Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Sitamet-Avenir 50 mg/850 mg
Film-coated tablets

Each tablet contains:
sitagliptin (as HCl monohydrate) 50 mg
metformin hydrochloride 850 mg

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Inactive ingredients and allergens: see section 2 sub-section "Important information about some of this medicine's ingredients" and section 6 "Additional information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about Sitamet-Avenir. If you have any further questions, consult your 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 medical condition is similar to yours.

This medicine is not intended for administration to children below the age of 18 years.

1. What is Sitamet-Avenir intended for?

Along with recommended diet and exercise plan, Sitamet-Avenir is intended to reduce blood sugar levels in patients with type 2 diabetes.

Therapeutic group: Sitagliptin: DPP-4 enzyme inhibitor. Metformin: biguanide.

Sitamet-Avenir is a tablet containing two active ingredients, sitagliptin and metformin, which reduce the blood sugar level.
Sitagliptin, which belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors), and metformin, which belongs to the class of biguanide medicines, act together to control blood sugar levels in patients with type 2 diabetes, for whom this combination is suitable.

2. Before using Sitamet-Avenir
Do not use Sitamet-Avenir if:

- You are sensitive (allergic) to the active ingredients or to any of the other ingredients in Sitamet-Avenir (see section 6 "Additional information" for complete list of the ingredients in Sitamet-Avenir). Symptoms of a serious allergic reaction to Sitamet-Avenir may include rash, raised red patches on the skin (hives) or swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing.
- You have type 1 diabetes.
- You have severely reduced renal function (Your doctor will inform you of the level of renal function impairment).
- You have diabetic ketoacidosis (elevated levels of ketones in blood or urine: a complication of diabetes including high blood sugar levels, rapid weight loss, nausea or vomiting).

Special warnings about using Sitamet-Avenir
Before treatment with Sitamet-Avenir, tell your doctor about all your medical problems, including if:
- You have or have had inflammation of the pancreas (pancreatitis). If you have had pancreatitis in the past, it is unknown whether you have a higher chance of developing pancreatitis while taking Sitamet-Avenir (see section 4 "Side effects")
- You have kidney problems
- You have liver problems
- You have or have had gallstones
- You have high blood levels of triglycerides
- You have heart failure
- You drink alcohol very often, or drink large amounts of alcohol in a short period. If you are or have been addicted to alcohol
- You are about to receive an injection of a dye or contrast media for an X-ray. You may have to stop taking Sitamet-Avenir for a short period. Consult your doctor about when to stop taking Sitamet-Avenir and when to start taking Sitamet-Avenir again (see section 4 "Side effects")
- You have low blood levels of vitamin B_{12}
- You are pregnant or are planning to become pregnant (see section 2 "Pregnancy, breastfeeding and fertility")
- You are breastfeeding or are planning to breastfeed (see section 2 "Pregnancy, breastfeeding and fertility")
- You are a premenopausal woman and you have irregular menstrual periods or no menstrual periods at all (see section 2 "Pregnancy, breastfeeding and fertility")

Stop taking Sitamet-Avenir and contact your doctor immediately if you have severe and persistent pain in the abdominal area. You may feel the pain passing from the abdomen to the back. The pain can appear with or without vomiting. These may be symptoms of pancreatitis.

Tests and follow-up
Check the blood sugar as your doctor instructed you.
Your doctor will monitor diabetes by regular blood tests, including blood sugar levels and hemoglobin A1C.
Your doctor may perform blood tests to check your vitamin B_{12} levels.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.
Particularly if you are taking:
- Topiramate (for treatment of seizures and migraines)
- Acetazolamide (for treatment of edema, glaucoma and sea sickness)
- Dolutegravir (for treatment of HIV infection)
- Cimetidine (for treatment of peptic ulcer)
- Ranolazine
- Vandetanib

Sitamet-Avenir may affect the way other medicines work, and other medicines may affect the way Sitamet-Avenir works.
Know the medicines you are taking. Keep a list of them and show it to the doctor and pharmacist when you receive a new medicine.

Using Sitamet-Avenir and food
Take Sitamet-Avenir with meals to reduce the chance of experiencing gastrointestinal disorders.

Pregnancy, breastfeeding and fertility
- If you are pregnant or are planning to become pregnant: It is not known whether Sitamet-Avenir may harm the fetus. If you are pregnant, consult your doctor regarding the best way to control blood sugar levels during pregnancy.
- If you are breastfeeding or are planning to breastfeed: It is not known whether Sitamet-Avenir may pass into breast milk. Consult your doctor regarding the best way to feed your baby if you are taking Sitamet-Avenir.
- If you are a premenopausal woman and you have irregular menstrual periods or no menstrual periods

at all: Sitamet-Avenir may cause oocyte release from the ovary (ovulation). This can increase your chance of becoming pregnant. Tell your doctor immediately if you become pregnant while taking Sitamet-Avenir.

