

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

GLUCOVANCE 500 mg/5 mg, film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin, and 5 mg glibenclamide.

Excipient(s) with known effect: lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow capsule-shaped, biconvex film-coated tablets with '5' engraved on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

#### Posology

Oral route.

For use in adults only.

#### **General:**

As for all hypoglycaemic agents, the dosage should be adapted according to the individual metabolic response (glycaemia, HbA1c).

Glucovance 500 mg/5 mg may preferentially be used in patients inadequately controlled with Glucovance 500 mg/2.5 mg.

*Adults with normal renal function ( $GFR \geq 90$  mL/min)*

#### **Initiation of treatment:**

Treatment should be initiated with a dose of the combination product equivalent to previous individual doses of metformin and glibenclamide; the dose being gradually increased depending on results on glycaemic parameters.

**Dose titration:**

The dosage should be adjusted every 2 weeks or longer, by increments of 1 tablet, depending on glycaemia results.

A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.

**Maximum daily recommended dose:**

- The maximum daily recommended dose is 3 tablets of Glucovance 500 mg/5 mg.
- In exceptional cases, an increase up to 4 tablets of Glucovance 500 mg/5 mg per day may be recommended.

**Combination with insulin therapy:**

No clinical data are available on the concomitant use of this product with insulin therapy.

*Renal impairment*

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Glucovance is available, individual mono-components should be used instead of the fixed dose combination.

GFR mL/min	Metformin	Glibenclamide
60-89	Maximum daily dose is 3000 mg.  Dose reduction may be considered in relation to declining renal function.	No dose reduction required.
45-59	Maximum daily dose is 2000 mg.  The starting dose is at most half of the maximum dose.	Maximum daily dose is 10.5 mg.
30-44	Maximum daily dose is 1000 mg.  The starting dose is at most half of the maximum dose.	Maximum daily dose is 10.5 mg. Initiation of therapy is not recommended due to the risk of hypoglycemia.
< 30	Metformin / glibenclamide are contraindicated	

*Geriatric population:*

The dosage of Glucovance should be adjusted depending on renal function parameters (start with 1 tablet of Glucovance 500 mg/2.5 mg); regular checks on the renal function are necessary (see section 4.4).

Patients aged 65 years and older: starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia. Treatment should be started with the lowest available dose and increased gradually if necessary (see section 4.4).

#### Paediatric population:

Glucovance is not recommended for use in children (see section 5.1).

#### Method of administration

The dosage regimen depends on the individual posology:

- Once a day, in the morning at breakfast, for a dosage of 1 tablet/day,
- Twice a day, morning and evening, for a dosage of 2 or 4 tablets/day,
- Three times a day, morning, noon and evening, for a dosage of 3 tablets/day.

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 the onset of hypoglycaemic episodes.

When Glucovance is co-administered with a bile acid sequestrant, it is recommended that Glucovance should be administered at least 4 hours prior to the bile acid sequestrant in order to minimize the risk of reduced absorption (see section 4.5).

### **4.3 Contraindications**

- hypersensitivity to metformin, glibenclamide or other sulphonylurea(s) and sulphonamide(s) or to any of the excipients listed in section 6.1;
- type 1 diabetes (insulin-dependent diabetes), diabetic pre-coma;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- severe renal failure (GFR < 30 mL/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock;
- disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock;
- hepatic insufficiency, acute alcohol intoxication, alcoholism;
- porphyria;
- lactation;
- in association with miconazole (see section 4.5).

### **4.4 Special warnings and precautions for use**

#### **Lactic acidosis**

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis,

prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

## **Hypoglycaemia**

As it contains a sulphonylurea, Glucovance exposes the patient to a risk of onset of hypoglycaemic episodes. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment should only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important that carbohydrate intake is regular since the risk of hypoglycaemia is increased by a late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycaemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol intake or during the administration of a combination of hypoglycaemic agents.

