Glucovance 500 mg/2.5 mg, film-coated tablets
Glucovance 500 mg/5 mg, film-coated tablets
Glucovance 1000 mg/5 mg, film-coated tablets

Active ingredients: metformin hydrochloride and glibenclamide

Composition

• Each tablet of Glucovance 500 mg/2.5 mg contains 500 mg metformin hydrochloride and 2.5 mg of glibenclamide as active ingredients.
• Each tablet of Glucovance 500 mg/5 mg contains 500 mg metformin hydrochloride and 5 mg of glibenclamide as active ingredients.
• Each tablet of Glucovance 1000 mg/5 mg contains 1000 mg metformin hydrochloride and 5 mg of glibenclamide as active ingredients.

• Excipients: microcrystalline cellulose, croscarmellose sodium, povidone K30, magnesium stearate and Opadry OY-L-24808 in Glucovance 500 mg/2.5 mg or Opadry 31-F-22700 in Glucovance 500 mg/5 mg or Opadry II OY-L-28900 in Glucovance 1000 mg/5 mg.

Properties

Glucovance is made up of two antidiabetic medicines, which belong to the groups of medicines called biguanide (metformin hydrochloride) and sulphonylurea (glibenclamide). Metformin hydrochloride and glibenclamide have different mechanisms and sites of action, but their action is complementary. Metformin reduces hepatic glucose production, increases insulin sensitivity in muscle and delays intestinal glucose absorption while glibenclamide stimulates the release of insulin by the pancreas.

Indication

Treatment of type 2 diabetes in adults as replacement for previous treatment with metformin and glibenclamide in patients whose glycaemia is stable and well controlled.

Contraindications

Glucovance must not be used if
• you are allergic (hypersensitive) to metformin hydrochloride, glibenclamide or other sulphonylurea and sulphonamides or any of the excipients of Glucovance
• you suffer from type 1 diabetes mellitus (i.e. insulin-dependent diabetes) or if you have severe loss of diabetes control with either pre-coma or ketoacidosis (a condition caused by substances called ‘ketone bodies’ accumulating in the blood; you may notice that your breath has an unusual, fruity odour)
• you have kidney insufficiency (creatinine clearance < 60 ml/min) or liver insufficiency
• you have a severe infection (for example an infection of the air passages or an urinary tract infection)
• you are dehydrated (for example due to persistent or severe diarrhoea, recurrent vomiting)
• you are treated for cardiac failure, have recently had a myocardial infarction, have severe circulatory problems or breathing difficulties
• you suffer from porphyria (a rare, hereditary disease due to an enzyme deficiency causing the body to produce and excrete too much porphyrin, a component used to make the part of blood pigment that carries oxygen)
• you need to undergo an elective major surgery (see section “Special warnings and precautions”)
• you need to have an X-ray examination involving the injection of an iodinated contrast medicine into the bloodstream (see section “Special warnings and precautions”).
• you use miconazole (a medicine to treat certain yeast infections) even for local use

• you drink alcohol excessively (either every day or only from time to time)
• you are breast-feeding.

Pregnancy and Lactation
• Tell your doctor if you are, you think you might be or are planning to become pregnant. During pregnancy, diabetes should be treated with insulin. If you find out that you are pregnant while taking Glucovance, consult your doctor so that he/she may change your treatment.
• You must not take Glucovance**,** if you are breast-feeding or if you are planning to breast-feed your baby.

Special Warnings and Precautions

Lactic acidosis
Take special care with Glucovance if you experience symptoms such as vomiting, abdominal pain with muscle cramps and a general feeling of discomfort with severe fatigue and difficulty in breathing. **If these symptoms occur, STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away.**
Lactic acidosis is a medical emergency that can occur due to metformin accumulation, especially in diabetic patients with significant renal failure. Other associated risk factors are poorly controlled diabetes, ketosis, prolonged fasting, alcoholism, liver insufficiency and any condition associated with hypoxia. **Lactic acidosis must be treated in a hospital. The most effective way to remove lactate and metformin from the blood is haemodialysis.**

