phase comparing insulin glulisine and insulin lispro, given at least twice daily within 15 minutes prior to a meal in combination with NPH insulin administered twice daily or insulin glargine administered once daily in the evening. Most patients were Caucasian (91%). Fifty percent of the patients were male. The mean age was 12.5 years (range 4 to 17 years). Mean BMI was 20.6 kg/m^2. Glycemic control (see **Error! Reference source not found.**) was comparable for the two treatment regimens.

Table 10: Type 1 Diabetes Mellitus–Pediatric

Treatment duration	**26 weeks** (mITT)	
Treatment in combination with following basal insulin:	**NPH or LANTUS (insulin glargine)**	
	APIDRA	**Insulin lispro**
Number of subjects treated	**271**	**291**
A1c (%)		
Baseline mean	8.20	8.17
Endstudy mean	8.31	8.37
Adjusted mean change from baseline	0.10	0.16
APIDRA – Insulin lispro	-0.06	
95% CI for treatment difference	(-0.24; 0.12)	
Basal insulin dose (U/day)		
Baseline mean	27.20	26.55
Endstudy mean	28.44	28.86
Rapid-acting insulin dose (U/day)		
Baseline mean	24.26	24.34
Endstudy mean	25.48	26.97
Percentage of patients with an average number of rapid-acting insulin injections per day ≥ 3	77.0	80.3
Body Weight (kg)		
Baseline mean	51.5	50.8
Endstudy mean	53.6	53.0
Mean weight change from baseline	2.2	2.2

14.2 Study Results

Type 2 Diabetes:

A 26-week, randomized, open-label, active-control study (n = 876) was conducted in insulin-treated patients with Type 2 diabetes to assess the safety and efficacy of APIDRA given within 15 minutes before a meal compared to regular human insulin 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. The average body mass index (BMI) of patients 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. Changes from baseline to endpoint in A1c were –0.46 in the insulin glulisine group and –0.30 in the regular insulin group. The difference in adjusted means between the 2 treatments was –0.16 (95% C1 ranging from –0.26 to –0.05) with respective p value of 0.0029. At end of treatment period, postprandial blood glucose levels in the APIDRA group were lower than in the regular human insulin group. The rates of hypoglycemia, requiring intervention from a third party, were comparable for the two treatment regimens. No differences between APIDRA and regular human insulin groups were seen in the number of daily injections or basal or short-acting insulin doses (see **Error! Reference source not found.**).

Table 11: Type 2 Diabetes Mellitus–Adult

Treatment duration	**26 weeks**	
Treatment in combination with following basal insulin:	**NPH human insulin**	
	APIDRA	**Regular Human Insulin**
Number of subjects treated	**435**	**441**
A1c (%)		
Endstudy mean	7.11	7.22
Adjusted 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 (U/day)		
Endstudy mean	65.34	63.05
Adjusted mean change from baseline	5.73	6.03
Short-acting insulin dose (U/day)		
Endstudy mean	35.99	36.16
Adjusted mean change from baseline	3.69	5.00
Severe hypoglycemia*		
Number of subjects (%)	6/416 (1.4)	5/420 (1.2)
Rate (events/month/patient)	0.00	0.00
Mean number of short-acting insulin injections per day	2.27	2.24

*Events requiring assistance from third party during the last 3 months of the study
CI = Confidence Interval

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

A 12-week, randomized, open-label, active-control study (n = 860) 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 or immediately after completing a meal or 20 minutes after starting a meal and regular human insulin was administered subcutaneously 30 to 45 minutes prior to a meal. The comparisons performed in this study were pre-meal APIDRA compared to regular human insulin, post-meal APIDRA compared to regular human insulin, and post-meal APIDRA compared to pre-meal APIDRA. Insulin glargine was administered once daily at bedtime as the basal insulin in all groups. Before start of the study there was a 4-week run-in period, with regular human insulin and insulin glargine followed by randomization. Glycemic control and the rates of hypoglycemia requiring intervention from a third party were comparable for the treatment regimens. Significant reductions from baseline in A1c were observed in all three treatment regimens. No changes from baseline between the treatments were seen in the total daily number of insulin injections. An increase in daily short-acting insulin dose was seen with regular human insulin (see Table 12).

Table 12: Type 1 Diabetes Mellitus–Adult			
Treatment duration	**12 weeks**	**12 weeks**	**12 weeks**
Treatment in combination with following basal insulin:	**LANTUS (insulin glargine)**	**LANTUS (insulin glargine)**	**LANTUS (insulin glargine)**
	APIDRA	**APIDRA**	**Regular Human Insulin**
	Pre-meal	**Post-meal**	**Pre-meal**
Number of subjects treated	**286**	**296**	**278**
A1c (%)			
Endstudy mean	7.46	7.58	7.52
Adjusted mean change from baseline*	-0.26	-0.11	-0.13
Basal insulin dose (U/day)			
Endstudy mean	29.49	28.77	28.46
Adjusted mean change from baseline	0.99	0.24	0.65
Short-acting insulin dose			
Endstudy mean (U/day)	28.44	28.06	29.23
Adjusted mean change from baseline	-0.88	-0.47	1.75
Severe hypoglycemia**			
Number of subjects (%)	24/286 (8.4)	25/296 (8.4)	28/278 (10.1)
Rate (events/month/patient)	0.05	0.05	0.13
Mean number of short-acting insulin injections per day	3.15	3.13	3.03

* Adjusted mean change from baseline treatment difference (98.33% Confidence Interval 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).

** Events requiring assistance from third party for the entire treatment phase.

Continuous Subcutaneous Insulin Infusion (CSII) (Type 1 Diabetes):

To evaluate the use of APIDRA for administration using an external pump, a 12-week randomized, open-label, active-control study (APIDRA versus insulin aspart) was conducted in Type 1 diabetes patients (n = 59). A low monthly rate of catheter occlusion in both treatment groups was observed (APIDRA: 0.08 occlusions/month; insulin aspart: 0.15 occlusions/ month). A similar incidence of infusion site reactions was seen with APIDRA (n = 3/29; 10.3%) and insulin aspart (n = 4/30; 13.3%).

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™ and D™, and Tender™); and with MiniMed® Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR™, and Quick-set™).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single and Repeated Dose Toxicity

Single- and repeated-dose toxicity studies were conducted in mice, rats and dogs in order to predict the safety profile for the therapeutic use of insulin glulisine in humans; all studies used normoglycemic animals. After a single injection of insulin glulisine, the approximate LD_{50} was >1000 U/kg in rats and mice and 40 U/kg in dogs. After repeated once daily subcutaneous injection of insulin glulisine, the No Observable Adverse Effect Level (NOAEL) in rats were 50 U/kg after 1 month and 5 U/kg after 6 months. The NOAEL in dogs were 1 U/kg in both the 1-month and 6-month studies.

The toxicological profile of insulin glulisine was limited to the effects resulting from excessive hypoglycemia attributed to the exaggerated pharmacodynamic action of the compound after high doses in normoglycemic animals. Repeated-dose toxicity studies in rats and dogs did not reveal any unexpected findings different from human regular insulin.

Insulin glulisine-related effects in toxicity studies were dose-dependent, reversible and restricted to toxic dose levels. Clinical observations and pathological findings obtained in these studies were similar or comparable to those in human beings observed after hyperinsulinemia/ hypoglycemia. In some cases, excessive hypoglycemia caused the deaths of animals. These findings in healthy, non-diabetic animals are not indicative of any specific toxicity on insulin glulisine in patients, where it is used for controlled glucose-lowering effects at therapeutic doses.

Carcinogenicity:

In Sprague Dawley rats, a 12-month repeat dose toxicity study was conducted with insulin glulisine at doses of 2.5, 5, 20 or 50 U/kg twice daily (dose resulting in an exposure equivalent to approximately 26, 54, 258, 662 times the human C_{max} at the average human dose, respectively). The incidence of mortality increased dose dependently in 2x20 and 2x50 U/kg insulin glulisine or IU/kg human insulin treated groups respectively. Generally, males were more severely affected than females and mortality at the comparable dose levels was always higher in the human insulin treated groups.

In this study, the effects of insulin glulisine on cellular proliferation in mammary glands were evaluated using Ki-67 immunohistochemistry. There were no significant differences in mammary cell proliferation between insulin glulisine, regular human insulin and control groups.

