

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

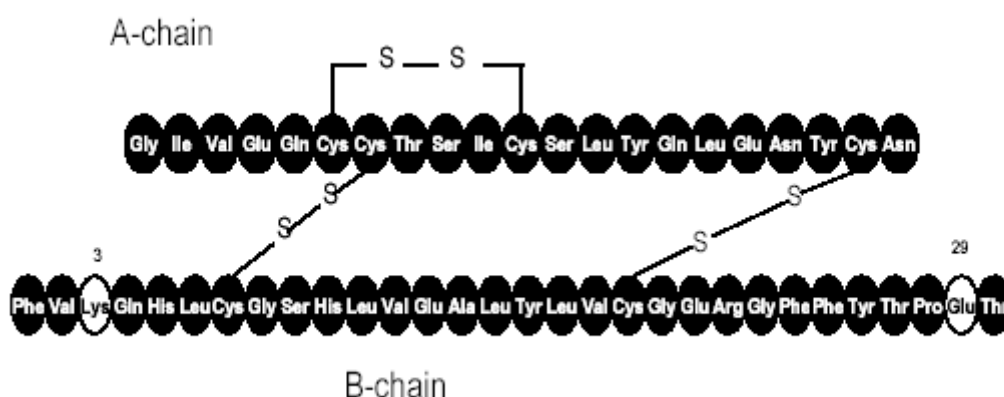
Active Ingredient

Insulin glulisine

Recombinant human insulin analogue.

Chemically, it is 3^B-lysine-29^B-glutamic acid-human insulin

Empirical formula C₂₅₈H₃₈₄N₆₄O₇₈S₆



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 subcutaneous injection within 15 minutes before or within 20 minutes after starting 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 \geq 6 years of age. Administration to children $<$ 6 years has not been studied.

Elderly

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

Hepatic impairment

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

Renal impairment

In patients with renal impairment, insulin requirements may be diminished (see Warnings/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) must be rotated from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis (see Sections Warnings/Precautions and Adverse reactions).

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 Warnings/Precautions).

Contraindications

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

Warnings/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.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized cutaneous amyloidosis. 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 Section Adverse reactions).

- ***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 1 unit 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.

Skin and subcutaneous tissue disorders

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Localized cutaneous amyloidosis at the injection site has occurred with insulins. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see Section Warnings/Precautions).

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 Vadpe, Bhiwandi, Thane - 421302.

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APIDRA® SOLOSTAR®

Instruction Leaflet

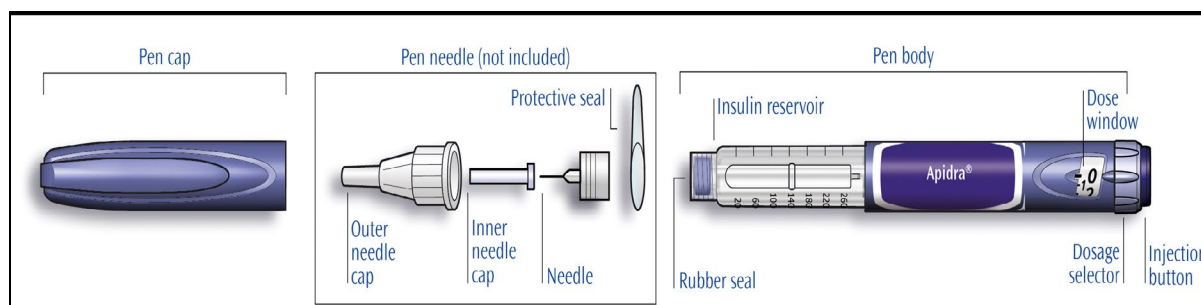
Solostar® is a prefilled pen for the injection of insulin. Your healthcare provider has decided that Solostar® is appropriate for you, based on your ability to handle SoloStar®. Talk with your healthcare provider about proper injection technique before using Solostar®.

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. 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.

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

Keep this leaflet for future reference.

If you have any questions about Solostar® or about diabetes, ask your healthcare provider.



Important information for use of Solostar®:

- Always attach a new needle before each use. Only use needles that have been approved for use with Solostar®
- 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).
- This pen is only for your use. Do not share it with anyone else.
- 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.

Step 1. Check the insulin

A. Check the label on your Solostar® to make sure you have the correct insulin. Apidra® SoloStar® is blue. It has a dark blue injection button with a raised ring on the top.

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.