Hypoglycaemia
As it contains a sulphonylurea, Glucovance exposes the patient to a risk of onset of hypoglycaemia. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment must only be prescribed if you adhere to a regular meal schedule (including breakfast).
Take special care with Glucovance if you experience some symptoms of hypoglycaemia. The warning signs may occur suddenly and can include cold sweat, cold and pale skin, dizziness, headache, rapid heart beat, feeling sick, feeling very hungry, temporary changes in vision, drowsiness, unusual tiredness and weakness, nervousness or tremor, feeling anxious, feeling confused, difficulty in concentrating. These symptoms can be absent when the hypoglycaemia is developed slowly, in case of autonomic neuropathy or when the patients takes beta-blocking agents, clonidine, reserpine, guanethidine or other sympathomimetics.
If you notice any of these signs: first eat glucose tablets or a high sugar snack (honey, sugar), then rest.
Severe hypoglycaemic reactions with coma, seizures or other neurological signs constitute a medical emergency requiring immediate treatment with intravenous glucose. **STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away** as you need to be hospitalised to bring your blood glucose back under control.
As a general advice, inform your family, friends and colleagues to turn you on your side and get medical aid straight away if you become unconscious. They should not give you any food or drink when you are unconscious. It could choke you.
A hypoglycaemia may occur if:
• you eat too little or miss a meal or if your diet contains insufficient or unbalanced levels of sugar
• you drink alcohol
• you exercise more than usual
• you have liver or kidney impairment. Hypoglycaemia may be prolonged in such circumstances.
• you have certain hormone problems such as thyroid or pituitary or adrenal gland insufficiency
• the dosage of Glucovance is too high
• you are an elderly person
• you are taking certain medicines and Glucovance at the same time (see section “Interactions”).
The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycaemic episodes. If the patient encounters repeated episodes of hypoglycaemia, which are either severe or associated with unawareness of the situation, antidiabetic treatment options other than Glucovance should be taken into consideration.

Infectious diseases
Inform your doctor if you suffer from any infectious illnesses such as flu, infection of the air passages or urinary tract infection.

Surgery
Inform your doctor if you are going to have an elective major surgery. Glucovance must be discontinued 48 hours before elective major surgery and may not be reinstituted until 48 hours afterwards, and only after kidney function has been re-evaluated and found to be normal.

Iodinated contrast media:
Inform your doctor if you need to have an X-ray examination involving the injection of an iodinated contrast medicine into the bloodstream. Depending on the kidney function**,** Glucovance must be discontinued 48 hours before the test or at the time of the test. Glucovance may not be reinstituted until 48 hours afterwards, and only after the kidney function has been tested and found to be normal.

Blood sugar imbalance
Contact your doctor in case of surgery or any other cause of diabetic decompensation since temporary treatment with insulin should be envisaged. The symptoms of hyperglycaemia are increased urinating, raging thirst and a dry skin**.**

Kidney function
Be aware that your kidney function (creatinine clearance and/or serum creatinine levels) must be determined before initiating treatment and regularly thereafter:
• at least annually in patients with normal kidney function,
• at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.
Special caution should be exercised in situations where kidney function may become impaired, for example in the elderly, when initiating antihypertensive therapy or diuretic therapy, and when starting therapy with a non-steroidal anti-inflammatory medicine (NSAID).

Lactose
Each Glucovance tablet contains lactose. If your doctor has told you that you have intolerance to certain sugars (galactosemia, glucose and galactose malabsorption syndrome or lactase deficiency), contact your doctor before taking this medicine.

Further monitoring recommendations
Continue to follow any dietary advice your doctor has given you including some energy-restricted diet if you are overweight. Get some regular exercise while you are taking this medicine.
Consult your doctor regularly to test your blood sugar levels and your kidney function, if any of the above-mentioned situations applies to you or if you feel unsure about using this medicine.
If you have an inherited condition where your red blood cells don't produce enough of the enzyme glucose-6-phosphatase dehydrogenase (G6PD deficiency), taking Glucovance may cause your red blood cells to be destroyed too quickly (haemolytic anaemia). Tell your doctor if you have this condition, as Glucovance may not be suitable for you.

Effects on the Ability to Drive and Use Machines
Do not drive or use machines:
• if your vision is blurred. This may happen at the beginning of the treatment because of a lower level of sugar in your blood.
• if you feel that symptoms of hypoglycaemia sugar begin to appear (see special warnings and precautions).
Reconsider your ability to drive or use machines in case you have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia.

Adverse Effects

Like all medicines, Glucovance can cause adverse effects, although not everybody gets them. The following adverse effects may occur during treatment with Glucovance:
• Transient visual disturbances at the start of treatment due to a decrease in glycaemia levels.
• Hypoglycaemia (see section “Special warnings and precautions”).
• Lactic acidosis (see section “Special warnings and precautions”).
• Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These adverse effects occur more frequently during treatment initiation and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability**. Should these symptoms continue, STOP taking this medicine and CONSULT your DOCTOR.**
• Skin reactions such as pruritus, urticaria, maculopapular rash, cutaneous or visceral allergic angiitis, erythema multiforme, exfoliative dermatitis, photosensitization, urticaria evolving to shock. A cross reactivity to sulphonamide(s) and their derivatives may occur.
• Liver function test abnormalities or hepatitis requiring treatment discontinuation.
• Crises of hepatic porphyria and porphyria cutanea.
• Disulfiram-like reaction with alcohol intake.
• Taste disturbance.
• Leucopoenia, thrombocytopenia, agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia. These are reversible upon treatment discontinuation.
• Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if you present with megaloblastic anaemia.
• Average to moderate elevations in serum urea and creatinine concentrations.
• Hyponatremia.