Table 13 Insulin glulisine – Incidence of female SD-rats with mammary tumors in a 12-month toxicity study (30 rats per group)

		Insulin glulisine				Human regular insulin		
	Controls	2 x 2.5 U/kg	2 x 5.0 U/kg	2 x 20 U/kg	2 x 50 U/kg	2 x 5.0 IU/kg	2 x 20 IU/kg	2 x 50 IU/kg
Total Tumor Bearers: Benign and Malignant	0	6*	3	6*	3	3	6*	4

*Significant increase in the one-sided Fisher Exact Test ($p<0.05$)
No dose-dependency for insulin glulisine treated groups in regard of tumor incidence indicated by Peto-Trend-Test ($p<0.01$)

Mutagenesis:
Insulin glulisine was not mutagenic in the following tests: Ames test, *in vitro* mammalian chromosome aberration test in V79 cells and *in vivo* mammalian chromosome aberration test (erythrocyte micronucleus test).

Reproductive and Developmental Toxicology:

Impairment of Fertility

In fertility studies in male and female rats at subcutaneous doses up to 10 U/kg once daily (dose resulting in an exposure equivalent to approximately 50 times the human C_{max} at the average human dose), no adverse effects on male and female fertility, or general reproductive performance of animals were observed.

Reproduction toxicity

Table 14: Reproductive & Developmental Toxicity: Fertility & Early Embryonic Development to Implantation

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Sprague Dawley rats	Subcutaneous	Dose levels of 0, 1, 3.15 or 10 U/kg body weight of insulin glulisine or HR1799 at the dose levels of 1 or 10 U/kg body weight Once daily as a solution in placebo prior to mating	23 male and females	• Administration of both insulin glulisine and HR1799 caused clinical signs and mortality at the daily dose of 10 U/kg body weight. • A slightly prolonged pre-coital interval and slightly decreased epididymidal sperm counts were observed in the group treated with 10 U HR1799/kg body weight. • With regard to the present study, the No Observable Adverse Effect Level is at the daily dose of 3.15 U insulin glulisine/kg body weight and at the daily dose of 1.0 U HR1799/kg body weight.

HR1799 = Reference compound (human insulin)

Table 15: Reproductive & Developmental Toxicity: Effects on Embryofetal Development

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Sprague Dawley rats	Subcutaneous	Insulin glulisine once daily as a solution in placebo solution at the dose levels of 0, 15, 50, 150 or 500 U/kg body weight from day 6 - 17 of pregnancy	Groups of 6 mated females	• There was treatment-related mortality and clinical signs due to hypoglycemia at all dose levels tested. • Food consumption was slightly higher at the dose level of 150 U/kg. • No compound-related findings were observed at necropsy. • The animals found dead exhibited only empty implantation sites or conceptuses in the uterus. • Fetal weight and crown/rump lengths were slightly decreased at 150 U/kg. No abnormalities were detected at caesarean section of the other animals. • Based on the results of this study, the dose of 10 U insulin glulisine/kg body weight per day is considered to be a suitable high dose for the main study.

Table 15: Reproductive & Developmental Toxicity: Effects on Embryofetal Development

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Sprague Dawley rats	Subcutaneous	Dose levels of 0, 1, 3.15 or 10 U /kg body weight of insulin glulisine or HR1799 at the dose levels of 1 or 10 U /kg body weight, once daily as a solution in placebo from day 6-17 of pregnancy	Groups of 20-25 mated female	• Administration of both insulin glulisine and HR1799 caused clinical signs and mortality at the daily dose of 10 U/kg body weight. • Slightly increased incidences of minor rib anomalies were seen at this maternally toxic dose level in the fetuses from the HR1799 group. • Neither maternal nor embryo-fetal toxicity were observed after administration of insulin glulisine at the daily dose of 3.15 U/kg body weight and after administration of HR1799 at the daily dose of 1 U/kg body weight.
Sprague Dawley rats	Subcutaneous	Insulin glulisine once daily as a solution in placebo solution at the dose levels of 1.0, 3.15 or 10.0 U/kg body weight from day 6 - 12 of pregnancy	Groups of 10 mated females	• Treatment-related mortality due to hypoglycemia was seen in the 10.0 U/Kg group. • No abnormalities were observed by caesarean section. • Rats displayed a systemic exposure to substantial concentrations of insulin glulisine over 1h and an overproportional increase of Cmax with escalating dose. • Highest plasma concentration of insulin glulisine were detected 15 minutes after administration of the test compound (first collection) in all groups and were 10.6, 46.7 and 159 ng/ml in the low, intermediate and high dose group, respectively.

Table 15: Reproductive & Developmental Toxicity: Effects on Embryofetal Development

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Himalayan rabbits	Subcutaneous	Insulin glulisine once daily as a solution in placebo solution at the dose levels of 0, 2, 10 or 50 U/kg body weight from day 6 - 18 of pregnancy	Groups of 6 mated female	• Treatment–related mortality and clinical signs due to hypoglycemia were seen at all dose levels tested. • Food consumption was slightly higher at the dose levels of 2 and 10 U/kg. • The animals found dead exhibited only empty implantation sites or conceptuses in the uterus. Foetal weight and crown/rump lengths were not altered in the dose groups. The number of intrauterine deaths was higher in the 2 and 10 U/kg group. • Based on the results of this study, the dose of 1.5 U insulin glulisine / kg body weight per day is considered to be a suitable high dose for the main study.

Table 15: Reproductive & Developmental Toxicity: Effects on Embryofetal Development

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Himalayan rabbits	Subcutaneous	Dose levels of 0, 0.25, 0.50 or 1.50 U/kg body weight of insulin glulisine or HR1799 at the dose levels of 0.25 or 1.50 U/kg body weight, once daily as a solution in placebo from day 6 - 18 of pregnancy	Groups of 20-26 mated female	• Administration of both insulin glulisine and HR1799 caused clinical signs and mortality at the daily dose of 1.5 U/kg body weight. • The incidence of dams with total litter loss and the incidence of resorptions were increased. Morphological examination of the fetuses revealed an increased incidence of fetuses showing anomalies in the region of vertebral column and ribs. • Clinical signs were also observed in one animal from the group dosed with 0.5 U insulin glulisine/kg body weight. The incidence of resorptions was slightly increased in this group. No compound-related effects were observed by morphological examination of the fetuses. • With regard to the present study the No Observable Adverse Effect Level is at the daily dose of 0.25 U insulin glulisine/kg body weight and at the daily dose of 0.25 U HR1799/kg body weight for maternal and developmental effects.

Table 15: Reproductive & Developmental Toxicity: Effects on Embryofetal Development

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Himalayan rabbits	Subcutaneous	Insulin glulisine once daily as a solution in placebo solution at the dose levels of 0.25, 0.5 or 1.5 U/kg body weight from day 6 - 12 of pregnancy	Groups of 10 mated females	• The animal of the 1.5 U/kg group found dead exhibited only 5 corpora lutea. • The insulin glulisine pharmacokinetic parameters following the 7th administration are found below: At 0.25 U/kg tmax : 0.25 h Cmax: 7.8ng/ml At 0.5 U/kg tmax : 0.25 h Cmax: 15.3ng/ml At 1.5 U/kg tmax : 0.50 h Cmax: 80.2ng/ml

HR1799 = Reference compound (human insulin)

Table 16: Reproductive & Developmental Toxicity: Effects on Pre- & Post-Natal Development Including Maternal Function

Species/ Strain	Route	Dosage/Duration	No. of Animals/ Group	Findings
Sprague Dawley rats	Subcutaneous	Dose levels 0, 1, 3.15 or 8 U/kg body weight of insulin glulisine or HR1799 at the dose levels of 1 or 8 U/kg body weight, once daily as a solution in placebo from day 6 of gestation until day 21 post partum.	Groups of 23 mated females	• Administration of both insulin glulisine and HR1799 caused clinical signs and mortality in the F0-animals at the daily dose of 8 U/kg body weight when administered during embryo- and fetogenesis and during lactation in Sprague-Dawley rats. There were no specific effects on birth parameters or lactation of the F0-animals and on postnatal development, fertility or pregnancy of the F1-animals. • With regard to the present study the No Observable Adverse Effect Level is at the daily dose of 3.15 U insulin glulisine/kg body weight and at the daily dose of 1.0 U HR1799/kg body weight.

HR1799 = Reference compound (human insulin)

PATIENT MEDICATION INFORMATION - APIDRA® VIALS

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

APIDRA® VIALS

insulin glulisine injection (rDNA origin)

Read this carefully before you start taking **APIDRA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APIDRA**.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including APIDRA.
- Blood glucose (blood sugar) monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic (low blood sugar) or hyperglycemic (high blood sugar) reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- When used as a mealtime insulin, the dose of APIDRA should be given within 15 minutes before 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 can also be used alone in insulin infusion pump therapy to maintain adequate glucose control.
- APIDRA can be mixed with NPH human insulin (except when administered with pump).
- Insulin products shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.

