PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Apidra

SANOFI

Solution for injection 100 U/ML
in 10 ml vials

The active ingredient and its quantity: each 1 ml contains: 100 Units of insulin glulisine.

Inactive ingredients - see section 2 and section 6.

Read this leaflet carefully in its entirety before using the medicine.

Keep this leaflet. You may need to read it again.

This leaflet contains concise information about the medicine.

If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

If a side effect worsens or if a side effect not mentioned in this leaflet occurs, please refer to a doctor or pharmacist.

1. WHAT IS THE MEDICINE INTENDED FOR?

Apidra is an antidiabetic preparation, used to reduce the blood sugar levels in patients with diabetes mellitus; it is used to treat adults, adolescents and children, 6 years of age and older.

Diabetes mellitus is a disease in which the body does not produce enough insulin to control the levels of blood sugar.

The preparation is produced using biotechnological techniques. It has a rapid onset, within 10-20 minutes, and acts for a short time - about 4 hours.

Therapeutic group: Medicines to treat diabetes, rapid-acting insulins and analog injectables.

2. BEFORE USING THE MEDICINE

Do not use the medicine:

- If you have a known sensitivity to insulin glulisine or to any of the additional ingredients contained in the medicine (see section 6).
- In case of hypoglycemia (blood sugar level that is too low), act as per the information at the end of the leaflet regarding hypoglycemia.

Special warnings regarding use of the medicine:
Talk with the doctor or pharmacist before commencing treatment with the medicine.

Strictly follow the instructions regarding dosage, monitoring (blood tests), diet and physical activity (physical work or exercise) that you were given by the doctor.

Before treatment with Apidra, inform the doctor if:
You are suffering, or have suffered in the past, from impaired function of: the liver, the kidney (you may need a lower dosage).

There are insufficient clinical data regarding use of Apidra in children below 6 years of age.

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 section 3 "How should you use the medicine?).

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.

Traveling
Before traveling, consult with your 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 insulin while traveling,
- timing of meals and insulin administration while traveling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you do not feel well or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require extra treatment:
- If you are ill or are suffering from a major injury - your blood sugar level may increase (hyperglycemia).
- If you do not eat enough - your blood sugar level may become too low (hypoglycemia).
  In most cases, you will need a doctor. **Make sure to contact a doctor early.**

If you have type 1 diabetes (insulin-dependent diabetes mellitus), do not stop your insulin and continue to consume enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

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

Drug interactions:
Some medicines can cause a change in your blood sugar level (decrease, increase or both, depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

If you are taking, or have recently taken, other medicines, including nonprescription medicines and nutritional supplements, inform the doctor or pharmacist.

Before taking a medicine ask the doctor if it can affect your blood sugar level and what action, if any, you need to take.

It is particularly important to inform the doctor or pharmacist if you are taking:

Medicines that may cause your blood sugar level to fall (hypoglycemia) include:
- other antidiabetic medicines,
- ACE enzyme inhibitors (to treat certain heart diseases or high blood pressure),
- disopyramide (to treat certain heart diseases),
- fluoxetine (to treat depression),
- fibrates (to lower high blood lipid levels),
- MAO enzyme inhibitors (to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycemia) include:
- corticosteroids (such as "cortisone", to treat inflammation),
- danazol (a medicine acting on ovulation),
- diazoxide (to treat high blood pressure),
- diuretics (to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone, used to treat severe hypoglycemia),
- isoniazid (to treat tuberculosis),
- estrogens and progestogens (present in contraceptive pills),
- phenothiazines (to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], or terbutaline, salbutamol, to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- new-generation antipsychotics (atypical) (such as olanzapine and clozapine),
- protease inhibitors (used to treat HIV).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (to treat high blood pressure),
- clonidine (to treat high blood pressure),
- lithium salts (to treat psychiatric disorders).

Pentamidine (to treat some infections caused by parasites) may cause hypoglycemia which may sometimes later develop into hyperglycemia.

