

Glyxambi 10/5, 25/5	Updated Prescribing Information May 2023
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Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed according to a doctor's prescription only

Glyxambi® 10 mg / 5 mg

Each film-coated tablet contains 5 mg linagliptin and 10 mg empagliflozin.

Glyxambi® 25 mg / 5 mg

Each film-coated tablet contains 5 mg linagliptin and 25 mg empagliflozin.

Inactive ingredients and allergens in the medicine - See section 6 'Additional information'.

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about the medicine. If you have further questions, consult your doctor or pharmacist.

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

1. What is this medicine intended for?

Glyxambi is intended, in combination with diet and exercise, to improve control of blood sugar level in adults with type 2 diabetes, in cases where combination therapy with two active ingredients, linagliptin and empagliflozin, is required.

Glyxambi is not recommended for treating type 1 diabetes or for treating diabetic ketoacidosis. Glyxambi has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk of developing pancreatitis while using Glyxambi.

Therapeutic group:

Glyxambi is a combination of two active ingredients: empagliflozin and linagliptin.

Empagliflozin is an SGLT2 (sodium-glucose co-transporter 2) inhibitor.

Linagliptin is a DPP-4 (dipeptidyl peptidase-4) inhibitor.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredients empagliflozin and/or linagliptin or to any of the additional ingredients in this medicine (for the inactive ingredients' list see section 6, 'Additional information'). Symptoms of a serious allergic reaction to Glyxambi may include:
 - skin rash, itching, flaking or peeling
 - raised red patches on your skin (hives)
 - swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
 - difficulty in swallowing or breathing

If you have any of these symptoms, stop taking Glyxambi and immediately contact your doctor or go to the nearest hospital emergency room.
- You have severe kidney problems, end-stage kidney disease, or if you are on dialysis.

Special warnings about using this medicine

Before treatment with Glyxambi, tell your doctor about all of your medical conditions including if:

- you have kidney problems
- you have liver problems
- you have had an infection in the vagina or penis
- you have had urinary tract infection or difficulty passing urine
- you are about to have surgery. Your doctor may decide to stop Glyxambi before you have surgery. If you are about to have surgery, ask your doctor when to stop taking Glyxambi and when to start your treatment again.

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- you are eating less or there has been a change in your diet
- you have or have had pancreas problems, including pancreatitis or pancreas surgery. Inflammation of the pancreas (pancreatitis) can occur in patients taking Glyxambi. This inflammation may be severe and even lead to death. Certain medical problems make pancreatitis more likely.
Therefore, before you start taking Glyxambi, tell your doctor if you have ever had:
 - inflammation of your pancreas (pancreatitis)
 - a history of alcoholism
 - stones in your gallbladder
 - high blood triglyceride levels
- you consume alcohol frequently, or drink a lot of alcohol in the short term (“binge” drinking).
- you have type 1 diabetes. Glyxambi is not intended to be used to treat people with type 1 diabetes
- you are pregnant or planning to become pregnant – see section 2 ‘Pregnancy and breastfeeding’
- you are breastfeeding or planning to breastfeed – see section 2 ‘Pregnancy and breastfeeding’
- you have ever had heart failure
- you are 75 years of age or older

For additional special warnings about using the medicine, please see section 4, ‘Side effects’.

Children and adolescents

It is not known whether the medicine is safe and effective in children. The medicine is not intended for use in children and adolescents under 18 years old.

Tests and follow-up

- The doctor may perform blood tests to evaluate your kidney function before and during the treatment with Glyxambi.
- Sugar may appear in your urine while taking the medicine, which will show up on a urine test.
- Diabetic foot: It is important to check your feet regularly according to the recommendations given by your health care professional.

Drug interactions

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Glyxambi may affect the way other medicines work, and other medicines may affect how Glyxambi works. In particular tell your doctor or pharmacist if you are taking any of the following medicines:

- other medicines for lowering blood sugar (such as insulin or sulphonylurea). Taking them with Glyxambi can increase the risk of low blood sugar levels (hypoglycemia).
- medicines used to remove fluids from the body (diuretics). Combining diuretics with empagliflozin (one of the ingredients in Glyxambi) increases urine volume and frequency of voids; this may result in loss of salts and body fluids (dehydration).
- rifampin – an antibiotic that is used to treat tuberculosis.
- lithium. Taking lithium with Glyxambi can lower the concentration of lithium in the blood. Therefore, blood lithium levels should be monitored more frequently after starting Glyxambi and at dose changes.

Know the medicines you are taking and keep a list of them to present to your doctor and pharmacist when you receive a new medicine.

Using this medicine and food

This medicine can be taken with or without food.

Pregnancy and breastfeeding

If you are pregnant, think you may be pregnant, plan to get pregnant, are breastfeeding or plan to breastfeed, consult your doctor before using this medicine.

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Glyxambi may harm your unborn baby. Tell your doctor as soon as possible if you become pregnant during the treatment with Glyxambi. Talk to your doctor about the best way to control your blood sugar levels during pregnancy.

Do not breastfeed during treatment with Glyxambi.

