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

Glucophage® XR 500 mg	**Glucophage® XR 750 mg**	**Glucophage® XR 1000 mg**
Prolonged release tablets	Prolonged release tablets	Prolonged release tablets

The active ingredient:
Each prolonged release tablet of Glucophage XR 500 mg contains:
metformin hydrochloride 500 mg, equivalent to metformin 390 mg
Each prolonged release tablet of Glucophage XR 750 mg contains:
metformin hydrochloride 750 mg, equivalent to metformin 585 mg
Each prolonged release tablet of Glucophage XR 1000 mg contains:
metformin hydrochloride 1000 mg, equivalent to metformin 780 mg

Inactive ingredients and allergens in the medicine: see section 2 under 'Important information regarding some of the ingredients of the medicine' and 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 any further questions, contact 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 medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR

- Glucophage XR is intended for reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) concentration and/or increased HbA1C, who are:
  - at high risk of developing overt type 2 diabetes mellitus, and
  - still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months.

  Treatment with Glucophage XR must be based on risk scores incorporating appropriate measures of glycaemic control and evidence of high cardiovascular risk.
  Lifestyle modification should be continued when treatment is initiated, unless the patient is unable to do so because of medical reasons.

- Glucophage XR is intended for treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control.
  Glucophage XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

Therapeutic group: Blood glucose lowering medicines. The active ingredient belongs to the biguanide group.

2. BEFORE USING THE MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients contained in the medicine (see section 6). An allergic reaction may cause rash, itching or shortness of breath.
- You have liver problems.
- You have severely reduced kidney function.
- You have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose levels), nausea, vomiting, diarrhoea, rapid weight loss.

- Any type of acute metabolic acidosis, such as lactic acidosis (see 'Risk of lactic acidosis' under 'Special warnings regarding use of the medicine') or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and may lead to diabetic pre-coma. Symptoms include abdominal pain, fast and deep breathing, sleepiness or breath developing an unusual, fruity smell.
- You have lost too much fluid from your body (dehydration). Dehydration may lead to kidney problems, which may cause lactic acidosis (see 'Special warnings regarding use of the medicine').
- You have a severe infection, such as an infection affecting the lungs, bronchi or kidneys. Severe infections may lead to kidney problems, which may cause lactic acidosis (see 'Special warnings regarding use of the medicine').
- You have been treated for acute heart problems or have recently had a heart attack, or have severe circulatory problems or breathing difficulties. This may lead to a lack in oxygen supply to tissues, which may cause lactic acidosis (see 'Special warnings regarding use of the medicine').
- You drink large amounts of alcohol.
- You are under 18 years of age.

Special warnings regarding use of the medicine
Before starting treatment with Glucophage XR, tell the doctor if:
Risk of lactic acidosis
Glucophage XR 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 increased with uncontrolled diabetes, severe infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical condition in which a part of the body has a reduced supply of oxygen (such as acute heart disease). If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Glucophage XR for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluids than normal. Talk to your doctor for further instructions.

Stop taking Glucophage XR 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.

Talk to your doctor promptly for further instructions if:
- You are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (mitochondrial encephalopathy, myopathy, lactic acidosis and stroke-like episodes) or maternal inherited diabetes and deafness (MIDD).
- You have any of these symptoms after starting metformin: seizures, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

If you need to have major surgery or X-ray imaging involving injection of dye for imaging, you must notify the doctor that you are taking Glucophage XR and stop taking Glucophage XR during and for some time

after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Glucophage XR.

If you are older than 75 years, treatment with Glucophage XR should not be started to lower the risk of developing type 2 diabetes.

You may see some remains of the tablets in the stool. Do not worry - this is normal for this type of tablet. You should continue following any dietary advice of your doctor and make sure that you eat carbohydrates regularly throughout the day.
Do not stop taking this medicine without speaking to your doctor.

Children and adolescents
This medicine is not intended for children and adolescents below the age of 18 years.
There is no information about the safety and efficacy of using this medicine in children and adolescents below the age of 18 years.

Tests and follow-up
Before you start using the medicine and during the treatment period, you may be referred by your doctor for a blood sugar test.
During treatment with the medicine, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.
If you have heart problems, your doctor will regularly monitor your heart function.
If you are at risk of vitamin B12 deficiency, your doctor will regularly monitor your blood vitamin levels.

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

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Glucophage XR. It is especially important to inform about the following medicines:
- Medicines which increase urine production (diuretics such as furosemide).
- 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 (ACE inhibitors and angiotensin II receptor antagonists).
- Steroids (such as prednisolone, mometasone, beclometasone).
- Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.
- Medicines that may change the amount of Glucophage XR in the blood, especially if you have reduced kidney function:
    - Medicines such as verapamil may reduce the medicine levels in the blood.
    - Medicines such as rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib may increase the medicine levels in the blood.

Use of the medicine and food
Swallow the tablets with food or immediately after eating.

Use of the medicine and alcohol consumption

Avoid excessive alcohol consumption while taking Glucophage XR, since this may increase the risk of lactic acidosis (see section 'Special warnings regarding use of the medicine').

Pregnancy and breastfeeding
If you are pregnant, think you may be pregnant or are planning to have a baby, speak to your doctor in case any changes will be needed to your treatment or monitoring of your blood glucose levels. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy. Your doctor will decide whether treatment with metformin alone or in combination with insulin is required.
Breastfeeding:
Metformin is excreted into breast milk; however, the existing information about the effect on the newborn is limited. Therefore, breastfeeding is not recommended during metformin treatment. Your doctor will decide if metformin treatment should be discontinued during breastfeeding.
Women of childbearing potential
Glucophage XR can stimulate ovulation (release of an egg from the ovaries), in women who do not ovulate properly. Beware of an increased chance of becoming pregnant when using Glucophage XR.