What is APIDRA used for?

APIDRA [insulin glulisine injection (rDNA origin)] is an antidiabetic agent (short-acting recombinant human insulin analogue), used to reduce high blood sugar in adults and children (6 years or older) with diabetes mellitus.

How does APIDRA work?

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs or when your body cannot use properly the insulin you normally produce.

When your body does not make enough insulin, you need an external source of insulin. That is why you must take insulin injections. APIDRA is similar to the insulin made by your body.

APIDRA has a rapid onset of action and a short duration of about 4 hours. APIDRA should normally be used with a longer-acting insulin to maintain adequate blood sugar. APIDRA can also be used with oral drugs to reduce blood sugar.

You have been instructed to test your blood and/or your urine regularly for glucose (sugar); it is especially important to test even more often when changing insulins or dosing schedule. If your blood tests consistently show above- or below-normal glucose levels, or your urine tests consistently show

the presence of glucose, your diabetes is not properly controlled, and you must let your health professional know.

What are the ingredients in APIDRA?

Medicinal ingredients: Insulin glulisine, (rDNA origin)

Non-medicinal ingredients: m-cresol, polysorbate 20, sodium chloride, trometamol, water, and hydrochloric acid and sodium hydroxide for pH adjustment

APIDRA comes in the following dosage forms:

Solution for injection: (100 U/mL)

Do not use APIDRA if:

- if you are allergic to this drug or to any ingredient in the formulation or component of the container.
- if your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your health care provider's instructions on the use of APIDRA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APIDRA. Talk about any health conditions or problems you may have, including if:

- you are planning to have a baby, are pregnant, or are nursing a baby;
- you drink alcohol;
- you are ill;
- you exercise more than usual or if you want to change your usual diet;
- you are traveling;
- you drive or use tools or machine;
- you have trouble with your kidneys or liver;
- you are taking any other medication;

If you have vision changes (diabetic retinopathy) and your blood glucose levels improve very fast, the vision changes may get worse. Ask your doctor about this.

Your ability to concentrate or react may be reduced if you have hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Please keep these possible problems in mind in all situations where you might put yourself or others at risk (for example driving a car or operating machinery).

You should contact your doctor about the advisability of driving if you have:

- frequent episodes of hypoglycemia
- reduced or absent warning signs of hypoglycemia.

Hypokalemia (low potassium) is a possible side effect. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to take APIDRA). Contact your health professional if you develop skin changes at the injection site or if you are currently injecting into a lumpy area before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your health professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Always keep an extra supply of insulin as well as the appropriate injection supplies on hand. Always wear medical alert identification and carry information about your diabetes so that appropriate

treatment can be given if complications occur away from home.

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

Your needles and syringes are only for you and must not be shared to avoid disease transmission.

Other warnings you should know about:

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

If you also take other oral drugs to reduce your blood sugar, their dose may need to be adjusted.

Insulin injections play an important role in keeping your diabetes under control. But the way you live – your diet, careful monitoring of your glucose levels, exercise, or planned physical activity and following your health professional's recommendations – all work with your insulin to help you control your diabetes.

In some situations, your need in insulin may change, for example if you are stress or suffering from other illnesses (e.g. infections).

Your diabetes may also be more difficult to control if you suffer from acromegaly (too much growth hormone), Cushing's syndrome (too much cortisol hormone), hyperthyroidism (too much thyroid hormone) or have a pheochromocytoma (tumor of the adrenal glands).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APIDRA:

- drugs that can increase blood sugar (drugs with hyperglycemic activity):
    - contraceptives (birth control pills, injections and patches)
    - hormone replacement therapies
    - corticosteroids
    - thyroid replacement therapy
    - sympathomimetic agents (such as decongestants and diet pills)
- drugs that can lower blood glucose (drugs with hypoglycemic activity):
    - oral antidiabetic agents
    - salicylates (aspirin)
    - sulfa antibiotics
    - blood pressure medications (including ACE inhibitors, beta-blockers)
    - psychiatric medications (including MAO inhibitors, antidepressants, anti-anxiety medications)
- alcohol

Substances including beta-blockers, used for conditions including blood pressure, heart arrhythmias, palpitations and headache, and alcohol may enhance or weaken the blood-glucose-lowering effect of insulins, and signs of hypoglycemia may be reduced or absent.

Other medicines, including non-prescription medicines, and dietary supplements (such as vitamins) can change the way insulin works. Your dose of insulin or other medications may need to be changed in consultation with your healthcare professional.

How to take APIDRA:

Your doctor has recommended the type of insulin that he/she believes is best for you. DO NOT USE ANY OTHER INSULIN EXCEPT ON THE ADVICE AND DIRECTION OF YOUR DOCTOR.

Mixing of Insulins:

APIDRA can be mixed with NPH human insulin (except for pump (see section below for use of continuous subcutaneous insulin infusion pump)). APIDRA should be drawn into the syringe first. Injection should be made immediately after mixing.

Mixtures should not be administered intravenously.

Correct Syringe

It is important to use a syringe that is marked for U-100 insulin preparations since APIDRA contains 100 units/mL. Using an incorrect syringe could lead to a mistake in dosing and cause medical problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON HOW TO USE SYRINGES TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE**

Disposable syringes and needles should be used only once and then properly discarded.

NEEDLES AND SYRINGES MUST NOT BE SHARED.

Preparing the Dose

1. To avoid medication errors, check the vial label of the insulin before each injection.
2. Inspect the insulin. APIDRA must only be used if the solution is clear, colorless, with no solid particles visible, and if it is of a water-like consistency. Do not use it if you notice anything unusual in the appearance of the solution. Do not use the insulin after the expiry date on the label.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. It is not necessary to shake or rotate the vial before use. Shaking the vial vigorously may cause frothing. Froth may interfere with the correct measurement of the dose.
6. If APIDRA is mixed with NPH human insulin, APIDRA should be drawn into the syringe first. Refer to the instructions for mixing below.
7. Before withdrawing insulin from the vial for the first time, remove the plastic protective cap, but DO NOT remove the stopper.
8. Wipe the top of the vial with an alcohol swab.
9. A new sterile syringe must be used.
10. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin vial and inject the air into the vial.
11. Turn the vial and syringe upside down. Hold the vial and syringe firmly in one hand.
12. Make sure the tip of the needle is in the insulin and withdraw the correct dose of insulin into

the syringe.

13. Before removing the needle from the vial, check your syringe for air bubbles. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
14. Remove the needle from the vial. Do not let the needle touch anything prior to injection.
15. An empty vial must never be reused and must be properly discarded.

Mixing of APIDRA with NPH human insulin

1. APIDRA should be mixed with NPH human insulin only on the advice of your doctor.
2. Before withdrawing insulin from the vials for the first time, remove the plastic protective cap, but DO NOT remove the stopper.
3. Wipe the top of the vials with an alcohol swab.
4. Draw back the plunger of the syringe to the number of NPH human insulin units you need. Put the syringe into the NPH human insulin vial and press the plunger down. This injects air into the vial. Remove the needle from the vial without taking insulin out.
5. Draw back the plunger of the syringe to the number of APIDRA units you need. Put the syringe into the APIDRA vial and press the plunger down. This injects air into the vial. Do not withdraw the needle.
6. Turn the vial and syringe upside down. Hold the vial with one hand and the syringe with the other. Pull back the plunger to five units past your dose.
7. If you get an air bubble, flick the syringe so the bubble rises to the top. Then push the air back into the vial. Adjust APIDRA to the correct dose. Remove the needle from the APIDRA vial.
8. Gently rotate the NPH human insulin vial to mix the insulin.
9. Put the needle with the APIDRA into the NPH human insulin vial, and turn upside down as before.
10. Pull back the plunger until you have the total number of units required (APIDRA + NPH human insulin units). Do not go past the total dose.
11. Make sure you do not push any APIDRA into the NPH human insulin vial. If you pull up too much of the NPH human insulin into the syringe, throw it out and start again. Do not put the insulin back into the vial.
12. Remove the needle from the vial. Do not let the needle touch anything prior to injection.
13. APIDRA should be injected immediately after mixing. It is important to be consistent in your method. Never use APIDRA if it has become cloudy.

Injection

There is no relevant difference in absorption of APIDRA between abdomen, thigh, buttock or upper arm subcutaneous injection areas. However, injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next. This will reduce the risk of skin shrinking or thickening or lumps at the site.

- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Cleanse the skin with alcohol where the injection is to be made. Pinch and hold the skin and insert the needle as instructed by your health professional. Slowly push the plunger of the syringe in completely. Slowly count to 10 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.