### *Diagnosis:*

The symptoms of hypoglycaemia are: headache, hunger, nausea, vomiting, extreme tiredness, sleep disorder, restlessness, aggression, impaired concentration and reactions, depression, confusion, speech impediment, visual disturbances, trembling, paralysis and paraesthesia, dizziness, delirium, convulsions, somnolence, unconsciousness, superficial breathing and bradycardia. Due to a counterregulation caused by the hypoglycaemia sweating, fear, tachycardia, hypertension, palpitations, angina and arrhythmia can occur. These latter symptoms can be absent when the hypoglycaemia is developed slowly, in case of autonomic neuropathy or when the patients take beta-blocking agents, clonidine, reserpine, guanethidine or sympathomimetics.

### *Management of hypoglycaemia:*

Moderate hypoglycaemic symptoms without loss of consciousness or neurological manifestations should be corrected by the immediate intake of sugar. An adjustment to the dosage and/or changes to meal patterns should be ensured. Severe hypoglycaemic reactions with coma, seizures or other neurological signs are also possible and constitute a medical emergency requiring immediate treatment with intravenous glucose once the cause is diagnosed or suspected, prior to prompt hospitalisation of the patient.

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.

### Factors favouring hypoglycaemia:

- concomitant administration of alcohol, especially combined with fasting,
- refusal or (more particularly in elderly patients) inability of the patient to co-operate,
- malnutrition, irregular meals, missed meals, fasting or changes to diet,
- poor balance between physical exercise and carbohydrate intake,
- renal failure,
- severe liver failure,
- overdose of Glucovance,
- certain endocrine disturbances: thyroid insufficiency, pituitary and adrenal gland insufficiency,
- concomitant administration of certain other drugs (see section 4.5).

### *Elderly patients:*

Age 65 years and older has been identified as a risk factor for hypoglycemia in patients treated with sulfonylureas. Hypoglycemia can be difficult to recognize in the elderly. Starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia (see section 4.2).

### *Renal and hepatic failure:*

The pharmacokinetics and/or pharmacodynamics of Glucovance may be modified in patients with hepatic failure or severe renal failure. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated.

### *Patient information:*

The risks of hypoglycaemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family. Similarly, the risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps accompanied by digestive disorders, abdominal pain and severe asthenia, dyspnoea attributed to acidose, hypothermia and coma.

In particular, the patient should be informed of the importance of adhering to a diet, following a programme of regular physical exercise and making regular checks on glycaemia.

### **Blood sugar imbalance**

In case of surgery or any other cause of diabetic decompensation, temporary insulin therapy should be envisaged instead of this treatment.

The symptoms of hyperglycaemia are: increased urinating, raging thirst and a dry skin.

### **Cardiac function**

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Glucovance may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Glucovance is contraindicated (see section 4.3).

### **Renal function**

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

### **Administration of iodinated contrast agents**

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Glucovance should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

### **Concomitant use of glibenclamide with other medicinal products**

The concomitant use of glibenclamide with alcohol, phenylbutazone or danazol is not recommended (see section 4.5).

### **Surgery**

Glucovance must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

### **Other precautions**

All patients should continue their diet, with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

Regular physical exercise is as necessary as taking Glucovance.

The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly,

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since glibenclamide belongs to the chemical class of sulphonylurea drugs, caution is recommended when using Glucovance in patients with G6PD-deficiency and a non-sulphonylurea alternative may be considered.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, i.e. essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

### Contraindicated combination

#### Related to glibenclamide

*Miconazole (systemic route, oromucosal gel)*: Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma (see section 4.3).

### Combinations not recommended

#### Related to sulphonylurea(s)

##### *Alcohol:*

Antabuse effect (intolerance to alcohol), notably for chlorpropamide, glibenclamide, glipizide, tolbutamide.

Increase of the hypoglycaemic reaction (inhibition of compensation reactions), which may facilitate the onset of a hypoglycaemic coma (see section 4.4).

Avoid consumption of alcohol and alcohol-containing medications.

##### *Phenylbutazone (systemic route):*

Increase in the hypoglycaemic effect of sulphonylurea(s) (displacement of sulphonylurea(s) from protein-binding sites and/or decrease in their elimination). Preferably use another anti-inflammatory agent exhibiting fewer interactions, or else warn the patient and step up self-monitoring; if necessary, adjust the dosage during treatment with the anti-inflammatory agent and after its withdrawal.