Glyxambi may pass into your breast milk and may harm your baby. Consult your doctor about the best way to feed your baby during the treatment with Glyxambi.

3. How to use this medicine?

Always use the medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about the dosage or about how to use the medicine.

Only your doctor will determine your dosage and how you should take this medicine. The recommended dosage is one tablet once a day in the morning, with or without food.

Your doctor may instruct you to take Glyxambi in combination with other diabetes medicines. Low blood sugar level can happen more often when Glyxambi is taken in combination with certain other medicines for diabetes. For more information, see section 2 – 'Drug interactions' and section 4 'Side effects'.

Do not exceed the recommended dose.

Do not crush, split, or chew the tablets.

If you have accidentally taken a higher dosage

If you have taken an overdose, or if a child has accidentally swallowed the medicine, go **immediately** to a doctor or a hospital emergency room and bring the medicine package with you.

If you forget to take this medicine at the scheduled time, take it as soon as you remember. If you remember when it is almost time for your next dose, skip the missed dose and take the next dose at the usual time. Do not take two doses at the same time.

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop treatment with the medicine without consulting the doctor.

If you stop taking the medicine

Do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and the dose every time you take 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 all medicines, using Glyxambi may cause side effects in some users. Do not be alarmed by the list of side effects; you may not experience any of them.

Glyxambi may cause the following severe side effects:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and even lead to death (frequency unknown). Certain medical problems make pancreatitis more likely. **Before you start taking Glyxambi, tell your doctor if you have ever had:**
 - inflammation of your pancreas (pancreatitis)
 - a history of alcoholism
 - stones in your gallbladder
 - high blood triglyceride levels**Stop taking Glyxambi and contact your doctor right away** if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going

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from the abdomen to the back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- **Ketoacidosis (increased levels of ketones in your blood or urine) (frequency unknown):** Ketoacidosis has occurred in people with **type 1 diabetes or type 2 diabetes** during treatment with empagliflozin, which is one of the ingredients in Glyxambi. Ketoacidosis has also occurred in people with diabetes who vomited or who had surgery during treatment with Glyxambi. Ketoacidosis is a serious medical condition which requires treatment in a hospital. Ketoacidosis may lead to death. **Ketoacidosis may occur during treatment with Glyxambi even if your blood sugar levels are lower than 250 mg/dL. Stop taking Glyxambi and contact your doctor immediately or go to the nearest emergency room if you experience any of the following symptoms:** nausea, vomiting, abdominal pain (stomach area), tiredness, and difficulty breathing. If you experience any of these symptoms during treatment with Glyxambi, check your urine for the presence of ketones, if possible, even if your blood sugar levels are lower than 250 mg/dL.
- **Dehydration:** Glyxambi may cause dehydration in some people (loss of body fluids and salts). Dehydration may cause dizziness, fainting or weakness, especially when you stand up after sitting/lying down. There have been reports of sudden worsening of kidney function in people who are taking Glyxambi. You may be at higher risk of dehydration if you: are taking medicines to lower blood pressure, including diuretics, are on a low sodium (salt) diet, have kidney problems, are 65 years of age and older. Consult with your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Contact the doctor **right away** if you reduce the amount of food you eat or the amount of liquid you drink, for example if you vomit and cannot eat, or start to lose liquids from your body, for example due to vomiting, diarrhea or being in the sun too long.
- **Severe urinary tract infections:** Severe urinary tract infections that may result in hospitalization have occurred in patients taking empagliflozin, which is one of the ingredients of Glyxambi. Tell your doctor if you experience signs or symptoms of urinary tract infection such as burning sensation while passing urine, passing urine frequently and urgently, pelvic pain, or blood in the urine. Sometimes people may also suffer from fever, back pain, nausea, or vomiting.
- **Low blood sugar levels (hypoglycemia) (common side effect – affects 1–10 in 100 users):** If you take Glyxambi with an additional medicine that can cause low blood sugar level, such as medicines from the sulfonylurea class or insulin, your risk of having low blood sugar level is higher. The dosage of your sulfonylurea medicine or insulin may need to be lowered while you are taking Glyxambi. Signs and symptoms of low blood sugar level may include:

 - headache
 - drowsiness
 - weakness
 - irritability
 - hunger
 - fast heartbeat
 - confusion
 - shaking or feeling jittery
 - dizziness
 - sweating
- **Contact a doctor as soon as possible if you notice any of the following side effects:** redness, pain, tenderness, or swelling in the area of the genitals to the anus with a fever higher than 38°C or feeling generally unwell and weak. These side effects could be signs of Fournier's gangrene. It is a **rare but life-threatening bacterial infection in the tissue under the skin in the area of the genitals (all the way to the anus)**. There are a number of reports of this side effect happening in women and men taking diabetes medicines from the same class as Glyxambi. This side effect may lead to hospitalization,

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may require surgery, and may even lead to death. The symptoms of Fournier's gangrene may get worse quickly **so it is important to get medical help quickly if you feel any of these symptoms.**

- **Vaginal yeast infection (common side effect – affects 1–10 in 100 users):**
Symptoms of a vaginal yeast infection include: vaginal odor, white or yellowish vaginal discharge (the discharge may be lumpy or look like cottage cheese), vaginal itching.
- **Yeast infection of the penis – infection of the glans penis alone or of the glans penis and foreskin in uncircumcised men (common side effect – affects 1–10 in 100 users):**
Swelling of the penis in uncircumcised patients may develop, which make it difficult to pull back the skin around the tip of the penis.
Additional symptoms of yeast infection of the penis include: redness, itching or swelling of the penis, rash on the penis, foul smelling discharge from the penis, pain of the skin around penis.