Beta-blockers, like other sympathomimetic medicines (such as guanethidine, clonidine, reserpine) may reduce or entirely suppress the first warning signs which help you to recognize hypoglycemia.

If you are not sure whether you are taking one of these medicines, ask your doctor or pharmacist.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant, or are planning a pregnancy, consult the doctor before using Apidra.

Tell your doctor if you are planning a pregnancy or if you are already pregnant. Your insulin dosage may be different during pregnancy and after delivery. Strict control of your diabetes and prevention of hypoglycemia are important for your baby's health.

There are insufficient data regarding use of Apidra in pregnant women.

If you are breastfeeding, consult your doctor, as you may require a change in your insulin dosage and diet.

Use of the medicine and alcohol consumption
The sugar levels in your blood may rise or decline if you drink alcohol.

Driving and operating machines
Your ability to concentrate or react may be impaired if you experience hypoglycemia (low blood sugar levels) or hyperglycemia (high blood sugar levels).

Keep this in mind in all situations where you might put yourself and others at risk (such as driving or operating machines).

Consult the doctor regarding driving if:
- You have experienced frequent episodes of hypoglycemia;
- The first warning signs which help you to recognize hypoglycemia have become reduced or have disappeared.

Important information regarding some of the ingredients of the medicine
This medicine contains less than 1 mmol (23 mg) sodium per ml; namely, it is essentially "sodium-free".

Apidra contains metacresol
Apidra contains metacresol, which may cause allergic reactions.

3. HOW SHOULD YOU USE THE MEDICINE?

Dosage
Always use this preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

Based on your lifestyle and the results of your blood sugar (glucose) test and your previous insulin usage, the doctor will determine how much Apidra you need.

Apidra is a short-acting insulin. Your doctor may instruct you to use it in combination with an intermediate or long-acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your doctor may have to adjust your dosage accordingly.

Many factors may influence your blood sugar level. You should recognize these factors so that you will be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low.

See the explanation at the end of the leaflet for further information.

Method of administration
Apidra is injected subcutaneously.

Your doctor will show you into which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall (via an insulin pump).

The effect will be slightly quicker if the insulin is injected into the abdomen. As for all insulins, injection sites and infusion sites within an injection area (abdomen, thigh or upper arm) should be changed from one injection to the next to help prevent skin changes at the injection area (see section 2 "Before using the medicine" and section 4 "Side effects").

Frequency of administration
Apidra should be taken shortly (0-15 minutes) before or immediately after a meal.

Instructions for use
Diabetic patients must be skilled in self-injection of insulin, monitoring blood sugar levels and in identifying states of hypoglycemia (low blood sugar level) and hyperglycemia (high blood sugar level).

Make sure that the liquid of the preparation in the vial is clear, colorless and has no visible particles in it.

Do not shake or mix before use!

If you see that there is an unexplainable worsening in the control of your blood sugar levels - the insulin in the vial in use may have lost its potency - use a new vial.

If you think there is a problem with Apidra, consult the doctor or pharmacist.

• Use of a vial
Apidra vials is intended for use with disposable insulin syringes or with an insulin pump.

If you have to mix two types of insulin

Do not mix Apidra with any other medicine other than NPH human insulin.

If you have to mix Apidra with NPH human insulin, first draw up the Apidra with an insulin syringe. Inject immediately after mixing.

Use of disposable insulin syringes

In order to inject insulin, use a syringe that has a measuring scale in Units. Use of the wrong syringe may lead to misdosage and cause hypo- or hyperglycemia.
Be sure to use disposable syringes and needles and dispose of them properly after use.

Do not share syringes or needles with others. Use a new syringe and needle at each injection.

Instructions for drawing insulin into the syringe:

Do not dilute or mix Apidra with any solution or other insulin in the same syringe.

