For the use only of a Registered Medical Practitioner, Hospital, Laboratories

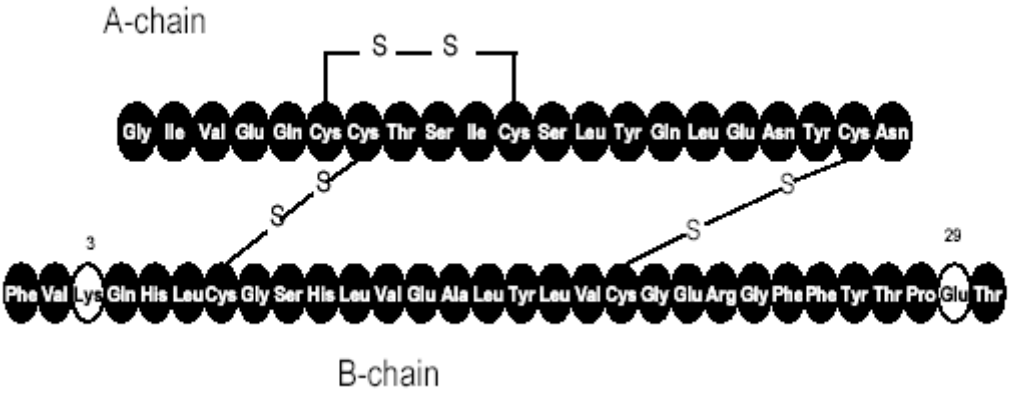
This package insert is continually updated: Please read carefully before using a new pack

INSULIN GLULISINE INJECTION
(Monocomponent Insulin Glulisine)
100IU/mL

APIDRA®
3mL cartridge , 10mL vial

APIDRA® SOLOSTAR®
3mL prefilled pen

Active Ingredient
Insulin glulisine
Recombinant human insulin analogue.
Chemically, it is 3^{B}-lysine-29^{B} -glutamic acid-human insulin
Empirical formula $C_{258}H_{384}N_{64}O_{78}S_6$



Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid.

Insulin glulisine is produced by recombinant DNA technology utilizing *Escherichia coli* (K12 strain).

Therapeutic or Pharmacological Class
Antidiabetic agent
Pharmacotherapeutic group: insulin and analogues, fast acting. ATC Code:A10AB

Pharmaceutical Form(s)
Solution for injection in vials, cartridges (designed to be used with AllStar®) and pre-filled disposable pen (Solostar®).

Composition
Active Ingredient
1 ml contains 3.5 mg insulin glulisine, corresponding to 100 IU human insulin.
Each cartridge and pre-filled disposable pen (Solostar®) contains 3 ml, equivalent to 300 IU insulin. Each vial contains 10 ml equivalent to 1000 IU.

Excipients
M-cresol, trometamol, sodium chloride, polysorbate 20, and water for injection.

Apidra® has a pH of approximately 7.3 and is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide

Indication:
Treatment of adults, adolescents and children of 6 years or older with diabetes mellitus, where treatment with insulin is required.

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

Apidra® should be given by injection within 15 minutes before or within 20 minutes after a meal.

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

Apidra®should normally be used in regimens that include a longer-acting insulin or basal insulin analogue. Blood glucose monitoring is recommended for all patients with diabetes.

Special Populations

Children
Apidra can be administered to children ≥ 6 years of age. Administration to children < 6 years has not been studied.

Elderly
Hypoglycaemia may be difficult to recognise in the elderly (see Precautions).

Hepatic impairment
In patients with hepatic impairment, insulin requirements may be diminished (see Precautions).

Renal impairment
In patients with renal impairment, insulin requirements may be diminished (see Precautions).

Administration :
- General

Apidra® is intended for subcutaneous administration by injection or by external infusion pump. Apidra® can also be administered intravenously.

Apidra® should be administered subcutaneously either by injection in the abdominal wall, the thigh or deltoid or by continuous subcutaneous infusion in the abdominal wall.

As with all insulins, injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next.

As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables.

• Mixing of Insulins for subcutaneous injection

Apidra® can be mixed with NPH human insulin.
If Apidra® is mixed with NPH human insulin, Apidra® should be drawn into the syringe first. Injection should be made immediately after mixing.
Mixtures should not be administered intravenously.

• Continuous subcutaneous infusion pump
Apidra® may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion.Patients using CSII should 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. These instructions may differ from general pump manual instructions. It is important that patients follow the Apidra® specific instructions when using Apidra®. Failure to follow Apidra® specific instructions may lead to serious adverse events.

When used with an insulin infusion pump or intravenously, Apidra® should not be mixed with diluents or any other insulin.

Patients administering Apidra® by CSII must have an alternative insulin delivery system available in case of pump system failure (See Precautions).