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may tell you to use an over-the-counter antifungal medicine. Contact your doctor **immediately** if you use an over-the-counter antifungal medicine and your symptoms do not go away.

- **Allergic reactions (hypersensitivity) (frequency unknown):** Serious allergic reactions have occurred in patients who were taking Glyxambi. Symptoms may include:
 - swelling of the face, lips, tongue, throat, and other areas on your skin
 - difficulty with breathing or swallowing
 - raised red areas on your skin (hives)
 - skin rash, itchy, flaking, or peeling skin
If you have any of these symptoms, stop taking Glyxambi and contact your doctor **immediately** or go to the nearest hospital emergency room.
- **Severe and disabling joint pain (frequency unknown):** Some patients taking DPP-4 inhibitors (linagliptin), which is one of the ingredients in Glyxambi, may develop joint pain which could be severe. Contact your doctor if you experience severe joint pain.
- **Skin reactions (frequency unknown):** Certain patients taking DPP-4 inhibitors, which is one of the ingredients in Glyxambi, may develop a skin reaction called bullous pemphigoid (an autoimmune skin disease that causes blisters and bubbles on the skin surface) which can require treatment in hospital. Contact your doctor **immediately** if blisters or wounds develop in the outer layer of the skin. Your doctor may tell you to stop taking Glyxambi.
- **Heart failure:** Heart failure means your heart does not pump blood well enough. **Before you start taking Glyxambi**, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor **immediately** if you experience any of the following symptoms:
 - increasing shortness of breath or difficulty breathing, particularly when lying down
 - swelling or fluid retention particularly in the feet, ankles, or legs
 - an unusually fast increase in weight
 - unusual tiredness
These may be symptoms of heart failure.

Very common side effects (affect more than 1 in 10 users) include:

- urinary tract infection

Common side effects (affect 1–10 in 100 users) include:

- upper respiratory tract infection
- stuffy or runny nose and sore throat
- increased urination

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- high levels of lipids in the blood (including rise in cholesterol level)
- joint pain
- nausea
- thirst
- dehydration-related events (low blood pressure and fainting). For more information, see 'Glyxambi may cause the following severe side effects: Dehydration', above.
- increased hematocrit level (percent of red blood cells in a blood test)
- diarrhea
- cough
- increased level of uric acid
- increased level of lipases (enzymes that break down fats)
- increased level of the enzyme amylase

Additional side effects include:

- muscle pains
- increased level of serum creatinine (in blood test), and decreased eGFR (estimated glomerular filtration rate)

Additional side effects whose frequency cannot be established include:

- inflammation of the renal pelvis (pyelonephritis) and sepsis as a result of a urinary tract infection (urosepsis)
- skin reactions such as rash, hives
- mouth ulcers
- constipation
- inflammation of the mouth and lips (stomatitis)
- breakdown of muscle (rhabdomyolysis)
- acute renal injury

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 (MoH) by following the link 'Reporting Side Effects of Drug Treatment' on the MoH 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! To prevent poisoning, keep this and all other medicines in a closed place out of reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the carton and blister. The expiry date refers to the last day of that month.

Storage conditions:

Do not store above 25°C.

6. Additional information

- In addition to the active ingredients the medicine also contains:

Tablet core:

mannitol, maize starch, pregelatinized starch, talc, copovidone, crospovidone, magnesium stearate.

Tablet coating (Glyxambi 10 mg / 5 mg) contains:

hypromellose 2910, mannitol, talc, titanium dioxide, macrogol 6000, iron oxide yellow.

Tablet coating (Glyxambi 25 mg / 5 mg) contains:

hypromellose 2910, mannitol, talc, titanium dioxide, macrogol 6000, iron oxide red.

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

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- Glyxambi 10 mg / 5 mg film-coated tablets - pale yellow, arc triangular, flat-faced, bevel-edged tablets. One side is debossed with Boehringer Ingelheim company symbol; the other side is debossed with "10/5".
- Glyxambi 25 mg / 5 mg film-coated tablets - pale pink, arc triangular, flat-faced, bevel-edged tablets. One side is debossed with Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

The packs contain blister trays. Each Pack contains 7 or 30 film-coated tablets.
Not all pack sizes may be marketed.

- **Manufacturer's name and address:** Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany.
- **Registration holder's name and address:** Boehringer Ingelheim Israel Ltd., 89 Medinat Ha-Yehudim St., P.O.Box 4124, Herzliya Pituach 4676672.
- **This leaflet was revised in May 2023 according to MOH guidelines.**
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Glyxambi 10 mg / 5 mg: 155-76-34531-00
Glyxambi 25 mg / 5 mg: 155-75-34509-00