Important information about some of this medicine's ingredients

Sitamet-Avenir contains sodium. This medicine contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially 'sodium-free'.

3. How to use Sitamet-Avenir?

Always use Sitamet-Avenir according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine.
Your doctor will tell you how many Sitamet-Avenir tablets to take and when to take them.
Do not exceed the recommended dose.
Your doctor may change the dose of Sitamet-Avenir if required.
Take Sitamet-Avenir with meals to reduce the chance of experiencing gastrointestinal disorders. Your doctor may tell you to take Sitamet-Avenir together with certain other antidiabetic medicines. Low blood sugar (hypoglycemia) may occur more often when Sitamet-Avenir is taken with certain other antidiabetic medicines (see section 4 "Side effects").
This medicine is not intended for administration to children below the age of 18 years.

There is no information regarding crushing, splitting or chewing these tablets. Tell your doctor if you cannot swallow Sitamet-Avenir tablets whole.
If you have reduced kidney function, your doctor may prescribe a lower dose.

If you have accidentally taken a higher dose
If you have taken too much Sitamet-Avenir, contact your doctor immediately.
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled time
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the forgotten dose and go back to your regular schedule. Do not take 2 doses of Sitamet-Avenir at the same time.

You may have to stop taking Sitamet-Avenir for a short period. Contact your doctor to receive instructions if you:

- are dehydrated (lost too much body fluids). Dehydration may occur if you are ill and experience severe vomiting, diarrhea or fever, or if you are drinking much less fluids than you usually do.
- are planning to undergo surgery
- are about to receive an injection of a dye or contrast medium for an X-ray (see section 2 sub-section "Special warnings about using Sitamet-Avenir" and section 4 "Side effects").

When the body is under various types of stress such as fever, trauma (e.g. a road accident), infection or surgery, the quantity of antidiabetic medicine you need may change. Tell your doctor immediately if you are in any of the above situations and follow the doctor's instructions.
Continue with the diet prescribed to you and the exercise plan while taking Sitamet-Avenir. Talk to your doctor about how to prevent and identify low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and to manage them and problems you encounter due to diabetes.
Continue taking Sitamet-Avenir as long as your doctor tells you to.
Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop treatment with the medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take a medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with any medicine, using Sitamet-Avenir may cause side effects in some users. Do not be alarmed by

this list of side effects; you may not experience any of them.
Sitamet-Avenir may cause serious side effects, including:

Lactic acidosis. Metformin, one of the medicines in Sitamet-Avenir, may cause a rare (may occur in up to 1 in 10,000 users) but serious condition called lactic acidosis (accumulation of acid in the blood), which may be fatal. Lactic acidosis is a medical emergency requiring treatment at the hospital.
Stop taking Sitamet-Avenir and talk to your doctor immediately if you have any of the following symptoms, which may be signs of lactic acidosis:
- Your hands or feet feel cold
- You feel dizzy or lightheaded
- You have a slow or irregular pulse
- You feel very weak or tired
- You have unusual (abnormal) muscle pain
- You have difficulties breathing
- You fell sleepy or somnolent
- You have abdominal pain, nausea or vomiting.

Most of the people who had lactic acidosis with metformin suffer from other conditions, which in combination with metformin led to lactic acidosis. Tell your doctor if you have any of the following, since you are at a higher risk of developing lactic acidosis with Sitamet-Avenir if you:
- have serious kidney problems or your kidneys are affected by certain X-ray tests involving the use of injected dye
- have liver problems
- drink alcohol very often, or drink a large amount of alcohol in a short period
- are dehydrated (lost a large quantity of body fluids). This may occur if you are ill and experience fever, vomiting or diarrhea. Dehydration may also occur if you are sweating excessively during activity or exercise and do not drink enough fluids.
- undergo surgery
- have had a heart attack, severe infection or stroke
- are 65 years old or older

The best way to avoid the problem of lactic acidosis due to metformin is to tell your doctor if you have any of the problems listed above. Your doctor may decide to stop your treatment with Sitamet-Avenir for a while if you have any of these conditions.

Pancreatitis (pancreas inflammation), which may be severe and fatal.
Certain medical problems increase the risk of developing pancreatitis. Stop taking Sitamet-Avenir and contact your doctor immediately if you have severe and persistent pain in the abdominal area. You may feel the pain passing from the abdomen to the back. The pain can appear with or without vomiting. These may be symptoms of pancreatitis.

Heart failure. Heart failure means that the heart does not pump blood properly.
Before you start taking Sitamet-Avenir, tell your doctor if you have ever had heart failure or if you have kidney problems. Contact your doctor immediately if you have any of the following symptoms:
- Increasing shortness of breath or difficulty breathing, especially when you are in lying position
- Swelling or fluid accumulation, especially in the feet, ankles or legs
- Especially rapid weight gain
- Unusual tiredness
  These may be signs of heart failure.