1. Wash your hands thoroughly.
2. When starting a new vial, remove the protective cover, but do not remove the rubber stopper and the metal ring under the cap.
3. Clean the rubber stopper with an alcohol swab.
4. Draw air into the insulin syringe, equal to the desired amount of insulin. Insert the syringe needle through the rubber stopper at the top of the insulin vial, inject the air into the vial.
5. Leave the syringe in the vial and turn the vial and the syringe upside down. Make sure that the tip of the needle is within the insulin fluid and draw out the proper amount into the syringe.
6. Before removing the needle from the vial, check the syringe for air bubbles, which can reduce the amount of insulin drawn out. If there are bubbles, hold the syringe upright and gently tap it until the bubbles float upwards. Use the syringe plunger to push the bubbles back into the vial; afterwards, slowly draw out the proper amount of insulin into the syringe again.
7. Remove the syringe needle from the rubber stopper. If you have to put the syringe down before injecting, cover the needle with its cover to protect it.

Instructions for injecting Apidra with a syringe:
1. Choose the injection area (thigh, abdomen or arm) as determined in coordination with your doctor.
   Each time, inject at a different point within the injection area that has been chosen.
2. Clean the injection area with an alcohol swab. Be sure that the injection area is dry before injecting.
3. Pinch up a wide bit of skin and hold it.
4. Insert the syringe needle into the skin and make sure that the entire needle is inside.
5. Slowly inject the contents of the syringe into the skin. Leave the needle in the skin for 10 seconds after completing the injection.
6. Pull the needle straight out, gently press the injection point with a cotton ball or gauze pad for a few seconds. Do not rub the injection site.

Use of an insulin pump

Before use of Apidra in a pump, you should receive comprehensive instructions for this use, as well as information about the measures to be taken in case of illness, too high or too low sugar level or failure of the pump. Use the type of pump recommended by your doctor. Read and follow the instructions provided with your insulin pump. Follow the doctor's instructions about the basal infusion rate and administration of a mealtime insulin bolus.

Measure your blood sugar level regularly to confirm that you obtain the optimal treatment from the insulin pump and that the pump is working properly.

Change the infusion set and reservoir at least every 48 hours using aseptic technique. This instruction may be different than that of the pump manufacturer. When you use Apidra in a pump, it is important to always follow these specific instructions; failure to follow these instructions may result in severe side effects.

Do not dilute or mix Apidra with any solution or other insulin when used in a pump.

What to do in case of a fault in, or improper use of, the pump

A problem with the pump or the infusion set or improper use of the pump may mean that you will not receive enough insulin. This can rapidly lead to a high blood sugar level and diabetic ketoacidosis (build-up of acid in the blood because the body breaks down fat instead of sugar).

If your blood sugar level begins to rise, contact the doctor/nurse/pharmacist immediately so they can tell you what to do.

You may need to use Apidra with syringes or injection pens. Be sure to always have another way of subcutaneously injecting Apidra, in case the pump breaks.

If you used more Apidra than necessary
If you injected too much Apidra, your blood sugar level may be too low (hypoglycemia).

Measure your blood sugar level regularly. In general, in order to prevent hypoglycemia, eat more food and monitor your blood sugar levels. See instructions about hypoglycemia at the end of the leaflet.

If you forgot to use Apidra
- If **you skipped an Apidra dose**, or if **you did not inject enough insulin**, your blood sugar level may be too high (hyperglycemia). Measure your blood sugar level regularly. See the instructions about hyperglycemia at the end of the leaflet.
- Do not inject a double dose to compensate for a missed dose.

If you stopped using Apidra
Discontinuation of use may cause severe hyperglycemia (very high blood sugar level) and ketoacidosis (accumulation of acid in the blood since the body breaks down fat instead of sugar).

Do not stop using Apidra without consulting the doctor, who will tell you what you should do.

Insulin mix-ups
Check the name of the preparation that appears on the label of the insulin, before each injection, to prevent mix-up between Apidra and other insulins.

Adhere to the treatment as recommended by the doctor. Even if there is an improvement in your health, do not discontinue treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take the medicine. Wear glasses if you need them.