Preparation and handling for continuous subcutaneous insulin infusion pump (CSII):

The instructions for using the APIDRA in a pump must be followed carefully.

APIDRA may be used for CSII in pump systems suitable for insulin infusion.

When used with an insulin infusion pump, APIDRA should not be mixed with any other insulin or diluted with any other solution.

Patients using CSII should be comprehensively instructed on the use of the system pump. The infusion set and reservoir must be changed at least every 48 hours using sterile technique. It is important that patients follow these instructions even if they differ from the general pump manual instructions.

Patients administering APIDRA by CSII must have an alternative insulin delivery system available in case of pump system failure.

Usual dose:

The dosage of APIDRA should be individualized and determined based on your health professional's advice in accordance with your needs.

APIDRA should be given by subcutaneous injection within 15 minutes before a meal or within 20 minutes after starting a meal. It can also be used in an external insulin pump for continuous subcutaneous insulin infusion (CSII).

Many factors may affect your usual APIDRA dose, which may include changes in your diet, activity, or work schedule. Follow your health professional's instructions carefully. Consult your health professional if you notice your insulin requirements changing markedly. Other factors that may affect your dose of insulin or your need to do additional blood/urine testing are:

Illness

Illness, especially with nausea and vomiting, diarrhea and/or fever, may change how much insulin you need. Even if you are not eating, you will still require insulin. You and your health professional should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your health professional as instructed.

Pregnancy

If you are planning to have a baby, are pregnant, or are nursing a baby, consult your health professional. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult.

Medication

Always discuss any medications you are taking, prescription or "over-the-counter", with your health professional (see section above: **The following may interact with APIDRA**). To prevent drug interactions, volunteer the names of everything you are taking even before they ask if there have been any changes.

Exercise

If your exercise routine changes, discuss with your health professional the possible need to adjust your insulin regimen. Exercise may lower your body's need for insulin during and for some time after the activity. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Travel

Consult your health professional concerning possible adjustments in your insulin schedule if you will be traveling across time zones. You may want to take along extra insulin and supplies whenever you travel.

Overdose:

If you have injected too much APIDRA, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. In general, to prevent hypoglycemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycemia, **see "Common problems of diabetes" below.**

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both.

In severe cases, coma, seizure and brain disorders may be seen and treated with glucagon (injected in the muscle or subcutaneous tissue) or glucose (injected in the vein).

You should continue checking your blood sugar even if you feel better because hypoglycemia may recur.

If you think you have taken too much APIDRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have **missed a dose of APIDRA** or if **you have not injected enough insulin**, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, **see "Common problems of diabetes" below**.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using APIDRA?

These are not all the possible side effects you may feel when taking APIDRA. If you experience any side effects not listed here, contact your healthcare professional. Please also see SERIOUS WARNINGS AND PRECAUTIONS BOX above.

Common problems of diabetes

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought on by situations such as:

- intercurrent conditions (illness, stress, or emotional disturbances),
- accidental injection of an increased insulin dose,
- malfunction and/or misuse of medical devices,
- too-low food intake, or skipped meals,
- an increase in exercise,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- abnormal behavior (anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, confusion or nervousness),
- fatigue,
- tingling in your hands, feet, lips, or tongue,

- tremor (shaking),
- unsteady gait (walking),
- dizziness, light-headedness, or drowsiness,
- headache,
- blurred vision,
- slurred speech,
- palpitations (rapid heartbeat),
- cold sweat,
- pale skin,
- nightmares or trouble sleeping,
- nausea,
- hunger.

Mild to moderate hypoglycemia can be treated by consuming foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy, juice or glucose tablets, prominently labelled for rescuers. Contact your health professional about appropriate proportions of carbohydrates.

Signs of severe hypoglycemia can include:

- disorientation,
- convulsions,
- loss of consciousness,
- seizures.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

The early warning symptoms of hypoglycemia may be changed, be less pronounced, or be absent, as for example, in patients whose sugar levels are markedly improved, in elderly patients, in patients with diabetic nerve disease, in patients with a long history of diabetes, or in patients receiving concurrent treatment with certain other drugs. Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) before a patient has symptoms.

Some people may not recognize when their blood sugar drops low. Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving a car or use mechanical equipment. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your health professional to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- intercurrent conditions (illness, stress, or emotional disturbances),
- not taking your insulin or taking less than recommended by your health professional,
- malfunction and/or misuse of medical devices,
- eating significantly more than your meal plan suggests,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

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),
- blurred vision,
- flushed dry skin,
- acetone odour of breath.

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

Diabetic ketoacidosis (DKA)

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and acetone.

Symptoms of diabetic ketoacidosis include:

First symptoms:

- drowsiness,
- flushed face,
- thirst,
- loss of appetite,
- fruity smelling breath,
- rapid, deep breathing,
- abdominal (stomach area) pain.

Severe symptoms:

- heavy breathing,
- rapid pulse.

Prolonged hyperglycemia or diabetic ketoacidosis can lead to:

- nausea,
- vomiting,
- dehydration,
- loss of consciousness,
- death.

Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional.

Allergic reactions

In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, seek medical help immediately.

Signs of insulin allergy include:

- a rash all over your body,
- shortness of breath,
- wheezing (trouble breathing),
- a fast pulse,
- sweating,
- low blood pressure.

Possible reactions on the skin 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),
- skin lumps (localized cutaneous amyloidosis),
- redness, itching, swelling, or hemorrhage at injection site.

You can reduce the chance of getting an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your health professional as a sudden change of site may result in hypoglycemia.

In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unopened Vial:
Unopened APIDRA vials should be stored in a refrigerator, between 2°C and 8°C. Keep APIDRA away from direct heat and light. APIDRA should not be stored in the freezer and should not be allowed to freeze. If APIDRA freezes or overheats, discard it.

Opened (In Use) Vial:
The opened vial can be kept refrigerated or unrefrigerated (15 to 25°C) for up to 28 days away from

direct heat and light, as long as the temperature is not greater than 25°C. Opened APIDRA vials, whether or not refrigerated, must be discarded after 28 days even if they contain insulin.

Opened APIDRA vials should not be stored in the freezer and should not be allowed to freeze. If a vial freezes or overheats, discard it.

Do not use a vial of APIDRA after the expiration date stamped on the label or if it is cloudy or if you see particles.

Infusion sets (when used with Continuous Subcutaneous Insulin Infusion pump)

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

Keep out of reach and sight of children.

If you want more information about APIDRA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.sanofi.ca, or by calling 1-888-852-6887.

This document plus the full product monograph, prepared for health professionals can be found at www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-888-852-6887. It is also available in large print format.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: November 03, 2021

PATIENT MEDICATION INFORMATION - APIDRA® CARTRIDGES

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

APIDRA® CARTRIDGES

insulin glulisine injection (rDNA origin)

Cartridges are for use ONLY with AllStar® PRO and JuniorSTAR® pens.

Read this carefully before you start taking **APIDRA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APIDRA**.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including APIDRA.
- Blood glucose (blood sugar) monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic (low blood sugar) or hyperglycemic (high blood sugar) reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- When used as a meal time insulin, the dose of APIDRA should be given within 15 minutes before 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 can also be used alone in insulin infusion pump therapy to maintain adequate glucose control.
- APIDRA can be mixed with NPH human insulin (except when administered with pump).
- Insulin products shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.

What is APIDRA used for?

APIDRA [insulin glulisine injection (rDNA origin)] is an antidiabetic agent (short-acting recombinant human insulin analogue), used to reduce high blood sugar in adults and children (6 years or older) with diabetes mellitus.

How does APIDRA work?

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs or when your body cannot use properly the insulin you normally produce.

When your body does not make enough insulin, you need an external source of insulin. That is why you must take insulin injections. APIDRA is similar to the insulin made by your body.

APIDRA has a rapid onset of action and a short duration of about 4 hours. APIDRA should normally be used with a longer-acting insulin to maintain adequate blood sugar. APIDRA can also be used with oral drugs to reduce blood sugar.

You have been instructed to test your blood and/or your urine regularly for glucose (sugar); it is especially important to test even more often when changing insulins or dosing schedule. If your blood

tests consistently show above- or below-normal glucose levels, or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled, and you must let your health professional know.

What are the ingredients in APIDRA?

