PATIENT INFORMATION LEAFLET:

SCHEDULING STATUS:

S3

APIDRA® 100 IU/mL solution for injection:

The active substance is insulin glulisine

Preservative: metacresol 0,3 % *m/v*.

Sugar free.

Read all of this leaflet carefully before you or your child start using APIDRA:

- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or ~~[your~~] pharmacist, nurse or other health care provider
- APIDRA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR:

APIDRA is an antidiabetic medicine, used to reduce high blood sugar in patients with diabetes mellitus.

2. WHAT YOU NEED TO KNOW BEFORE YOU OR YOUR CHILD USE OR RECEIVE APIDRA:

Do not use APIDRA:

- If you or your child is hypersensitive (allergic) to insulin glulisine or to any of the other ingredients of APIDRA (see WHAT APIDRA CONTAINS)
- If your child is under 4 years of age
- If you or your child has symptoms suggestive of low blood sugar (hypoglycaemia).

Warnings and precautions:

Please follow the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor closely.

Special patient groups:

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

Skin changes at the injection site:

If you develop skin changes at the injection site. 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 use APIDRA). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel:

Before travelling consult you or your child's doctor. You may need to talk about:

- the availability of your insulin in the country you are visiting
- supplies of insulin, syringes etc.
- correct storage of your insulin while travelling
- timing of meals and insulin administration while travelling
- the possible effects of changing to different time zones
- possible new health risks in the countries to be visited.

Illnesses and injuries:

- If you or your child is ill or has a major injury then your blood sugar may increase (hyperglycaemia).
- If you or your child is not eating enough your blood sugar may become too low (hypoglycaemia).

In such situations, the management of diabetes may require a lot of care. **Make sure that you contact a doctor immediately.**

Do not stop insulin and continue to take enough carbohydrates. Always tell people who are caring for or treating you or your child that you are using/receiving insulin.

Combination of APIDRA with pioglitazone:

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin (such as APIDRA) experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and APIDRA:

If you or your child are taking medicines on a regular basis, concomitant use of APIDRA may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice.

Some medicines cause the blood sugar level to fall, some cause it to rise, while others may have both effects, depending on the situation. In each case, it may be necessary to adjust your or your child's insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it. Tell your doctor about all medicines that you or your child is taking, including those you have bought without a prescription and complementary or traditional medicines. Before taking a medicine ask you or your child's doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause you or your child's blood sugar to fall include:
All other medicine for the treatment of diabetes; angiotensin converting enzyme (ACE) inhibitors; disopyramide; fluoxetine; fibrates; monoamine oxidase (MAO) inhibitors; pentoxifylline; salicylates and sulfonamide antibiotics.

Medicines that may cause you or your child's blood sugar to rise include:
Corticosteroids (cortisone); danazol; diazoxide; diuretics; glucagon; isoniazid; [o]estrogens and progestogens (e.g. in the contraceptive pill); phenothiazine derivatives; somatropin; sympathomimetic medicines (e.g. epinephrine (adrenalin); salbutamol; terbutaline); thyroid hormones; protease inhibitors and atypical antipsychotic medications (e.g. clozapine).

You or your child's blood sugar level may either rise or fall if you take:

Beta-blockers; clonidine; lithium salts or drink alcohol.

Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

Beta-blockers, like other sympatholytic medicines (e.g. clonidine, guanethidine and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you or your child's [~~are~~] is taking one of those medicines ask your doctor or pharmacist.

APIDRA with food and drink and alcohol:

If you or your child's has insulin-dependent diabetes (Type I), your doctor will prescribe both insulin and a personalised meal plan for you. It is very important that you or your child carefully follow your meal plan.

Pregnancy and breastfeeding and fertility:

Pregnancy:

If you are pregnant or breastfeeding your baby while using APIDRA please consult your doctor, pharmacist or other healthcare professional for advice.

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control

of your diabetes and prevention of hypoglycaemia, is important for the health of your baby.

There is no adequate data for the use of APIDRA in pregnant women.

If you are breastfeeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines:

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:

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

Important information about some of the ingredients of APIDRA:

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

APIDRA contains metacresol, which may cause allergic reaction.

3. HOW TO USE APIDRA:

Do not share medicines prescribed for you or your child with any other person.