If you have further questions regarding use of this medicine, consult a doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Apidra may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Severe side effects

Hypoglycemia (low blood sugar level) can be very serious. Hypoglycemia is an effect reported very frequently **(affects more than 1 in 10 users). Hypoglycemia (low blood sugar level) means that there is not enough sugar in the blood.** If your blood sugar level falls too much, you may lose consciousness. Severe hypoglycemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar level, take actions to increase your blood sugar level **immediately**.

See further information on hypoglycemia and its treatment at the end of the leaflet.

If you experience one of the following effects, refer to a doctor immediately:
Systemic allergic reactions are effects not commonly reported (affect up to 1 in 100 users).

Generalized allergy to insulin can be manifested by large scale skin reactions (rash and itching all over the body), severe swelling of skin or the mucous membranes (angioedema), shortness of breath, sharp fall in blood pressure with rapid heartbeats and sweating. These may be symptoms of severe cases of **generalized allergy to insulin, including anaphylactic reaction which may be life-threatening.**

Hyperglycemia (high blood sugar level) means that there is too much sugar in the blood. The frequency of hyperglycemia cannot be estimated. If your blood sugar level is too high, you may need more insulin than you injected.
Severe hyperglycemia can cause diabetic ketoacidosis (accumulation of acid in the blood since the body breaks down fat instead of sugar).
These are severe side effects.
These conditions can occur when there is a problem with the insulin pump or upon improper use of the pump. This will mean that you will not always receive enough insulin to treat your diabetes.
If this happens, refer for medical assistance immediately. Always be sure to have another means of subcutaneously injecting Apidra (see section 3).

See further information on the signs and symptoms of hyperglycemia at the end of the leaflet.

Other side effects

• Skin changes at the injection site
If you inject insulin too often at the same place, the fatty tissue may either shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 1,000 users). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

Common reported side effects (affect up to 1 in 10 users)
• Skin and allergic reactions at the injection site
Reactions at the injection site may occur (such as redness, unusually intense pain on injection, itching, rash, swelling or inflammation). They can also spread around the injection site. Most of the minor reactions to insulins usually resolve within a few days to a few weeks.

Side effects occurring at a frequency that cannot be estimated from the available data
• Eye reactions
A marked change (improvement or worsening) in control of blood sugar levels can temporarily disturb vision. If you have proliferative retinopathy (an eye disease associated with diabetes), severe hypoglycemic attacks may cause temporary loss of vision.

If a side effect occurs, if one of the side effects worsens, or if you are suffering from a side effect not mentioned in this leaflet, consult the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il.

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning!

This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

Storage conditions:

Before use:
If you do not plan to use the insulin immediately, store the vials or cartridges in the package (protected from light) in the refrigerator (between 2 and 8 degrees Celsius).

Do not freeze.

After starting use/removing from the refrigerator:

The vial can be used within 4 weeks of first opening or taking out of the refrigerator, when stored at a temperature that does not exceed 25°C and in a dark place.

It is recommended to write the date of first use/removal from the refrigerator on the label of the preparation.

Do not use the medicine if it does not appear clear and colorless.

Do not store different medications in the same package.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains the following inactive ingredients:

Trometamol, sodium chloride, m-cresol, polysorbate 20, sodium hydroxide, hydrochloric acid, water for injection.

What the medicine looks like and the contents of the pack:

A package with one vial that contains 10 ml, which includes a clear, colorless solution with no particles.

The leaflet does not contain all of the information about the preparation. If you have any question or are not sure about something, please refer to a doctor.

License holder, importer and address: sanofi-aventis Israel ltd., 10 Beni Gaon Netanya 4250499.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 132-94-31195

Revised in December 2020 according to MOH guidelines.

HYPERGLYCEMIA AND HYPOGLYCEMIA

Always have at least 20 grams of sugar with you, in addition to information identifying you as a diabetic.

Hyperglycemia (high blood sugar level)

If your blood sugar level is too high (hyperglycemia), you may not have injected enough insulin.