Medicinal ingredients: Insulin glulisine, (rDNA origin)

Non-medicinal ingredients: m-cresol, polysorbate 20, sodium chloride, trometamol, water, and hydrochloric acid and sodium hydroxide for pH adjustment

APIDRA comes in the following dosage forms:

Solution for injection: 100 U/mL

Do not use APIDRA if:

- if you are allergic to this drug or to any ingredient in the formulation or component of the container.
- if your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your health care provider's instructions on the use of APIDRA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APIDRA. Talk about any health conditions or problems you may have, including if:

- you are planning to have a baby, are pregnant, or are nursing a baby;
- you drink alcohol;
- you are ill;
- you exercise more than usual or if you want to change your usual diet;
- you are traveling;
- you drive or use tools or machine;
- you have trouble with your kidneys or liver;
- you are taking any other medication;

If you have vision changes (diabetic retinopathy) and your blood glucose levels improve very fast, the vision changes may get worse. Ask your doctor about this.

Your ability to concentrate or react may be reduced if you have hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Please keep these possible problems in mind in all situations where you might put yourself or others at risk (for example driving a car or operating machinery).

You should contact your doctor about the advisability of driving if you have:

- frequent episodes of hypoglycemia
- reduced or absent warning signs of hypoglycemia.

Hypokalemia (low potassium) is a possible side effect. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to take APIDRA). Contact your health professional if you develop skin changes at the injection site or if you are currently injecting into a lumpy area before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your health professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Always keep an extra supply of insulin as well as the appropriate injection supplies on hand. Always wear medical alert identification and carry information about your diabetes so that appropriate treatment can be given if complications occur away from home.

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

Your needles and syringes are only for you and must not be shared to avoid disease transmission.

Other warnings you should know about:

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Please contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these agents.

If you also take other oral drugs to reduce your blood sugar, their dose may need to be adjusted.

Insulin injections play an important role in keeping your diabetes under control. But the way you live – your diet, careful monitoring of your glucose levels, exercise, or planned physical activity and following your health professional's recommendations – all work with your insulin to help you control your diabetes.

In some situations, your need in insulin may change, for example if you are stress or suffering from other illnesses (e.g. infections).

Your diabetes may also be more difficult to control if you suffer from acromegaly (too much growth hormone), Cushing's syndrome (too much cortisol hormone), hyperthyroidism (too much thyroid hormone) or have a pheochromocytoma (tumor of the adrenal glands).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APIDRA:

- drugs that can increase blood sugar (drugs with hyperglycemic activity):
    - contraceptives (birth control pills, injections and patches)
    - hormone replacement therapies
    - corticosteroids
    - thyroid replacement therapy
    - sympathomimetic agents (such as decongestants and diet pills)
- drugs that can lower blood glucose (drugs with hypoglycemic activity):
    - oral antidiabetic agents
    - salicylates (aspirin)
    - sulfa antibiotics

- blood pressure medications (including ACE inhibitors, beta-blockers)
- psychiatric medications (including MAO inhibitors, antidepressants, anti-anxiety medications)

- alcohol

Substances including beta-blockers, used for conditions including blood pressure, heart arrhythmias, palpitations and headache, and alcohol may enhance or weaken the blood-glucose-lowering effect of insulins, and signs of hypoglycemia may be reduced or absent.

Other medicines, including non-prescription medicines, and dietary supplements (such as vitamins) can change the way insulin works. Your dose of insulin or other medications may need to be changed in consultation with your healthcare professional.

How to take APIDRA:

Your doctor has recommended the type of insulin that he/she believes is best for you. DO NOT USE ANY OTHER INSULIN EXCEPT ON THE ADVICE AND DIRECTION OF YOUR DOCTOR.

The instructions for using the APIDRA in the injection pen must be followed carefully.

It is important to use the APIDRA cartridge only with AllStar PRO and JuniorSTAR pens. Using the cartridge in any other injection pen not suitable for the APIDRA cartridge could lead to a mistake in dosing and cause medical problems for you, such as a blood glucose level that is too low or too high.

JuniorSTAR delivers APIDRA in 0.5 unit dose increments. AllStar PRO delivers APIDRA in 1 unit dose increments.

CAREFULLY FOLLOW THE PACKAGE DIRECTIONS SUPPLIED FOR AllStar PRO and JuniorSTAR TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

Do not reuse needles. INJECTION PENS, CARTRIDGES, NEEDLES, AND SYRINGES MUST NOT BE SHARED. To prevent the possible transmission of disease, never share an injection pen or APIDRA cartridge between patients, even if the needle on the injection pen is changed.

Preparing the APIDRA Cartridge for Insertion into the injection pen

1. To avoid medication errors, check the cartridge label of the insulin before each insertion.
2. Inspect the insulin cartridge. APIDRA should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution. Do not use the insulin after the expiry date on the label.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. Carefully follow the injection pen directions for loading the cartridge into the injection pen.

Injecting Each Dose

1. Wash your hands.
2. Inspect the insulin. APIDRA should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of solution.
3. It is not necessary to shake or rotate the cartridge inserted into the injection pen before use.
4. Remove the protective cap.
5. Follow the injection pen directions for attaching and changing the needle.
6. Check the cartridge inserted into the injection pen for air bubbles. If bubbles are present,

remove them as instructed in the injection pen directions.

7. Follow the injection pen directions for performing the Safety Test or Priming.
8. Set the injection pen to the correct APIDRA dose as instructed in the injection pen directions.
9. There is no relevant difference in absorption of APIDRA between abdominal, thigh, buttock or upper arm subcutaneous injection areas. However, injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next. This will reduce the risk of skin shrinking or thickening or lumps at the site.
    - **Do not** inject where the skin has pits, is thickened, or has lumps.
    - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
10. Cleanse the skin with alcohol where the injection is to be made.
11. Pinch and hold the skin and insert the needle attached to the injection pen as instructed by your health professional.
12. To inject APIDRA, follow the directions for the injection pen.
13. Slowly count to 10 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.
14. Remove the needle from the injection pen immediately after each injection as instructed in the directions for the injection pen. Dispose of the needle appropriately. Do not reuse the needle.
15. An empty cartridge must never be reused and must be properly discarded.

Usual dose:

The dosage of APIDRA should be individualized and determined based on your health professional's advice in accordance with your needs.

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

Many factors may affect your usual APIDRA dose, which may include changes in your diet, activity, or work schedule. Follow your health professional's instructions carefully. Consult your health professional if you notice your insulin requirements changing markedly. Other factors that may affect your dose of insulin or your need to do additional blood/urine testing are:

Illness

Illness, especially with nausea and vomiting, diarrhea and/or fever, may change how much insulin you need. Even if you are not eating, you will still require insulin. You and your health professional should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your health professional as instructed.

Pregnancy

If you are planning to have a baby, are pregnant, or are nursing a baby, consult your health professional. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult.

Medication

Always discuss any medications you are taking, prescription or "over-the-counter", with your health professional (see section above: **The following may interact with APIDRA**). To prevent drug interactions, volunteer the names of everything you are taking even before they ask if there have been any changes.

Exercise

If your exercise routine changes, discuss with your health professional the possible need to adjust your insulin regimen. Exercise may lower your body's need for insulin during and for some time after the activity. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Travel

Consult your health professional concerning possible adjustments in your insulin schedule if you will be traveling across time zones. You may want to take along extra insulin and supplies whenever you travel.

Overdose:

If you have injected too much APIDRA, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. In general, to prevent hypoglycemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycemia, see "Common problems of diabetes" below.

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both.

In severe cases, coma, seizure and brain disorders may be seen and treated with glucagon (injected in the muscle or subcutaneous tissue) or glucose (injected in the vein).

You should continue checking your blood sugar even if you feel better because hypoglycemia may recur.

If you think you have taken too much APIDRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have **missed a dose of APIDRA** or **if you have not injected enough insulin**, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, see "Common problems of diabetes" below.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using APIDRA?

These are not all the possible side effects you may feel when taking APIDRA. If you experience any side effects not listed here, contact your healthcare professional. Please also see SERIOUS WARNINGS AND PRECAUTIONS BOX above.

Common problems of diabetes

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought on by situations such as:

- intercurrent conditions (illness, stress, or emotional disturbances),
- accidental injection of an increased insulin dose,
- malfunction and/or misuse of medical devices,
- too-low food intake, or skipped meals,

- an increase in exercise,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- abnormal behavior (anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, confusion or nervousness),
- fatigue,
- tingling in your hands, feet, lips, or tongue,
- tremor (shaking),
- unsteady gait (walking),
- dizziness, light-headedness, or drowsiness,
- headache,
- blurred vision,
- slurred speech,
- palpitations (rapid heartbeat),
- cold sweat,
- pale skin,
- nightmares or trouble sleeping,
- nausea,
- hunger.

Mild to moderate hypoglycemia can be treated by consuming foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy, juice or glucose tablets, prominently labelled for rescuers. Contact your health professional about appropriate proportions of carbohydrates.