#### Related to all antidiabetic agents

##### *Danazol:*

If the combination cannot be avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with danazol and after its withdrawal.

#### Related to metformin

##### *Alcohol:*

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

##### *Iodinated contrast agents:*

Glucovance must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

### Combinations requiring precautions

#### Related to all antidiabetic agents

##### *Chlorpromazine:*

At high dosages (100 mg per day of chlorpromazine), elevation in blood glucose (reduction in release of insulin).

Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with the neuroleptic and after its withdrawal.



*Corticosteroids (glucocorticoids) and tetracosactides (systemic and local routes):*

Elevation in blood glucose, sometimes accompanied by ketosis (decreased carbohydrate tolerance with corticosteroids).

Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with corticosteroids and after their withdrawal.

*β<sub>2</sub>-agonists:*

Elevation in blood glucose due to the β<sub>2</sub>-agonists.

Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to insulin therapy.

### Related to metformin

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

*Organic cation transporters (OCT)*

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

### Related to glibenclamide

*Beta-blockers:*

All beta-blockers mask some of the symptoms of hypoglycaemia: palpitations and tachycardia; Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia.

Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.

*Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril):*

ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of Glucovance during therapy with an ACE inhibitor and upon its discontinuation.

*Fluconazole:*

Increase in the half-life of sulphonylurea with possible onset of hypoglycaemic manifestations.

Warn the patient and step up blood glucose self-monitoring, and possibly adjust the dosage of the antidiabetic treatment during treatment with fluconazole and after its withdrawal.

*Bosentan:*

Risk of decreased hypoglycaemic effect of glibenclamide because bosentan reduces the plasma concentration of glibenclamide. An increased risk of liver enzyme elevations was reported in patients receiving glibenclamide concomitantly with bosentan.

Warn the patient, set-up monitoring of glycaemia and liver enzymes and adjust the dosage of the antidiabetic treatment if necessary.

*Bile acid sequestrants:*

When co-administered simultaneously the plasma concentration of glibenclamide is reduced which may lead to a reduced hypoglycaemic effect. This effect was not observed if glibenclamide is given in a certain period of time before taking the other medicine. It is recommended that Glucovance should be administered at least 4 hours prior a bile acid sequestrant.

**Other interaction: combination to be taken into account:**

Related to glibenclamide

*Desmopressin:*

Reduction in antidiuretic activity.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

No preclinical and clinical data on exposed pregnancies are available for Glucovance.

Risk related to diabetes

When uncontrolled, diabetes (gestational or permanent) gives rise to an increase in congenital abnormalities and perinatal mortality. Diabetes must be controlled as far as possible during the period of conception in order to reduce the risk of congenital abnormalities.

Risk related to metformin (see section 5.3)

Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities.

Risk related to glibenclamide (see section 5.3)

Studies in animals have shown no evidence of teratogenic activity. In the absence of a teratogenic effect in animals, foetal malformation in humans is not to be expected since to date, substances known to cause malformation in humans have proved to be teratogenic in well-conducted animal studies in two species.

In clinical practice, there are currently no relevant data on which to base an evaluation of potential malformation or fetotoxicity due to glibenclamide when administered during pregnancy.

**Management**

Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. Glucovance must not be used for the treatment of diabetes during pregnancy.

It is imperative that insulin be used to achieve adequate blood glucose control. It is recommended that the patient be transferred from oral antidiabetic therapy to insulin as soon as she plans to become pregnant or if pregnancy is exposed to this medicinal product. Neonatal blood glucose monitoring is recommended.

## **Breast-feeding**

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants of mothers treated with metformin alone. However, in humans, in the absence of data concerning passage of glibenclamide into breast milk, and in view of the risk of neonatal hypoglycaemia, this medicinal product is contraindicated in the event of breast-feeding.

## **Fertility**

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Fertility of male or female rats was unaffected by glibenclamide when administered orally at dose of 100 and 300 mg/kg/day.

### **4.7 Effects on ability to drive and use machines**

Patients should be alerted to the symptoms of hypoglycaemia and should be advised to exercise caution when driving or using machines.

### **4.8 Undesirable effects**

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take Glucovance in 2 or 3 daily doses and to increase slowly the doses. Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.