Always use APIDRA exactly as you or your child's doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

APIDRA should be given by injection shortly (0 - 15 minutes) before or soon after meals.

Based on your life-style and the results of blood sugar (glucose) tests and you or your child's previous insulin usage, your doctor will determine how much APIDRA you or your child will need.

APIDRA is a short-acting insulin. You or your child's doctor may tell you to use it in combination with a longer-acting insulin or a basal insulin or with tablets for high blood sugar.
If you or your child switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You or your child should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. Refer to the section on side effects for further information.
APIDRA is injected under the skin, subcutaneously.
APIDRA can also be administered intravenously, but this should be carried out by healthcare professionals.

You or your child's doctor will advise you in which area of the skin you should inject APIDRA.

How to inject APIDRA:

- Inject APIDRA into the front of the waist (abdomen), the front of the thigh or upper arm. You will feel the effect slightly quicker if the insulin is injected into your abdomen
- Change the place within the area you inject each day. This will reduce the risk of skin shrinking or thickening or lumps at the site (see section 4)
- **Do not** use the exact same spot for each injection
- **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.

How to handle the vial/cartridge:

Look at the vial/cartridge before you use it. **Always check the label before each injection to prevent mix-ups.** Only use it if the solution is clear, colourless and has no visible particles in it. APIDRA is a solution and does not require shaking or mixing before use.

APIDRA cartridges are for use with reusable insulin pens. Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instructions for using pen). The instructions for using the pen must be followed carefully. Empty cartridges must not be refilled. If the pen malfunctions, the solution may be drawn from the cartridge into a syringe suitable for an insulin with 100 I.U./mL and injected.

APIDRA cartridges for use in a reusable pen and included in pre-filled disposable pens is only suitable for subcutaneous injections. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.

How to handle an infusion pump system:

Before using APIDRA in the pump system you should have been given detailed instructions on how to use the pump system. In addition, you or your child should have been provided with information about what to do if you become ill or if your blood sugar levels get too high or too low, of if the pump system fails.

Use the pump system recommended by your or your child's doctor. Read and follow the instructions that come with your insulin infusion pump. Follow your doctor's instructions about the basal infusion rate and the mealtime insulin boluses to be taken. Measure your blood sugar level regularly to make sure you get the benefit of the insulin infusion and to make sure that the pump is working properly.

Change the infusion set and reservoir at least every 48 hours using aseptic technique. These instructions may differ from the instructions that come with your insulin infusion pump. When you use APIDRA in the pump system, it is important that you always follow these specific instructions. Failure to follow these specific instructions may lead to serious side effects.

APIDRA must never be mixed with diluents or any other insulin when used in a pump.

What to do if the pump system fails or when the pump is used incorrectly:

Pump or infusion set problems or using the pump incorrectly can result in you or your child not getting enough insulin. This can quickly cause you or your child to have high blood sugar and diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar).

If you or your child's blood sugar level starts to rise, contact your doctor, pharmacist or healthcare professional as soon as possible. They will tell you what needs to be done.

You or your child may need to use APIDRA with syringes or pens. You should always have an alternative insulin delivery system available for injection under the skin in case the pump system fails.

Mistakes in dosage:

Please discuss in advance with your doctor what you should do if you or your child inject too much APIDRA, if you miss a dose or if you inject too low a dose.

If you inject or your child received more APIDRA than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison centre. If you have injected too much APIDRA, you may

develop hypoglycaemia (low blood sugar). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, refer to the section on side effects.

If you or your child forget to inject APIDRA:

If you or your child have missed a dose or if you have injected or received too low a dose, your blood sugar level may become too high. Check you or your child's blood sugar frequently. Refer to the section on side effects for further information on hyperglycaemia.

Effects when treatment with APIDRA is stopped:

If you or your child stop using/receiving APIDRA, it could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop treatment without consulting your or your child's doctor or pharmacist, who will tell you what needs to be done.

If you or your child have the impression that the effect of APIDRA is too strong or too weak, tell your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS:

APIDRA can have side effects.

Not all side effects reported for APIDRA are included in this leaflet. Should you or your child's general health worsen while using APIDRA, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop using APIDRA and tell you or your child's doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing
- Rash or itching
- Fainting
- Yellowing of the skin and eyes, also called jaundice.

These are all very serious side effects. If you or your child have them, you may have had a serious allergic reaction to APIDRA. You may need urgent medical attention or hospitalisation.