Why does hyperglycemia occur?
Examples include:
- you did not inject insulin or did not inject enough insulin, or if the insulin became less effective, for example, due to incorrect storage,
- you are performing less physical activity than usual, you are under stress (emotional distress, excitement), or you have been injured, underwent surgery, have an infection or fever,
- you are taking or have taken certain other medicines (see section 2).

Warning symptoms of hyperglycemia
Thirst, increased need to urinate, tiredness, dry skin, redness of the face, loss of appetite, low blood pressure, fast heartbeat, glucose and ketone bodies in the urine. Stomach pain, rapid and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycemia? Check your blood sugar level and the ketones in your urine as soon as any of the above symptoms occur. Severe hyperglycemia or ketoacidosis must always be treated by a doctor, usually in a hospital.

Hypoglycemia (low blood sugar level)

If your blood sugar level drops too low, you may lose consciousness. Severe hypoglycemia may cause heart attack or brain damage and may be life-threatening. Usually, you should be able to detect when your blood sugar level has dropped too low, so you will be able to take the right actions.

Why does hypoglycemia occur?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough or eat food containing less carbohydrates than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners **are not** carbohydrates),
- you lose carbohydrates due to vomiting or diarrhea,
- you drink alcohol, especially if you are not eating much,
- you are performing more physical activity than usual or a different type of physical activity,
- you are recovering from an injury or surgery or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2).

Hypoglycemia is also more likely to occur if:
- you have just started treatment with insulin or you have changed the type of insulin,
- your blood sugar levels are almost regular or are unstable,
- you changed the area of skin where you inject insulin (for example, from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease, such as hypothyroidism.

Warning symptoms of hypoglycemia

- in your body

Examples of symptoms that indicate that your blood sugar level is falling too much or too fast:

Sweating, damp skin, anxiety, rapid heartbeats, high blood pressure, palpitations and irregular heartbeat. These symptoms often occur before the symptoms of a low sugar level in the brain.

- in your brain

Examples of symptoms indicating low sugar level in the brain: Headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behavior, difficulty concentrating, impaired reactions, depression, confusion, speech disturbances (sometimes loss of ability to speak), visual disorders, trembling, paralysis, tingling sensation, numbness and tingling in the mouth area, dizziness, loss of self control, inability to care for yourself, convulsions and loss of consciousness.

The first signs which alert you to hypoglycemia ("warning signs") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nerve disease (diabetic autonomic neuropathy),
- you have recently suffered from hypoglycemia (e.g., the day before) or if it develops slowly,
- your blood sugar levels are almost regular or have at least significantly improved,
- you are taking or have stopped taking certain other medicines (see section 2).

In such a case, you may develop severe hypoglycemia (and even faint) before you are aware of the problem. Be familiar with your warning signs. If necessary, more frequent sugar level tests can help identify mild hypoglycemic events, that may otherwise be overlooked.

If you are not sure about your warning signs, avoid situations (e.g., driving a car) in which you or others will be at risk due to hypoglycemia.

What should you do if you experience hypoglycemia?
1. Do not inject insulin. Immediately take approximately 10 to 20 grams of sugar, such as glucose, sugar cubes or a sugar-sweetened drink. Caution: artificial sweeteners and foods with artificial sweeteners (such as diet drinks) will not help treat hypoglycemia.
2. Eat something that has a long-acting effect in raising your blood sugar level (e.g., bread or pasta). The doctor or nurse have probably already discussed this topic with you in the past.
3. If the hypoglycemia recurs, take another 10 or 20 grams of sugar.
4. Speak with your doctor immediately if you are unable to control the hypoglycemia or if it recurs.

Tell your relatives, friends and colleagues that:
If you are unable to swallow or if you lose consciousness, you will need an injection of glucose or glucagon (a medicine which increases the blood sugar level). These injections are justified even if it is not certain that you have hypoglycemia.

It is recommended to check your blood sugar level immediately after taking glucose, to check that you really have hypoglycemia.