SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

APIDRA® solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 1 mL contains:

- 3,5 mg insulin glulisine, corresponding to 100 units insulin
- Preservative: metacresol 0,3 % *m/v*.

Each cartridge or pre-filled pen contains 3 mL, equivalent to 300 units insulin.

Each vial contains 10 mL equivalent to 1 000 units insulin.

Sugar free.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

A clear colourless solution for injection in vials, cartridges (to be used with re-usable pens) or a pre-filled disposable pen.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

For the treatment of adults, adolescents and children of 4 years and older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration:

APIDRA should be given by injection within 15 minutes before or immediately after a meal.

The dosage of APIDRA should be individualised and determined based on the healthcare professional 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.

Paediatric use: Safety and efficacy of APIDRA have been demonstrated in adolescents and children > 4 years of age.

Geriatric use: Hypoglycaemia may be difficult to recognise in the elderly (see section 4.4).

Special populations: In patients with hepatic or renal impairment, insulin requirements may be diminished (see section 4.4).

Administration:

APIDRA is intended for subcutaneous administration by injection or by continuous pump infusion.

APIDRA can also be administered intravenously.

APIDRA should be administered subcutaneously by injection in the abdominal wall, the thigh or deltoid or by continuous infusion in the abdominal wall. 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 cutaneous amyloidosis (see section 4.4 and 4.8).

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

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 water-like consistency. The instructions/manuals for using APIDRA in a pump or in a disposable or reusable pen must be followed carefully. An empty vial, cartridge or disposable pen must never be reused and must be properly discarded.
See section 6.6 for further detail on handling.

Cartridges:

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

If the reusable pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for insulin with 100 I.U./mL) and injected. Air bubbles must be removed from the cartridge before injecting.
APIDRA in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.

Intravenous use:

For intravenous use, APIDRA should be diluted (see section 6.6). See section 6.2 for incompatibilities.

Disposable pens:

APIDRA in disposable pens is only suitable for subcutaneous injections. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used. See section 6.6 for further detail on handling.

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 (see section 6.4). 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, APIDRA must 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 section 4.4).

4.3 Contraindications:

- Patients hypersensitive to insulin glulisine or any of its excipients (see section 4.2)
- Children < 4 years, as in this group, efficacy and safety have not been demonstrated.

4.4 Special warnings and precautions for use:

Because of the short duration of action of APIDRA, patients with diabetes also require a longer-acting insulin 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, neutral protamine Hagedorn (NPH), analogues), species (animal, human) or method of manufacture (rDNA versus animal-source insulin), may result in the need for a change of 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.

Skin changes at the injection site:

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 4.8).

Hypoglycaemia: The time and 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 the warning symptoms of hypoglycaemia may be changed, less pronounced or absent, for example:

- if glycaemic control is markedly improved
- if hypoglycaemia develops 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 medicinal products (see section 4.5).

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 may be reduced in patients with renal impairment (see section 5.1).

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

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 in case of pump system failure (see section 4.2).

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

APIDRA in a cartridge:
APIDRA in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used (see section 4.2).

APIDRA in a disposable pre-filled pen (Solostar):
APIDRA in a disposable pen is only suitable for subcutaneous injections. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used (see section

4.2). Before using the pre-filled pen, the instructions for use included in the package leaflet must be read carefully (see section 6.6).

Excipients

APIDRA contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

APIDRA contains the preservative metacresol, which may cause allergic reactions.

Combination of APIDRA with pioglitazone:

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and APIDRA is considered.

If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interactions with other medicines and other forms of interaction:

A number of substances affect glucose metabolism and may require dose adjustment of APIDRA.

Substances that may enhance the blood glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicines; angiotensin converting enzyme (ACE) inhibitors; disopyramide; fibrates; fluoxetine; monoamine oxidase (MAO) inhibitors; pentoxifylline; salicylates and sulfonamide antibiotics.

Substances that may reduce the blood glucose-lowering effect include: corticosteroids; danazol; diazoxide; diuretics; glucagon; isoniazid; estrogens and progestogens (e.g. in oral contraceptives); phenothiazine derivatives; somatropin; sympathomimetic medicines (e.g. epinephrine (adrenaline), salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (e.g. 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 beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety and efficacy in pregnancy have not been established.

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.

Breastfeeding:

It is unknown whether APIDRA is excreted in human milk.

Lactating women may require adjustments in insulin dose and diet.

4.7 Effects on the ability to drive and use machines:

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.

4.8 Undesirable effects:

The following frequency rating has been used:

Very common: (≥ 1/10); Common: (≥ 1/100, < 1/10); Uncommon: (≥ 1/1000, < 1/100); Rare: (≥ 1/10 000, < 1/1000); Very rare: (< 1/10 000), including rare isolated cases.

Metabolism and nutrition disorders

Very common: Hypoglycaemia

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

Skin and subcutaneous tissue disorders

Common: Injection site reactions and local hypersensitivity reactions

Local hypersensitivity reactions (redness, swelling and itching at the site of the APIDRA 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 APIDRA, such as irritants in a skin cleansing agent or poor injection technique.

Rare: Lipodystrophy

Lipodystrophy may occur at the injection site and delay APIDRA absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Uncommon: Systemic allergic reactions

Such reactions to APIDRA 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.

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

Post-marketing side effects:

Skin and subcutaneous tissue disorders:

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: Email: za.drugsafety@sanofi.com or Tel: 011 256-3700, or

SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms:

Hypoglycaemia may occur as a result of an excess of APIDRA 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 APIDRA, 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.