The following adverse reactions may occur under treatment with Glucovance. Frequencies are defined as follows: very common:  $\geq 1/10$ ; common  $\geq 1/100$ ,  $< 1/10$ ; uncommon:  $\geq 1/1,000$ ,  $< 1/100$ ; rare  $\geq 1/10,000$ ,  $< 1/1,000$ ; very rare  $< 1/10,000$ .

#### **Blood and lymphatic system disorders:**

These are reversible upon treatment discontinuation.

*Rare:* Leukopenia, thrombocytopenia.

*Very rare:* Agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.

#### **Metabolism and nutrition disorders:**

Hypoglycaemia (see section 4.4).

*Uncommon:* Crises of hepatic porphyria and porphyria cutanea.

*Common:* Vitamin B12 decrease/deficiency (see section 4.4).

*Very rare:* Lactic acidosis (see section 4.4).

Disulfiram-like reaction with alcohol intake.

#### **Nervous system disorders:**

*Common:* Taste disturbance.

#### **Eye disorders:**

Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.

#### **Gastrointestinal disorders:**

*Very common:* Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment initiation and resolve spontaneously in most cases. To prevent them, it is recommended that Glucovance be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.

**Skin and subcutaneous tissue disorders:**

A cross reactivity to sulphonamide(s) and their derivatives may occur.

*Rare:* Skin reactions such as pruritus, urticaria, maculopapular rash.

*Very rare:* Cutaneous or visceral allergic angiitis, erythema multiforme, exfoliative dermatitis, photosensitization, urticaria evolving to shock.

**Hepatobiliary disorders:**

*Very rare:* Liver function test abnormalities or hepatitis requiring treatment discontinuation

**Investigations:**

*Uncommon:* Average to moderate elevations in serum urea and creatinine concentrations.

*Very rare:* Hyponatremia.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V.**

**4.9 Overdose**

Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea (see section 4.4).

High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin (see section 4.4). Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis.

The plasma clearance of glibenclamide may be prolonged in patients suffering from liver disease. Since glibenclamide is extensively bound to proteins, it is not eliminated by dialysis.

**5. PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Biguanides and sulphonamide(s) in combination. ATC code: A10BD02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- (1) by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- (3) and by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL-cholesterol and triglyceride levels. In clinical trials conducted so far with combination therapy with metformin and glibenclamide, these favourable effects on lipid metabolism have not been shown.

Glibenclamide is a second generation sulphonylurea with a medium half-life: it causes acute lowering of blood glucose by stimulating the release of insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans.

The stimulation of insulin secretion by glibenclamide in response to a meal is of major importance.

The administration of glibenclamide to diabetics induces an increase in the postprandial insulin-stimulating response. The increased postprandial responses in insulin and C-peptide secretion persist after at least 6 months of treatment.

Metformin and glibenclamide have different mechanisms and sites of action, but their action is complementary. Glibenclamide stimulates the pancreas to secrete insulin, while metformin reduces cell resistance to insulin by acting on peripheral (skeletal muscle) and hepatic sensitivity to insulin.

Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with metformin or glibenclamide combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation.

#### **Paediatric population:**

In a 26-week, active controlled, double-blind, clinical study performed in 167 paediatric patients aged 9 to 16 years with type 2 diabetes not adequately controlled with diet and exercise, with or without an oral antidiabetic treatment, a fixed combination of metformin hydrochloride 250 mg and glibenclamide 1.25 mg was not shown more effective to either metformin hydrochloride or glibenclamide in reducing HbA1c from baseline. Therefore, Glucovance should not be used in paediatric patients.

## **5.2 Pharmacokinetic properties**

### **Related to the combination**

The bioavailability of metformin and glibenclamide in the combination is similar to that noted when one tablet of metformin and one tablet of glibenclamide are taken simultaneously. The bioavailability of metformin in the combination is unaffected by the ingestion of food. The bioavailability of glibenclamide in the combination is unaffected by the ingestion of food, but the absorption speed of glibenclamide is increased by eating.