Kidney problems (unknown frequency), sometimes requiring dialysis.

Low level of vitamin B_{12} (vitamin B_{12} deficiency). Long term use of metformin may cause a decrease in the quantity of vitamin B_{12} in blood, especially if you have had low vitamin B_{12} levels in the past.

Low blood sugar (hypoglycemia), common (may occur in up to 1 in 10 people). If you are taking Sitamet-Avenir with an additional medicine that may cause low blood sugar, such as sulfonylurea or insulin, the risk of experiencing low blood sugar is higher. Reduction of the sulfonylurea medicine or insulin dose while taking Sitamet-Avenir may be required.

Signs and symptoms of low blood sugar may include headache, somnolence, weakness, dizziness, confusion, irritability, hunger, rapid pulse, sweating, sensation of nervousness.

Serious allergic reactions (unknown frequency) may occur with Sitamet-Avenir or sitagliptin, one of the medicines in Sitamet-Avenir. Symptoms of a serious allergic reaction to Sitamet-Avenir may include rash, raised red patches on the skin (urticaria, hives) or swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing. If you experience any symptoms of a serious allergic reaction, stop taking Sitamet-Avenir and immediately talk to your doctor or seek urgent medical assistance. Your doctor may prescribe a medicine for the allergic reaction and a different medicine for diabetes.

Joint pain (unknown frequency). People taking medicines called DPP-4 inhibitors, one of the medicines in Sitamet-Avenir, may develop joint pain that can be severe. Contact your doctor if you experience severe joint pain.

Skin reactions (unknown frequency). Some people taking medicines called DPP-4 inhibitors, one of the medicines in Sitamet-Avenir, may develop a skin reaction called bullous pemphigoid, which may have to be treated in a hospital. Tell your doctor immediately if you develop blisters or injury of the external skin layer (erosion). Your doctor may tell you to stop taking Sitamet-Avenir.

Most common side effects (may occur in more than one in 10 people) of Sitamet-Avenir include:

- Stuffy or runny nose and sore throat
- Upper respiratory tract infection
- Diarrhea
- Nausea and vomiting
- Flatulence, abdominal discomfort, dyspepsia
- Weakness
- Headache
- Low blood sugar (hypoglycemia) when used in combination with certain medicines, such as sulfonylurea or insulin

Taking Sitamet-Avenir with meals may help to reduce the common abdominal side effects of metformin, which usually occur in the beginning of treatment. If you experience unusual or sudden abdominal problems, talk to your doctor. Abdominal problems starting in a later treatment phase may indicate something more serious.

Sitamet-Avenir may cause other side effects including:

- **Swelling of the arms or legs**. Swelling of the arms or legs may occur if you are taking Sitamet-Avenir in combination with rosiglitazone. Rosiglitazone is another type of antidiabetic medicine.
- Joint pain
- Muscle pain
- Pain in the arm or leg
- Back pain
- Itching
- Blisters

These are not all the possible side effects of Sitamet-Avenir. For further information, ask your doctor.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects:
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store Sitamet-Avenir?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.

- Do not use Sitamet-Avenir after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions

- Store Sitamet-Avenir below 25°C.
- Do not throw away any medicine via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredients, this medicine also contains:

Microcrystalline cellulose, povidone, sodium stearyl fumarate and sodium lauryl sulfate.
Tablet coating contains the following inactive ingredients:
Polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc
The coating of Sitamet-Avenir 50 mg/1000 mg contains, in addition, iron oxide yellow

What the medicine looks like and contents of the pack

Sitamet-Avenir tablets are available in 2 strengths:

Sitamet-Avenir 50 mg/850 mg: Capsule-shaped, white to off-white film-coated tablets debossed with "S18" and a score line on one side and "H" on the other side.

Sitamet-Avenir 50 mg/1000 mg: Capsule-shaped, yellow film-coated tablets debossed with "S19" and a score line on one side and "H" on the other side.

Pack sizes:
Blister packs containing 14, 28, 56, 60, 112, 168, 180, 196 tablets.
Bottles with child-proof caps containing 30 or 90 tablets.
Not all pack sizes may be marketed.

Manufacturer:

Hetero Labs Limited, Unit–V, TSIIC Formulation SEZ, Survey No. 439, 440, 441 & 458 ,Polepally village, Jadcherla (Mandal), Mahaboob Nagar (District) – 509301,Telangana, India.

Registration holder's name and address:

BioAvenir Ltd., 1 David Hamelech St., Herzliya Pituach 466101

Revised in February 2022 according to the Ministry of Health guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Sitamet-Avenir 50 mg/850 mg:
Sitamet-Avenir 50 mg/1000 mg: