PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

Eucreas® 50/500 mg	**Eucreas® 50/850 mg**	**Eucreas® 50/1000 mg**
Film-Coated Tablets	Film-Coated Tablets	Film-Coated Tablets

Composition:

Each tablet contains:
Eucreas 50/500 mg: vildagliptin 50 mg and metformin hydrochloride 500 mg.

Eucreas 50/850 mg: vildagliptin 50 mg and metformin hydrochloride 850 mg.

Eucreas 50/1000 mg: vildagliptin 50 mg and metformin hydrochloride 1000 mg.

Inactive ingredients: See section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, contact the doctor or pharmacist.

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

1. WHAT IS THE MEDICINE INTENDED FOR?

Both active ingredients are oral antidiabetic agents.
Eucreas is intended for treatment of type 2 diabetes: Eucreas is intended for treatment in adults already receiving combined treatment with separate tablets of vildagliptin and metformin hydrochloride, or whose diabetes is not adequately controlled with metformin hydrochloride alone.
Your doctor will prescribe Eucreas either alone or in combination with another diabetic medicine depending on your condition. Eucreas can also be taken in combination with insulin or with a medicine from the sulfonylurea group, by adults, together with diet and exercise.

Therapeutic group:
vildagliptin - dipeptidyl-peptidase-4 (DPP-4) inhibitor.
metformin - biguanides.

Type 2 diabetes develops when the body does not produce enough insulin, or when the insulin that the body produces does not work properly or when the body produces too much glucagon.
Insulin is a substance which helps to lower the level of glucose in the blood, especially after meals. Glucagon is a substance that stimulates the liver to produce more glucose, causing the blood glucose level to rise. Both of these substances are produced in the pancreas. Both active substances in the medicine Eucreas help to control the level of glucose in the blood.
Eucreas makes the pancreas produce more insulin and less glucagon (effect of vildagliptin), and also helps the body to make better use of the secreted insulin (effect of metformin hydrochloride).

2. BEFORE USING THE MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to vildagliptin, metformin hydrochloride or any of the other ingredients in this medicine (see section 6 "Further information"). If you think you may be allergic to any of these ingredients, talk to the doctor before taking Eucreas**.**
- Your diabetes is uncontrolled with, for example, severe hyperglycemia (high blood glucose level), nausea, vomiting, diarrhea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis.
  Ketoacidosis is a condition in which substances called ketone bodies accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include abdominal pain, fast and deep breathing, sleepiness or breath with an unusual fruity smell.
- You have recently had a heart attack or if you have heart failure or serious problems with the blood circulation or difficulties in breathing, which could be a sign of heart problems.
- You have severely reduced kidney function.
- You have a severe infection or are seriously dehydrated (have lost a lot of water from your body).
- You are going to have an x-ray (a specific type of x-ray involving injection of an iodine-containing contrast agent) (see section "Drug interactions").
- You have liver function problems.
- You drink alcohol excessively (whether every day or only from time to time).
- You are breastfeeding (see also "Pregnancy and breastfeeding").

Special warnings regarding use of the medicine

Risk of lactic acidosis

Eucreas may cause a very rare but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver function problems, and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above conditions apply to you, talk to your doctor to receive further instructions.

Stop taking Eucreas for a short time if you have a condition that is associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhea, fever, exposure to heat or if you are drinking less fluids than normal. Talk to your doctor for further instructions.

Stop taking Eucreas and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- abdominal pain
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Eucreas is not a substitute for insulin. Therefore, you should not receive Eucreas for the treatment of type 1 diabetes.

Before treatment with Eucreas, inform the doctor if:
- You have or have had a disease of the pancreas.
- You are taking a medicine to treat diabetes from the sulfonylurea group. Your doctor may want to reduce your dose of the medicine from the sulfonylurea group when it is given together with Eucreas in order to prevent a low level of glucose in the blood (hypoglycemia).
- You have previously taken vildagliptin but had to stop taking it because of liver disease; do not take this medicine.
- You have decreased kidney function. Your doctor may prescribe you a lower dose of Eucreas, depending on your kidney function.

During treatment with Eucreas:
- Skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking Eucreas. If these occur, you should immediately consult the doctor.
- If you are about to undergo surgery, you must stop taking Eucreas during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Eucreas.

Children and adolescents
Use of Eucreas is not intended for children and adolescents under 18 years of age.

Tests and follow-up
- Before starting treatment with Eucreas, the doctor will refer you for a liver function test. During the first year of treatment with this medicine a test should be performed every three months, and afterwards, should be performed periodically so that increased liver enzymes can be detected at an early stage.
- During treatment with Eucreas, the doctor will monitor the levels of glucose in your blood and urine from time to time.
- Before you start and during treatment with Eucreas, the doctor will check your kidney function at least once a year, and at a higher frequency if you are elderly and/or there is worsening of your kidney function.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, inform the doctor or pharmacist.
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example during an X-ray or scan, you must stop taking Eucreas before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Eucreas.

If you are taking other medicines, your doctor may refer you for more frequent testing of blood glucose levels and kidney function, or you doctor may need to adjust the dose of Eucreas accordingly.
It is especially important to mention medicines you are taking from the following groups:
- glucocorticoids generally used to treat inflammation;

- beta-2 agonists usually used to treat respiratory disorders;
- other medicines used to treat diabetes;
- medicines which increase urine production (diuretics);
- medicines used to treat pain and inflammation (non-steroidal anti-inflammatory drugs [NSAIDs] and COX-2 inhibitors, such as ibuprofen and celecoxib);
- certain medicines for the treatment of high blood pressure (angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor antagonists);
- certain medicines affecting the thyroid;
- certain medicines affecting the nervous system;
- certain medicines used to treat angina (such as ranolazine);
- certain medicines used to treat HIV infection (such as dolutegravir);
- certain medicines used to treat a specific type of thyroid cancer (medullary thyroid cancer) (such as vandetanib);
- certain medicines used to treat heartburn and peptic ulcers (such as cimetidine).

Using Eucreas and food
It is advisable to take the tablets either with or just after a meal. This will reduce the risk of getting an upset stomach.

Using Eucreas and alcohol consumption
Avoid excessive consumption of alcohol during treatment with Eucreas**,** since alcohol may increase the risk of lactic acidosis (see section "Special warnings regarding use of the medicine").

Pregnancy, breastfeeding, and fertility
Pregnancy
Tell your doctor if you are pregnant, think you might be pregnant, or are planning to become pregnant. Your doctor will discuss with you the potential risk of taking Eucreas during pregnancy. There is insufficient information about using Eucreas during pregnancy, so do not use Eucreas if you are pregnant.

Breastfeeding
Do not use Eucreas if you are breastfeeding (also see "Do not use this medicine if:").

Fertility
There are no available data from clinical studies.

Driving and using machines
If you feel dizzy while taking Eucreas, avoid driving vehicles and using tools or machines.

3. HOW TO USE THE MEDICINE?

Always use this medicine according to the doctor's instructions.
You should check with the doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
The dosage and manner of treatment will be determined only by the doctor.
The usual dosage is generally one tablet, twice daily. If you have abnormal kidney function or you are taking a medicine from the sulfonylurea group, your doctor may prescribe a lower dose of Eucreas.
The medicine may be prescribed for you alone or with other medicines that lower the level of glucose in your blood.
Do not exceed the recommended dose.
If you have questions about how long to take Eucreas**,** talk to the doctor.

Do not chew! The tablets are film-coated. Swallow the tablets whole with a glass of water.
It is advisable to take the tablets either with or just after a meal. This will reduce the chance of getting an upset stomach.
Take one tablet in the morning and one tablet in the evening.
During treatment, continue to follow any instructions about diet that your doctor has given you, particularly if you are following a diabetic weight control diet.

If you have accidently taken an overdose, or if a child has accidentally swallowed the medicine, **refer immediately to a doctor or to a hospital emergency room** and bring the package of the medicine with you. Medical treatment might be necessary.

If you forget to take the medicine at the scheduled time, take a dose with the next meal. If you are due to take a dose at the next meal anyway, skip the forgotten dose. Never take a double dose (two tablets at once) to compensate for a missed dose.

Adhere to the treatment recommended by the doctor, so that the medicine can continue to control your blood glucose.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

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

4. <u>SIDE EFFECTS</u>
As with any medicine, using Eucreas may lead to side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Stop taking Eucreas and contact a doctor immediately if you experience one or more of the following symptoms:

- **Lactic acidosis** (very rare: affects up to 1 in 10,000 patients):
  Eucreas may cause a very rare but very serious side effect called lactic acidosis (see section "Special warnings regarding use of the medicine"). If this happens, you must **stop taking Eucreas and contact a doctor or the nearest hospital immediately,** as lactic acidosis may lead to coma.
- Angioedema (rare: affects 1-10 in 10,000 patients): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate a reaction called angioedema.
- Liver disease (hepatitis) (uncommon: effects that appear in 1-10 in 1,000 patients): Symptoms include yellow skin and eyes, nausea, loss of appetite, dark-colored urine, which may indicate liver disease (hepatitis).
- Inflammation of the pancreas (pancreatitis) (uncommon: effects that appear in 1-10 in 1,000 patients): Symptoms include severe and persistent pain in the stomach area, which may radiate to your back, as well as nausea and vomiting.

Other side effects:
Some patients have experienced the following side effects while taking Eucreas:

- Common side effects (affect 1-10 in 100 patients): sore throat, runny nose, fever, itchy rash, excessive sweating, joint pain, dizziness, headache, uncontrollable tremor, constipation, nausea (feeling sick), vomiting, diarrhoea, flatulence, heartburn, pain in and around the stomach (abdominal pain).

- Uncommon side effects (affect 1-10 in 1,000 patients): tiredness, weakness, metallic taste, low blood glucose, loss of appetite, swollen hands, ankles or feet (oedema), chills, inflammation of the pancreas, muscle pain.
- Very rare side effects (affect less than 1 in 10,000 patients): signs of a high level of lactic acid in the blood (a condition called lactic acidosis) such as sleepiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heartbeat or deep, rapid breathing; redness of the skin, itching; decreased vitamin B12 levels (paleness, tiredness, signs such as confusion or memory disturbances).

Since this medicine has been marketed, the following side effects have also been reported:
Frequency not known (cannot be estimated from the available data): localized peeling of skin or blisters, blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

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 of side effects
Side effects can be reported 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 THE MEDICINE?

- Avoid poisoning! This medicine, and all other medicines, should be kept in a closed 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 this medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.

Storage conditions:

- Store below 25°C and keep in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. This will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredients, Eucreas tablets contain:
Hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide (E 171), polyethylene glycol 4000, talc, iron oxide yellow (E 172), iron oxide red (E 172) (50/500 mg only).

What Eucreas looks like and contents of the pack:
Eucreas 50/500 mg: light yellow, oval, film-coated tablets, with beveled edges, imprinted with NVR on one side and LLO on the other side.
Pack size: 60 tablets.

Eucreas 50/850 mg: yellow, oval, film-coated tablets, with beveled edges, imprinted with NVR on one side and SEH on the other side.
Pack size: 60 tablets.

Eucreas 50/1000 mg: dark yellow, oval, film-coated tablets, with beveled edges, imprinted with NVR on one side and FLO on the other side.
Pack size: 60 tablets.

Registration holder and importer's name and address: Novartis Israel Ltd., POB 7126, Tel Aviv, Israel.

Revised in September 2022 according to MOH guidelines.

Registration numbers of the medicine in the National Drug Registry at the Ministry of Health:
Eucreas 50/500 mg: 147 89 33623
Eucreas 50/850 mg: 143 88 32042
Eucreas 50/1000 mg: 147 90 33627