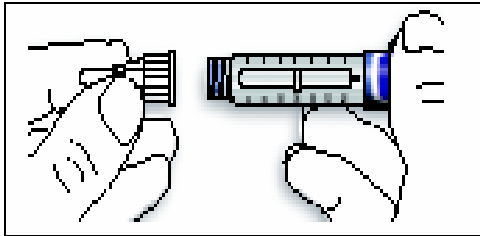
Before use of needle, carefully read the “Instructions for Use” accompanying the needles.

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

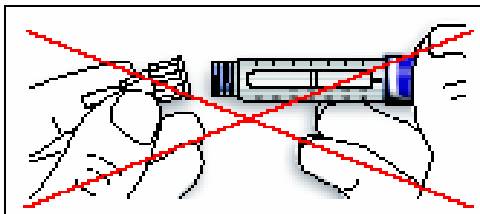
Wipe the Rubber Seal with alcohol.

A. Remove the protective seal from a new needle.

B. 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.

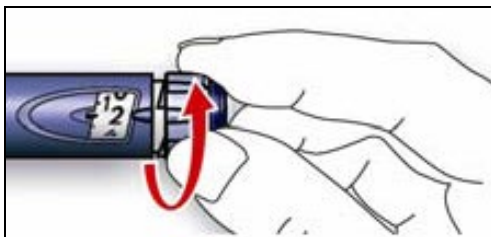


Step 3. Perform a safety test

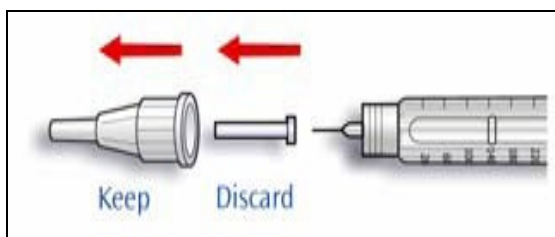
Always perform the safety test before each injection. This ensures that you get an accurate dose by:

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

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

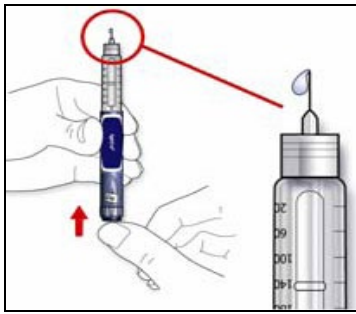


B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



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®.

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.

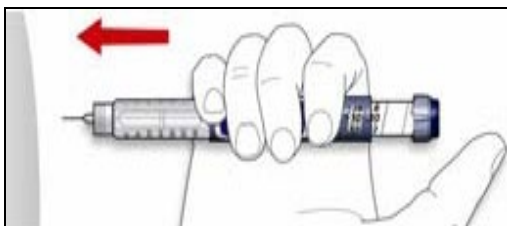
- A. Check that the dose window shows “0” following the safety test.
- B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



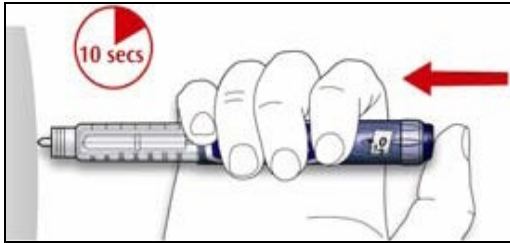
- ◆ Do not push the injection button while turning, as insulin will come out.
- ◆ You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new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

Step 5. Inject the dose

- A. Use the injection method as instructed by your healthcare professional.
- B. Insert the needle into the skin.



- C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to “0” as you inject.



D. 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 have 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.

- ◆ 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 healthcare provider) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely

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

Storage Instructions

Please check the leaflet of insulin for instructions on how to store Solostar®.

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.

Keep Solostar out of the reach and sight of children.

Keep your Solostar® in cool storage (between +2°C and +8°C) until first use (e.g., in a refrigerator). Do not allow it to freeze. Do not put it next to the freezer compartment of your refrigerator or next to the freezer pack.

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 can be safely kept at room temperature up to 25°C and must not be stored in the refrigerator. Do not use it after this time.

Do not use Solostar® after the expiration date printed on the label of the pen or on the carton.

Protect Solostar® from light.

Discard your used Solostar® as required by regulations.

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.

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

Importer: Sanofi India Ltd., City Link Warehousing Complex, Vadpe, Bhiwandi, Thane.

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