Tell you or your child's doctor immediately or go to the casualty department at your nearest hospital if you notice the following:

- Too low blood sugar levels (hypoglycaemia).

This is a serious side effect. You or your child may need urgent medical attention.

Too low blood sugar levels (hypoglycaemia):

If you or your child's blood sugar level falls too much, you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You or your child should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions.

Symptoms of low blood sugar may be masked by certain medicines such as beta-blockers.

Warning symptoms of hypoglycaemia (low blood sugar levels):

Symptoms that tell you that you or your child's blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heartbeat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: Headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you or your child to hypoglycaemia ("warning symptoms") may change, be less obvious or may possibly be missing if:

- you are elderly, if you have had diabetes for a long time or if you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy)
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly
- you have almost normal or, at least, greatly improved blood sugar levels
- you are taking or have taken certain other medicines.

In such a case, you or your child may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your

warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. as glucose, sugar cubes or a sugar-sweetened beverage. Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising you or your child's blood sugar (e.g. bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

It is advisable to test you or your child's blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Always carry some sugar (at least 20 grams) or glucose tablets with you. Carry some information (MedicAlert) with you to show you are diabetic.

If you or your child are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar).

Too high blood sugar levels (hyperglycaemia):

If you or your child's blood sugar level is too high, this tells you that you or your child may have needed more insulin than you injected or received. For more information on signs and symptoms of hyperglycaemia refer to the end of section 4.

Tell your or your child's doctor as soon as possible if you notice any of the following:
Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Skin changes at the injection site:
If you or your child inject/receive your insulin too often at the same place, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (localized cutaneous amyloidosis). Insulin that you or your child inject into such a lumpy area may not work very well. Change the place within the area you inject with each injection to help to prevent such skin changes.

If you or your child's blood sugar is too high (hyperglycaemia):
You or your child's blood sugar level may be too high if, for example:

- you have not injected/received your insulin or not injected/received enough, or if it has become less effective, e.g. through incorrect storage
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, illness with fever or certain other diseases
- you are taking or have taken certain other medicines.

Warning symptoms of hyperglycaemia (high blood sugar levels):

Thirst, increased need to pass water, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heartbeat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin. Test you or your child's blood sugar level and your urine for ketones as soon as any such symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, usually in a hospital.

If you or your child notices any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects:

If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can report side effects directly to Sanofi's Pharmacovigilance Unit at Email: za.drugsafety@sanofi.com or Tel: 011 256 3700 or

You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

By reporting side effects, you can help provide more information on the safety of APIDRA.

5. HOW TO STORE APIDRA:

Store all medicines out of reach of children.

Store APIDRA at 2 °C to 8 °C in a refrigerator (not too near the freezer compartment).

Do not freeze. If frozen then throw away.

Once in use, vials or cartridges must be used within 28 days.

They must be discarded if not used within 28 days.

With infusion pumps, the 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.

Once a cartridge is placed in a reusable pen, the pen must not be put in a refrigerator.

In order to protect from light, keep the cartridges and vials in the outer carton.
Do not use after the expiry date stated on the label and carton.
Do not use APIDRA if it does not appear clear and colourless.
An empty vial or cartridge must NEVER be reused and must be properly discarded.

6. CONTENTS OF THE PACK AND OTHER INFORMATION:

What APIDRA contains:

Each mL of the solution contains 3,5 mg insulin glulisine, corresponding to 100 I.U. human insulin.
Each cartridge contains 3 mL of solution, equivalent to 300 I.U. insulin.
Each vial contains 10 mL of solution equivalent to 1 000 I.U. insulin.

The other ingredients are: hydrochloric acid (for pH adjustment)
metacresol 0,3 % *m/v (as preservative),* polysorbate 20, sodium chloride, sodium hydroxide (for pH adjustment), trometamol and water for injection.

What APIDRA looks like and contents of the pack:

A clear, colourless aqueous solution for injection in a colourless glass cartridge or vial.

Packs containing 5 x 3 mL cartridges containing 3 mL of solution, to be used in conjunction with a reusable pen.

Packs containing 5 x disposable pens. Each pen contains 3 mL cartridge containing 3 mL of solution.

Packs containing 1 x 10 mL vial containing 10 mL of solution.

Holder of Certificate of Registration:

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