Signs of severe hypoglycemia can include:

- disorientation,
- convulsions,
- loss of consciousness,
- seizures.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

The early warning symptoms of hypoglycemia may be changed, be less pronounced, or be absent, as for example, in patients whose sugar levels are markedly improved, in elderly patients, in patients with diabetic nerve disease, in patients with a long history of diabetes, or in patients receiving concurrent treatment with certain other drugs. Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) before a patient has symptoms.

Some people may not recognize when their blood sugar drops low. Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving a car or use mechanical equipment. If the blood glucose is

below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your health professional to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- intercurrent conditions (illness, stress, or emotional disturbances),
- not taking your insulin or taking less than recommended by your health professional,
- malfunction and/or misuse of medical devices,
- eating significantly more than your meal plan suggests,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

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),
- blurred vision,
- flushed dry skin,
- acetone odour of breath.

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

Diabetic ketoacidosis (DKA)

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and acetone.

Symptoms of diabetic ketoacidosis include:

First symptoms:

- drowsiness,
- flushed face,
- thirst,
- loss of appetite,
- fruity smelling breath,
- rapid, deep breathing,
- abdominal (stomach area) pain.

Severe symptoms:

- heavy breathing,
- rapid pulse.

Prolonged hyperglycemia or diabetic ketoacidosis can lead to:

- nausea,
- vomiting,
- dehydration,
- loss of consciousness,
- death.

Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional.

Allergic reactions

In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, seek medical help immediately.

Signs of insulin allergy include:

- a rash all over your body,
- shortness of breath,
- wheezing (trouble breathing),
- a fast pulse,
- sweating,
- low blood pressure.

Possible reactions on the skin 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),
- skin lumps (localized cutaneous amyloidosis),
- redness, itching, swelling, or hemorrhage at injection site.

You can reduce the chance of getting an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your health professional as a sudden change of site may result in hypoglycemia.

In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unopened Cartridge:
Unopened APIDRA cartridges should be stored in a refrigerator, between 2°C and 8°C. Keep APIDRA away from direct heat and light. APIDRA should not be stored in the freezer and should not be allowed to freeze. If APIDRA freezes or overheats, discard it.

Opened (In Use) Cartridge:
The opened cartridge in use must be kept unrefrigerated (15 to 25°C) for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C. If the cartridge overheats or if there is any remaining insulin after 28 days, discard it. The opened cartridge in use must never be removed from and reinserted into the injection pen.

Do not use a cartridge of APIDRA after the expiration date stamped on the label or if it is cloudy or if you see particles.

Keep out of reach and sight of children.

If you want more information about APIDRA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.sanofi.ca, or by calling 1-888-852-6887.

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This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: November 03, 2021

PATIENT MEDICATION INFORMATION - APIDRA® SOLOSTAR®

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

APIDRA® SoloSTAR®

insulin glulisine injection (rDNA origin)

Read this carefully before you start taking **APIDRA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APIDRA**.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including APIDRA.
- Blood glucose (blood sugar) monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic (low blood sugar) or hyperglycemic (high blood sugar) reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- When used as a meal time insulin, the dose of APIDRA should be given within 15 minutes before 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 can also be used alone in insulin infusion pump therapy to maintain adequate glucose control.
- APIDRA can be mixed with NPH human insulin (except when administered with pump).
- Insulin products shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.

What is APIDRA used for?

APIDRA [insulin glulisine injection (rDNA origin)] is an antidiabetic agent (short-acting recombinant human insulin analogue), used to reduce high blood sugar in adults and children (6 years or older) with diabetes mellitus.

How does APIDRA work?

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs or when your body cannot use properly the insulin you normally produce.

When your body does not make enough insulin, you need an external source of insulin. That is why you must take insulin injections. APIDRA is similar to the insulin made by your body.

APIDRA has a rapid onset of action and a short duration of about 4 hours. APIDRA should normally be used with a longer-acting insulin to maintain adequate blood sugar. APIDRA can also be used with oral drugs to reduce blood sugar.

You have been instructed to test your blood and/or your urine regularly for glucose (sugar); it is especially important to test even more often when changing insulins or dosing schedule. If your blood tests consistently show above- or below-normal glucose levels, or your urine tests consistently show

the presence of glucose, your diabetes is not properly controlled and you must let your health professional know.

What are the ingredients in APIDRA?

Medicinal ingredients: Insulin glulisine, (rDNA origin)

Non-medicinal ingredients: m-cresol, polysorbate 20, sodium chloride, trometamol, water, and hydrochloric acid and sodium hydroxide for pH adjustment

APIDRA comes in the following dosage forms:

Solution for injection 100 U/mL

Do not use APIDRA if:

- if you are allergic to this drug or to any ingredient in the formulation or component of the container.
- if your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your health care provider's instructions on the use of APIDRA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APIDRA. Talk about any health conditions or problems you may have, including if:

- you are planning to have a baby, are pregnant, or are nursing a baby;
- you drink alcohol;
- you are ill;
- you exercise more than usual or if you want to change your usual diet;
- you are traveling;
- you drive or use tools or machine;
- you have trouble with your kidneys or liver;
- you are taking any other medication;

If you have vision changes (diabetic retinopathy) and your blood glucose levels improve very fast, the vision changes may get worse. Ask your doctor about this.

Your ability to concentrate or react may be reduced if you have hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Please keep these possible problems in mind in all situations where you might put yourself or others at risk (for example driving a car or operating machinery).

You should contact your doctor about the advisability of driving if you have:

- frequent episodes of hypoglycemia
- reduced or absent warning signs of hypoglycemia.

Hypokalemia (low potassium) is a possible side effect. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to take APIDRA). Contact your health professional if you develop skin changes at the injection site or if you are currently injecting into a lumpy area before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your health professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

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treatment can be given if complications occur away from home.

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    - hormone replacement therapies
    - corticosteroids
    - thyroid replacement therapy
    - sympathomimetic agents (such as decongestants and diet pills)
- drugs that can lower blood glucose (drugs with hypoglycemic activity):
    - oral antidiabetic agents
    - salicylates (aspirin)
    - sulfa antibiotics
    - blood pressure medications (including ACE inhibitors, beta-blockers)
    - psychiatric medications (including MAO inhibitors, antidepressants, anti-anxiety medications)
- alcohol

Substances including beta-blockers, used for conditions including blood pressure, heart arrhythmias, palpitations and headache, and alcohol may enhance or weaken the blood-glucose-lowering effect of insulins, and signs of hypoglycemia may be reduced or absent.

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CAREFULLY FOLLOW THE PACKAGE DIRECTIONS SUPPLIED WITH THE SOLOSTAR TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

Do not reuse needles. INJECTION PENS, CARTRIDGES, NEEDLES, AND SYRINGES MUST NOT BE SHARED. To prevent the possible transmission of disease, this injection pen is for single patient use. Do not share it with anyone including other family members, even if the needle on the injection pen is changed. Do not use on multiple patients.

Preparing the Dose

1. To avoid medication errors, check the label on the SoloSTAR pen to make sure you have the correct insulin. The APIDRA SoloSTAR is blue.
2. Inspect the insulin. APIDRA should be a clear and colorless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution. Do not use the insulin after the expiry date on the label.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. It is not necessary to shake or rotate the SoloSTAR before use.
6. Remove the protective cap.
7. **Follow the SoloSTAR directions for attaching and changing the needle.**
8. Check the SoloSTAR for air bubbles. If bubbles are present, remove them as instructed in the SoloSTAR directions.
9. **Follow the SoloSTAR directions for performing the Safety Test.**
10. Set the SoloSTAR to the correct APIDRA dose as instructed in the SoloSTAR directions.
11. There is no relevant difference in absorption of APIDRA between abdominal, thigh, buttock or upper arm subcutaneous injection areas. However, injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next. This will reduce the risk of skin shrinking or thickening or lumps at the site.
    - **Do not** inject where the skin has pits, is thickened, or has lumps.
    - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
12. Cleanse the skin with alcohol where the injection is to be made.
13. Pinch and hold the skin and insert the needle attached to the SoloSTAR as instructed by your health professional.
14. To inject APIDRA, follow the directions for the SoloSTAR.
15. Slowly count to 10 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.
16. Remove the needle from the SoloSTAR immediately after each injection as instructed in the directions for the SoloSTAR. Dispose of the needle appropriately. Do not reuse the needle.

Usual dose:

The dosage of APIDRA should be individualized and determined based on your health professional's advice in accordance with your needs.

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

Many factors may affect your usual APIDRA dose, which may include changes in your diet, activity, or work schedule. Follow your health professional's instructions carefully. Consult your health professional if you notice your insulin requirements changing markedly. Other factors that may affect your dose of insulin or your need to do additional blood/urine testing are:

Illness

Illness, especially with nausea and vomiting, diarrhea and/or fever, may change how much insulin you need. Even if you are not eating, you will still require insulin. You and your health professional should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your health professional as instructed.