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Precautions
Because of the short duration of action of Apidra®, patients with diabetes also require a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.
Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.
Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

- ***Hypoglycaemia***

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Under certain conditions, as with all insulins, the warning symptoms of hypoglycaemia may be changed, less pronounced or absent, for example:
- if glycaemic control is markedly improved
- if hypoglycaemia is developing gradually
- in elderly patients
- where an autonomic neuropathy is present
- in patients with a long history of diabetes
- in patients receiving concurrent treatment with certain drugs (see interactions)

Such situations may result in severe hypoglycaemia (and possibly, loss of consciousness) prior to the patient's awareness of hypoglycaemia.

- ***Renal Impairment***

The requirements for Apidra®, as with all insulins, may be reduced in patients with renal impairment.

- ***Hepatic Impairment***

In patients with hepatic impairment, insulin requirements may be diminished due to a reduced capacity for gluconeogenesis and reduced insulin metabolism.

Pens to be used with Apidra® cartridges

The Apidra® cartridges should only be used with AllStar® which delivers Apidra® in 1unit dose increments.These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the above listed pen.

Continuous subcutaneous infusion pump
Malfunction of the insulin pump or infusion set or handling errors can rapidly lead to hyperglycaemia, ketosis and diabetic ketoacidosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis or diabetic ketoacidosis is necessary.
Interim subcutaneous injections with Apidra® may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin delivery system available (see Administration).

Interactions
A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include: corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine, salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

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

In addition, under the influence of sympatholytic medicinal products such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

Pregnancy
There are no well-controlled clinical studies of the use of Apidra® in pregnant women.

A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin glulisine indicates no safety issues in use of insulin glulisine during pregnancy or on the foetus and newborn child.

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

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

Lactation
It is unknown whether Apidra® is excreted in human milk. Lactating women may require adjustments in insulin dose and diet.

Driving a Vehicle or Performing other Hazardous Tasks
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

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

Hypoglycaemia, in general, the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

Local allergy in patients occasionally occurs as redness, swelling and itching at the site of insulin injection. These reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic allergic reactions to insulin (including insulin glulisine) may, for example, be associated with rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised allergy, including anaphylactic reaction, may be life threatening.

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

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

Overdose

Signs and Symptoms
Hypoglycaemia may occur as a result of an excess of insulin relative to food intake, energy exposure or both.

Management
Mild/moderate episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dosage of the medicinal product, meal patterns, or physical activity may be needed.

Severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

Abuse and Dependence
No risk of abuse or dependence is likely to occur with Apidra®.

Storage Conditions
Unopened Vial/Cartridge/ Solostar®:
Unopened Apidra® vials, cartridges, or Solostar® should be stored in a refrigerator, 2°C - 8°C (36°F - 46°F). Apidra® should not be stored in the freezer and it should not be allowed to freeze. Discard if frozen.

Open (In Use) Vial/Cartridge/ / Solostar®::
Opened Apidra® vials, cartridges, or Solostar®, whether or not refrigerated, must be used within 28 days. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial,

cartridges, or Solostar® in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C (77°F). Once a cartridge is placed in a pen, it **must not** be put in a refrigerator.

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 (98.6°F).

Intravenous use:
Infusion bags prepared as indicated in the section below are stable at room temperature for 48 hours.

Shelf life
Refer outer carton
Once in use, the vial, cartridge, or Solostar® may be kept for up to four weeks. This applies irrespective of whether it is immediately used or is first carried as a spare for a while.

Preparation and Handling
General
Before first use, Apidra® must be kept at room temperature for 1 to 2 hours. 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.
The instructions/manuals for using the Apidra® in a pump or in the pens must be followed carefully.
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.

Cartridges
Apidra® cartridges are not designed to allow any other insulin to be mixed in the cartridge.
If the AllStar® malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 IU/ml) and injected.

Intravenous use
For intravenous use, Apidra® should be used at a concentration of 1 unit/mL insulin glulisine in infusion systems with the infusion fluid sterile 0.9% sodium chloride solution using PolyVinyl Chloride (PVC) infusion bags with a dedicated infusion line.
After dilution for intravenous use the solution should be inspected before use visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use the solution if it has become cloudy or contains particles; use it only if it is clear and colorless.

Apidra® was found to be incompatible with Dextrose solution and Ringers solution and, therefore, can not be used with these solution fluids. The use of other solutions has not been studied.

Handling of the Pens (Solostar®, AllStar®)
For detailed instructions on handling of the pen refer to the manual.

Manufactured by:
Sanofi-Aventis Deutschland GmbH
65926,Frankfurt am Main,Germany

Importer :
Sanofi India Ltd.
Gala No.3,4,5,6B &6C,7F, City Link Warehousing Complex,
Village Vadape, Bhiwandi, Thane - 421302.

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