Interactions

<u>While taking Glucovance, you must not use any of the following medicines:</u>
• Miconazole even for local use (see section “Contraindications”)
• Iodinated contrast agents (see section, “Contraindications”)

<u>Special precautions may be required if you take Glucovance and any of the following medicines at the same time:</u>
• Angiotensin-converting enzyme inhibitors may potentiate the hypoglycaemic action of glibenclamide. Self-monitoring is recommended.
• Diuretics (loop diuretics specially) may increase the risk of lactic acidosis. Kidney function monitoring is recommended.
• Beta-blockers,clonidine, reserpine, guanethidine or sympathomimetics may mask the warning symptoms of a hypoglycaemia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Self-monitoring is recommended, especially at start of treatment.
• Bosentan increases the risk of liver toxicity when it is combined with Glucovance. It is recommended to avoid this combination. The hypoglycaemic effect of glibenclamide may also be reduced.
.• Beta-2 agonists increase glycaemia. Self-monitoring is recommended and insulin therapy should be considered if necessary.
• Corticosteroids and tetracosactides increase glycaemia. Self-monitoring is recommended and dose adjustment of Glucovance should be considered during and after treatment.
• Phenylbutazone increases the hypoglycaemic effect of glibenclamide. If the combination cannot be avoided, self-monitoring is recommended and dose adjustment of Glucovance should be considered.
• Fluconazole increases the risk of hypoglycaemia. If the combination cannot be avoided, self-monitoring is recommended and dose adjustment of Glucovance should be considered during and after treatment.
• Chlorpromazine and danazol may increase glycaemia. If the combination cannot be avoided, self-monitoring is recommended and dose adjustment of Glucovance should be considered during and after treatment.

• Desmopressin: Glucovance may reduce the antidiuretic effect of desmopressin.

Avoid alcohol and medicines containing alcohol. Intolerance to alcohol may occur. Alcohol increases hypoglycaemic symptoms and the risk of lactic acidosis.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicinal products, including medicinal products obtained without a prescription.

Dosage and Administration

This medicine is for adults only.

Initial treatment: The starting dose should not exceed the daily dose of glibenclamide and metformin already being taken. You should be monitored closely for signs and symptoms of hypoglycaemia.

Titration: The daily dose may be titrated every two weeks or longer in increments of no more than 500 mg/5 mg up to the minimum effective dose. Your doctor will determine the dosage according to glycaemia and HbA1c.

Maximum dose: The maximum dose is 2000 mg metformin hydrochloride/20 mg glibenclamide per day

Elderly subjects**:**
The initial dosage is one tablet of Glucovance 500 mg/2.5 mg daily. The dosage should then be adjusted depending on renal function parameters (see section “Special warnings and precautions”).

Administration:
The tablets should be taken with meals. The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent hypoglycaemia. Patients should avoid alcohol when taking Glucovance. Take the tablets
• once a day, in the morning (breakfast) if you take 1 tablet per day
• twice a day, in the morning (breakfast) and evening (dinner) if you take 2 or 4 tablets per day
• three times a day, in the morning (breakfast), noon (lunch) and evening (dinner), if you take 3 tablets per day.

Missed dose:
You must not take a double dose to make up for a forgotten dose. You should take the next dose at the usual time.

Overdose

If you have taken more Glucovance tablets than you should have, **TALK to your DOCTOR IMMEDIATELY.** You may indeed experience:
• hypoglycaemia due to the presence of glibenclamide. Treatment is directed to symptoms (see section “Special warnings and precautions”). However, glibenclamide is not dialyzable.
• lactic acidosis due to the presence of metformin (see section “Special warnings and precautions ”). Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis.

Storage and Stability

Store below 30°C.
Do not use Glucovance after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Keep out of the reach and sight of children.

Presentations

• Glucovance 500 mg/2.5 mg tablets are orange capsule-shaped, biconvex, film-coated tablets with “2.5” engraved on one side.
• Glucovance 500 mg/5 mg tablets are yellow capsule-shaped, biconvex, film-coated tablets with “5” engraved on one side.
• Glucovance 1000 mg/5 mg tablets are white to off-white oval-shaped, biconvex, film-coated tablets with '1000' engraved on one side and '5' engraved on the other side.

The tablets are supplied in blister packs containing 30 tablets (PVC/Aluminium).

Date of information:

June 2009

Manufacturer
Merck Santé s.a.s.
2, rue du Pressoir Vert
45400 SEMOY - FRANCE

THIS IS A MEDICAMENT

Medicament is a product, which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.