Pregnancy

If you are planning to have a baby, are pregnant, or are nursing a baby, consult your health professional. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult.

Medication

Always discuss any medications you are taking, prescription or "over-the-counter", with your health professional (see section above: **The following may interact with APIDRA**). To prevent drug interactions, volunteer the names of everything you are taking even before they ask if there have been any changes.

Exercise

If your exercise routine changes, discuss with your health professional the possible need to adjust your insulin regimen. Exercise may lower your body's need for insulin during and for some time after the activity. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Travel

Consult your health professional concerning possible adjustments in your insulin schedule if you will be traveling across time zones. You may want to take along extra insulin and supplies whenever you travel.

Overdose:

If you have **injected too much APIDRA**, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. In general, to prevent hypoglycemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycemia, **see "Common problems of diabetes" below.**

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both.

In severe cases, coma, seizure and brain disorders may be seen and treated with glucagon (injected in the muscle or subcutaneous tissue) or glucose (injected in the vein).

You should continue checking your blood sugar even if you feel better because hypoglycemia may recur.

If you think you have taken too much APIDRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have **missed a dose of APIDRA** or **if you have not injected enough insulin**, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, **see "Common problems of diabetes" below.**

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using APIDRA?

These are not all the possible side effects you may feel when taking APIDRA. If you experience any side effects not listed here, contact your healthcare professional. Please also see SERIOUS WARNINGS AND PRECAUTIONS BOX above.

Common problems of diabetes

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought on by situations such as:

- intercurrent conditions (illness, stress, or emotional disturbances),
- accidental injection of an increased insulin dose,
- malfunction and/or misuse of medical devices,
- too-low food intake, or skipped meals,
- an increase in exercise,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- abnormal behavior (anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, confusion or nervousness),
- fatigue,
- tingling in your hands, feet, lips, or tongue,
- tremor (shaking),
- unsteady gait (walking),
- dizziness, light-headedness, or drowsiness,
- headache,
- blurred vision,
- slurred speech,
- palpitations (rapid heartbeat),
- cold sweat,
- pale skin,
- nightmares or trouble sleeping,

- nausea,
- hunger.

Mild to moderate hypoglycemia can be treated by consuming foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy, juice or glucose tablets, prominently labelled for rescuers. Contact your health professional about appropriate proportions of carbohydrates.

Signs of severe hypoglycemia can include:

- disorientation,
- convulsions,
- loss of consciousness,
- seizures.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

The early warning symptoms of hypoglycemia may be changed, be less pronounced, or be absent, as for example, in patients whose sugar levels are markedly improved, in elderly patients, in patients with diabetic nerve disease, in patients with a long history of diabetes, or in patients receiving concurrent treatment with certain other drugs. Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) before a patient has symptoms.

Some people may not recognize when their blood sugar drops low. Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving a car or use mechanical equipment. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your health professional to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- intercurrent conditions (illness, stress, or emotional disturbances),
- not taking your insulin or taking less than recommended by your health professional,
- malfunction and/or misuse of medical devices,
- eating significantly more than your meal plan suggests,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the counter medications, herbs, vitamins and street drugs.

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),
- blurred vision,
- flushed dry skin,
- acetone odour of breath.

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

Diabetic ketoacidosis (DKA)

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and acetone.

Symptoms of diabetic ketoacidosis include:

First symptoms:
- drowsiness,
- flushed face,
- thirst,
- loss of appetite,
- fruity smelling breath,
- rapid, deep breathing,
- abdominal (stomach area) pain.

Severe symptoms:
- heavy breathing,
- rapid pulse.

Prolonged hyperglycemia or diabetic ketoacidosis can lead to:
- nausea,
- vomiting,
- dehydration,
- loss of consciousness,
- death.

Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional.

Allergic reactions

In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, seek medical help immediately.

Signs of insulin allergy include:
- a rash all over your body,
- shortness of breath,
- wheezing (trouble breathing),
- a fast pulse,
- sweating,
- low blood pressure.

Possible reactions on the skin 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),
- skin lumps (localized cutaneous amyloidosis),
- redness, itching, swelling, or hemorrhage at injection site.

You can reduce the chance of getting an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your health professional as a sudden change of site may result in hypoglycemia.

In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unopened SoloSTAR:
Unopened APIDRA SoloSTAR should be stored in a refrigerator, between 2°C and 8°C. Keep APIDRA SoloSTAR away from direct heat and light. APIDRA SoloSTAR should not be stored in the freezer and should not be allowed to freeze. If APIDRA SoloSTAR freezes or overheats, discard it

Opened (In Use) SoloSTAR:
Opened APIDRA SoloSTAR in use must be kept unrefrigerated (15 to 25°C) for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C. If the APIDRA SoloSTAR overheats or if there is any remaining insulin after 28 days, discard it.

Opened APIDRA SoloSTAR should not be stored in the freezer and should not be allowed to freeze. If APIDRA SoloSTAR freezes discard it.

Do not use an APIDRA SoloSTAR after the expiration date stamped on the label or if it is cloudy or if you see particles.

Keep out of reach and sight of children**.**

If you want more information about APIDRA:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.sanofi.ca, or by calling 1-888-852-6887.

This document plus the full product monograph, prepared for health professionals can be found at www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-888-852-6887. It is also available in large print format.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: November 03, 2021

INSTRUCTIONS FOR USE: APIDRA® SOLOSTAR ®

SoloSTAR® is a prefilled pen for the injection of insulin. Your health professional has decided that SoloSTAR is appropriate for you, based on your ability to handle SoloSTAR. Talk with your health professional about proper injection technique before using SoloSTAR.

Read these instructions carefully before using your SoloSTAR. If you are not able to use SoloSTAR or to follow all the instructions completely on your own, you must use SoloSTAR only if you have help from a person who is able to follow the instructions completely.

Keep this leaflet for future reference.

If you have any questions about SoloSTAR or about diabetes, ask your health professional or call sanofi-aventis at 1-888-852-6887.

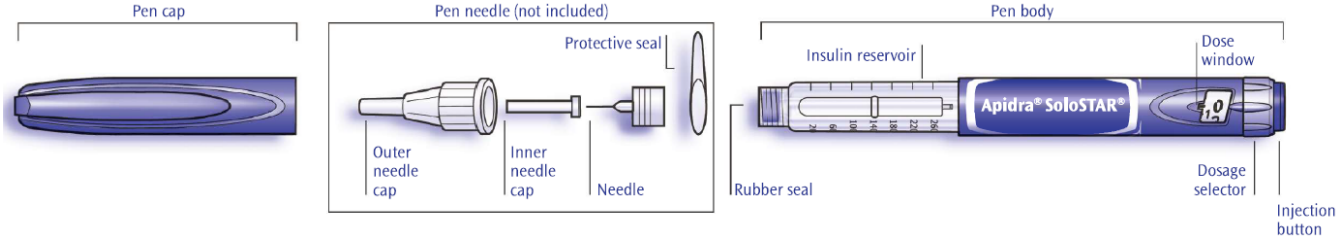
IMPORTANT INFORMATION FOR USE OF SOLOSTAR:

- To avoid transmission of disease do not share injection pens, cartridges, needles or syringes. This injection pen is for single patient use. Do not share it with anyone including other family members, even if the needle on the injection pen is changed. Do not use on multiple patients.
- Always attach a new needle before each use. Needles are available in different lengths and gauges. Only use needles that have been approved for use with SoloSTAR. Contact your health professional for further information.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloSTAR if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloSTAR in case your SoloSTAR is lost or damaged.

Check the pen

Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Each SoloSTAR contains in total 300 units of insulin. You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.



Step 1: Check the insulin

A. Check the label on your SoloSTAR to make sure you have the correct insulin. The Apidra SoloSTAR is blue. It has a dark blue injection button with a raised ring on the top. Check the expiry date printed on the label of your pen. Do not use your Apidra SoloSTAR after the expiration date.

B. Take off the pen cap.

C. Check the appearance of your insulin. Apidra is a clear insulin. Do not use this SoloSTAR if the insulin is cloudy, colored or has particles.

Step 2: Attach the needle

Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

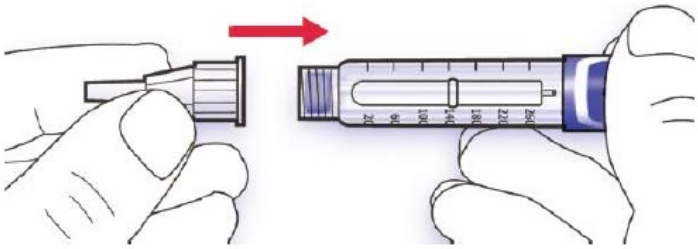
Before use of needle, carefully read "Instructions for Use" accompanying the needles.