Driving and using machines
Glucophage XR alone does not cause 'hypos' (symptoms of low blood sugar or hypoglycaemia, such as fainting, confusion and increased sweating), and therefore should not affect your ability to drive or use machines.
You should be aware, however, that Glucophage XR taken with other antidiabetic medicines can cause hypos, so in this case you should take extra care when driving or operating machines.

Important information regarding some of the ingredients of the medicine
This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say it is essentially 'sodium free'.

3. HOW SHOULD YOU USE THE MEDICINE
Always use the medicine in accordance with the doctor's instructions. Check with the doctor or pharmacist if you are not sure about your dosage or about how to take this medicine. The dosage and treatment regimen will be determined by the doctor only.
Your doctor may prescribe Glucophage XR for you to take on its own, or in combination with other oral antidiabetic medicines or insulin.

The recommended dosage for adults with normal kidney function is usually:
To reduce the risk or delay the onset of type 2 diabetes:
Usually you will start treatment with 500 mg Glucophage XR daily. After you have been taking Glucophage XR for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Glucophage XR.
Your doctor will regularly check your blood sugar level and risk factors for developing diabetes, and will adjust the treatment accordingly.
To treat type 2 diabetes:
Usually you will start treatment with 500 mg Glucophage XR daily. After you have been taking Glucophage XR for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Glucophage XR.

If you have reduced kidney function, your doctor may prescribe a lower dose.
Normally, you should take the tablets once a day, with your evening meal.
In some cases, your doctor may recommend that you take the tablets twice a day. Always take the tablets with food.
Do not exceed the recommended dose.

Method of administration
Glucophage XR should be taken orally.

Swallow the tablets whole with a glass of water, do not chew, crush or split.

If you accidentally take a higher dosage, you don't need to worry, but if you have unusual symptoms, contact your doctor.
If the dose taken is large, lactic acidosis is more likely. Symptoms of lactic acidosis are non-specific, and may include vomiting, abdominal pain with muscle cramps, a general feeling of not being well with severe tiredness and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. If you experience some of these symptoms, you should immediately seek medical attention, as lactic acidosis may lead to coma. Stop taking Glucophage XR immediately and contact a doctor or the nearest hospital straightaway.

If you took an overdose or if a child accidentally swallowed the medicine, immediately contact the doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take the medicine, take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.

Adhere to the treatment regimen recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the doctor.

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

4. SIDE EFFECTS

As with any medicine, using Glucophage XR may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Stop the treatment and contact the doctor immediately:
Glucophage XR may cause a very rare (may affect up to 1 in 10,000 people) but very serious side effect called lactic acidosis (see section 'Special warnings regarding use of the medicine'). If you experience this side effect, you must **stop taking Glucophage XR and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Contact your doctor immediately:
Glucophage XR may cause abnormal liver function tests and hepatitis (inflammation of the liver), which may result in jaundice (may affect up to 1 in 10,000 people). If you develop yellowing of the eyes and/or skin, contact your doctor immediately.

<u>Additional side effects</u>:
Very common side effects (may affect more than 1 in 10 people):
- Diarrhoea, nausea, vomiting, abdominal pain or loss of appetite. If you experience these side effects, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks. It can help if you take the tablets with or immediately after a meal.

Common side effects (may affect up to 1 in 10 people):
- Taste disturbance.
- Decreased or low vitamin B12 levels in the blood [symptoms may include extreme tiredness, a sore and red tongue (glossitis), sensation of pins and needles (paraesthesia), or pale and yellow skin]. Your doctor may order some tests to find out the cause of your symptoms, because some of them may be caused by diabetes or due to other unrelated health problems.

Very rare side effects (may affect up to 1 in 10,000 people):
- Skin rashes including redness, itching and hives.

If a side effect occurs, if one of the side effects worsens, or if you suffer 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 an 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, should be kept in a safe place out of the reach and sight of children and/or infants, in order 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) indicated on the package. The expiry date refers to the last day of that month.
- No special storage conditions. Storage at room temperature is recommended.
- Do not dispose of medicines via wastewater or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  hypromellose (hydroxypropyl methylcellulose), carmellose sodium (sodium carboxymethylcellulose), magnesium stearate.
- **What the medicine looks like and contents of the packs:**
  Glucophage XR 500 mg tablets are white to off-white and round, with '500' on one side.
  Each pack contains 20, 28, 30, 50, 56, 60, 84, 90, 100, 112 or 120 prolonged release tablets.
  Glucophage XR 750 mg tablets are white to off-white and capsule-shaped, with '750' on one side and 'MERCK' on the other side.
  Each pack contains 20, 28, 30, 50, 56, 60, 84, 90, 100, 112 or 120 prolonged release tablets.
  Glucophage XR 1000 mg tablets are white to off-white and capsule-shaped, with '1000' on one side and 'MERCK' on the other side.
  Each pack contains 20, 28, 30, 50, 56, 60, 84, 90, 100, 112 or 120 prolonged release tablets.
  Not all pack sizes may be marketed.
- **License holder and address:** Merck Serono Ltd., 18 Hakishon St., Yavne 81220.
- **Manufacturer and address:** Merck Sante s.a.s, Semoy, France.
- This leaflet was revised in May 2025.
- Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
  Glucophage XR 500 mg **174-24-37479-99**
  Glucophage XR 750 mg **174-25-37480-99**
  Glucophage XR 1000 mg **174-26-37481-99**