5. PHARMACOLOGICAL PROPERTIES:

A 21.1 Insulin preparations.

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting.

ATC code: A10AB06

5.1 Pharmacodynamic properties:

Insulin glulisine is a rapid-acting recombinant [~~human~~] insulin analogue. Insulin glulisine is produced by recombinant DNA technology utilising *Escherichia coli* (K12 strain).

Insulin lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Intravenous use: Insulin glulisine and regular human insulin have equipotent glucose lowering activity when administered by the intravenous route. Two phase I studies evaluated intravenous administration. Insulin glulisine was demonstrated to be safe and well tolerated.

5.2 Pharmacokinetic properties:

Absorption and bioavailability: Pharmacokinetic profiles in healthy volunteers and diabetes patients (Type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with peak concentration approximately twice as high, compared to regular insulin. Bioavailability following abdominal subcutaneous injection is 73 %.

Distribution and elimination: Following intravenous injection, the apparent volume of distribution is 13 L. The elimination half-life is 13 + 1,3 minutes.

Special Populations:

Paediatric Patients: The pharmacokinetics and pharmacodynamics of insulin glulisine in paediatric patients aged 7 – 16 years, with Type 1 diabetes, were similar to those in healthy adult subjects and adults with Type 1 diabetes.

Race and Gender: Information on the effect of race and gender on pharmacokinetics of insulin glulisine is not available. However, in phase III clinical trials in adults, subgroup analyses based on gender did not show differences in safety and efficacy.

Renal Impairment: In a study performed in 24 non-diabetic subjects covering a wide range of renal function [CrCl > 80 mL/min; 30 - 50 mL/min; < 30 mL/min], the pharmacokinetic properties of insulin glulisine were generally maintained (refer to section 4.4).

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of insulin glulisine has not been studied. However, some studies with insulin have shown increased circulating levels of insulin in patients with liver failure.

Pregnancy: The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glulisine has not been studied.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Hydrochloric acid (for pH adjustment)

Metacresol 0,3 % *m/v (as preservative)*

Polysorbate 20

Sodium chloride

Sodium hydroxide (for pH adjustment)

Trometamol

Water for injection.

6.2 Incompatibilities:

APIDRA was found to be incompatible with dextrose solution and Ringer's solution and therefore, cannot be used with these solution fluids. The use of other solutions has not been studied.

When used with an insulin infusion pump, APIDRA must not be mixed with diluents or any other insulin.

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Protect vial, cartridge and disposable pen from light. Keep in the carton until required for used.

Unopened vial/cartridge/disposable pen:

Store in a refrigerator, between 2 °C and 8 °C. Do not store in a freezer and it should not be allowed to freeze. Discard if frozen.

Open (in-use) vial/cartridge/disposable pen:

Once in use vials, cartridges and disposable pens must be used within 28 days. This applies irrespective of whether it is immediately used or if first carried as a spare for a while. They must be discarded if not used within 28 days. Once in-use, the vial, cartridge or disposable pen may be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature does not exceed 25 °C. Once in use, the reusable pen containing a cartridge must not be stored in the refrigerator.

Infusion sets:

Infusion sets (reservoirs, tubing and catheters) and the APIDRA in the reservoir must be discarded after no more than 2 days (48 hours) of use or after exposure to temperatures that exceed 37 °C.

Intravenous use:

Infusion bags prepared as indicated under section 6.6 - ***Preparation and handling*** are stable at room temperature for 48 hours.

6.5 Nature and contents of container:

Packs containing 5 x 3 mL cartridges (type I colourless glass) with a plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (bromobutyl rubber); containing 3 mL of solution. Cartridges to be used in conjunction with a reusable pen.

Packs containing 5 x disposable pre-filled pens. Each pen contains 3 mL solution in a cartridge (colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). The cartridge is sealed in a disposable pre-filled pen.

Packs containing 1 x 10 mL vial (type I colourless glass) with a stopper (flanged aluminium overseal, chlorobutyl rubber) and a polypropylene tear-ff cap[1]; containing 10 mL of solution.

6.6 Special precautions for disposal and other handling:

Inspect the vial before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Since Apidra is a solution, it does not require resuspension before use. Insulin label must always be checked before each injection to avoid medication errors between insulin glulisine and other insulins (see section 4.4). See section 6.4 for storage of APIDRA that is open and in-use.

Cartridges:

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

APIDRA in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.

Vials:

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

Intravenous use:

For intravenous use, APIDRA should be used at a concentration of 1 I.U./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 visually inspected for particulate matter and discolouration 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 colourless.
See section 6.3 for storage of the diluted solution.

When used intravenously, APIDRA must not be mixed with diluents (except 0,9 % sodium chloride), or any other insulin.
See section 6.2 for incompatibilities.

Handling of disposable and reusable pens:

For detailed instructions on handling of the pens, refer to the manuals for each pen.

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.

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

Continuous subcutaneous infusion pump:

See section 4.2 and 4.4 for advice.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand

1685

South Africa

011 256 3700

8. REGISTRATION NUMBERS:

A38/21.1/0506

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Registration date: 17 February 2006

10. DATE OF REVISION OF THE TEXT:

10 December 2022

NAMIBIA:

Scheduling status: NS1

Registration No.: 11/20.1/0091

Botswana:

Scheduling status: NS2

Registration No.: BOT1402589A (cartridge)

Registration No.: BOT1402589B (vial)

Registration No.: BOT1402589C (Solostar)