Please note: The needles shown are for illustrative purposes only.

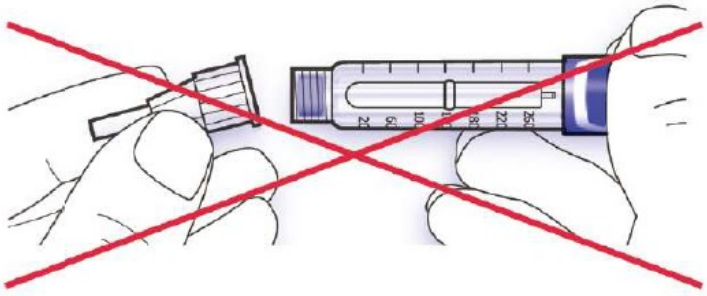
A. Wipe the rubber seal with alcohol.

B. Remove the protective seal from a new needle.

C. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.

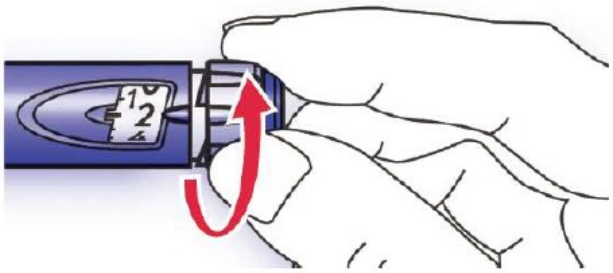


Step 3: Perform a safety test

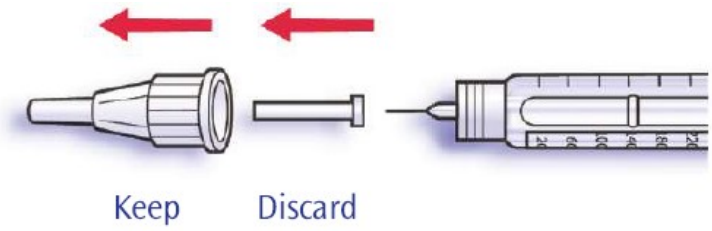
Always perform the safety test before each injection. This ensures that you get an accurate dose by:

- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector clockwise.



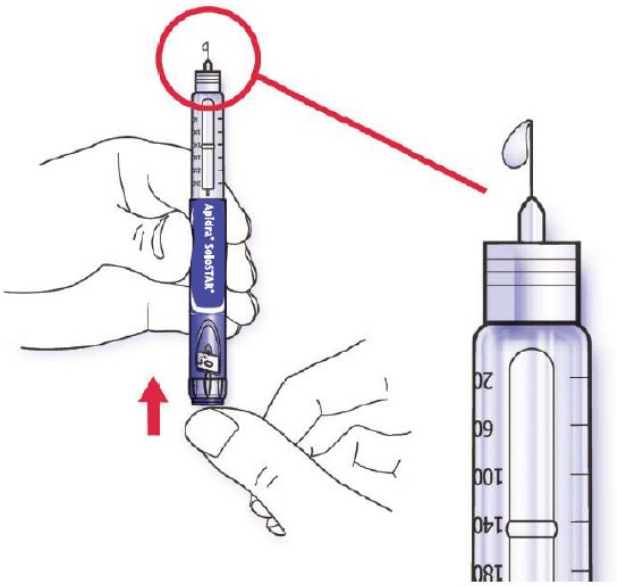
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

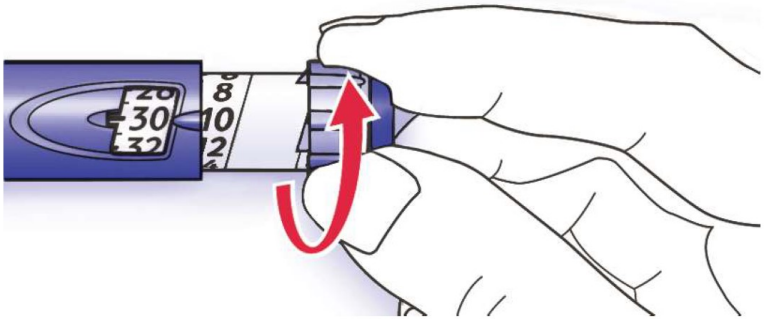
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloSTAR may be damaged. Do not use this SoloSTAR, as you could get no insulin at all. This could cause high blood sugar.

Step 4: Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose turning the dosage selector clockwise (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down. (counter-clockwise).



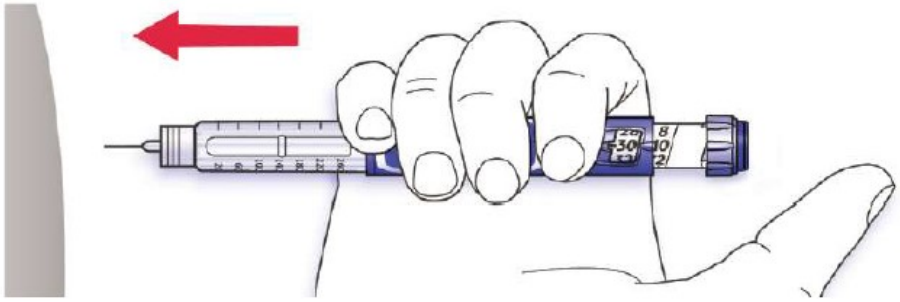
- Do not push the injection button while turning, as insulin will come out.
- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloSTAR or use a new SoloSTAR for your full dose.

Step 5: Inject the dose

A. Clean the area of skin to be injected (e.g. with rubbing alcohol).

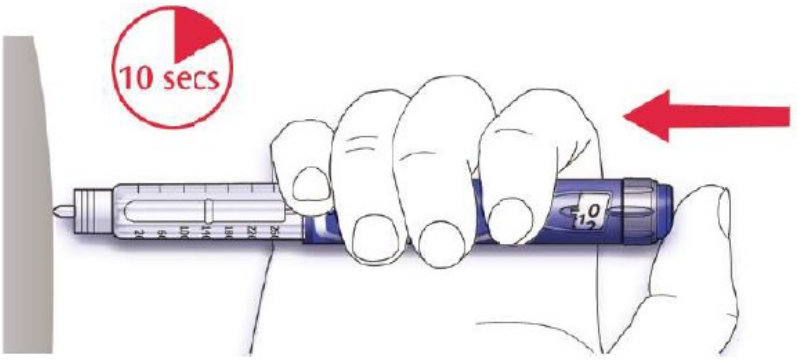
B. Use the injection method as instructed by your health professional.

C. Insert the needle into the skin.



D. Deliver the dose by pressing the injection button in all the way. The number in the dose window will progressively return to "0" as you inject.

E. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.



The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6: Remove and discard the needle

Always remove the needle after each injection and store SoloSTAR without a needle attached. This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

  - Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back and push firmly on. The needle can puncture the cap if it is recapped at an angle
  - Grip and squeeze the widest part of the outer need cap. Turn your pen several times with your other hand to remove the needle. Try again if the needle does not come off the first time.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your

health professional) in order to reduce the risk of accidental needle injury and transmisison of infectious diseases.

B. Dispose of the needle safely. Used needles should be placed in sharps containers (such as 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.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

STORAGE INSTRUCTIONS

Keep SoloSTAR out of the reach and sight of children.

Keep your SoloSTAR in cool storage (2°C to 8°C) until first use.

Do not allow it to freeze. Do not put it next to the freezer compartment of your refrigerator, or next to a freezer pack.

If your SoloSTAR is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Once you take your SoloSTAR out of cool storage, for use or as a spare, you can use it for up to 28 days. During this time it should be kept at room temperature (15 to 25°C) and must not be stored in the refrigerator. If there is any remaining insulin after 28 days, discard it.

Do not use SoloSTAR after the expiration date printed on the label of the pen or if it is cloudy, colored or if you see particles.

Protect SoloSTAR from light.

Discard your used SoloSTAR as required by your local authorities

MAINTENANCE

Protect your SoloSTAR from dust and dirt.

You can clean the outside of your SoloSTAR by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloSTAR is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloSTAR might be damaged. If you are concerned that your SoloSTAR may be damaged, use a new one.

Manufacturer: Sanofi-aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany
Importer/Distributor: Sanofi-aventis Canada Inc. Laval, Quebec, Canada H7V 0A3
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Call toll free **1-888-852-6887**