### **Related to metformin**

#### **Absorption:**

After an oral dose of metformin tablet, maximum plasma concentration ( $C_{max}$ ) is reached in approximately 2.5 hours ( $t_{max}$ ). Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1  $\mu\text{g/ml}$ . In controlled clinical trials, maximum metformin plasma levels ( $C_{max}$ ) did not exceed 5  $\mu\text{g/ml}$ , even at maximum doses.

### Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution  $V_d$  ranged from 63 to 276 l.

### Biotransformation:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

### Elimination:

Renal clearance of metformin is  $> 400$  ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

## **Related to glibenclamide**

### Absorption:

Glibenclamide is very readily absorbed ( $> 95\%$ ) following oral administration. The peak plasma concentration is reached in about 4 hours.

### Distribution:

Glibenclamide is extensively bound to plasma albumin (99%), which may account for certain drug interactions.

### Biotransformation:

Glibenclamide is completely metabolised in the liver to two metabolites. Hepatocellular failure decreases glibenclamide metabolism and appreciably slows down its excretion.

### Elimination:

Glibenclamide is excreted in the form of metabolites via biliary route (60%) and urine (40%), elimination being complete within 45 to 72 hours. Its terminal elimination half-life is 4 to 11 hours.

Biliary excretion of the metabolites increases in cases of renal insufficiency, according to the severity of renal impairment until a creatinine clearance at 30 ml/min. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 ml/min.

## **Paediatric population**

There were no differences in pharmacokinetics of glibenclamide and metformin between paediatric patients and weight-and gender-matched healthy adults.

### **5.3 Preclinical safety data**

No preclinical studies have been performed on the combination product. Preclinical evaluation of the constituents metformin and glibenclamide revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Animal studies on metformin and glibenclamide do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/ foetal development, parturition or postnatal development. (see section 4.6).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose

Sodium croscarmellose

Povidone K30

Magnesium stearate

#### Film-coating

Opadry 31-F-22700 (yellow) (lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol, yellow iron oxide (E172), red iron oxide (E172), Quinoline Yellow Lake (E104)).

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

20, 28, 30, 50, 56, 60, 84, 90, 100, 120, 180 and 600 tablets in clear or opaque blister (PVC/Aluminium).

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORIZATION HOLDER**

[To be completed nationally]

**8. MARKETING AUTHORISATION NUMBER**

[To be completed nationally]

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

**10. DATE OF REVISION OF THE TEXT**

[To be completed nationally]



## **LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

GLUCOVANCE 500 mg/5 mg, film-coated tablets  
metformin hydrochloride/glibenclamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin and 5 mg glibenclamide.

**3. LIST OF EXCIPIENTS**

Lactose.  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

20 tablets  
28 tablets  
30 tablets  
50 tablets  
56 tablets  
60 tablets  
84 tablets  
90 tablets  
100 tablets  
120 tablets  
180 tablets  
600 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

GLUCOVANCE 500 mg/5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

GLUCOVANCE 500 mg/5 mg, film-coated tablets  
metformin hydrochloride/glibenclamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PACKAGE LEAFLET**

**Package leaflet: Information for the user**  
**GLUCOVANCE 500 mg/2.5 mg, film-coated tablets**  
**GLUCOVANCE 500 mg/5 mg, film-coated tablets**

metformin hydrochloride and glibenclamide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet:**

1. What **Glucovance** is and what it is used for
2. What you need to know before you take **Glucovance**
3. How to take **Glucovance**
4. Possible side effects
5. How to store **Glucovance**
6. Contents of the pack and other information

**1. What Glucovance is and what it is used for**

**Glucovance is**

made up of two antidiabetic medicines, which belong to the groups of medicines called biguanide (metformin hydrochloride) and sulphonylurea (glibenclamide).

Insulin is a hormone that enables body tissues to take up glucose (sugar) from the blood and to use it for producing energy or to store it for future use. Patients with type 2 diabetes mellitus (i.e. non-insulin dependent diabetes) do not produce enough insulin in their pancreas or their body does not respond properly to the insulin it produces. This causes an increased level of glucose in the blood. Glucovance helps to reduce their blood sugar towards a normal level.

**Glucovance is used for**

the oral treatment (via the mouth) of **type 2 diabetes mellitus in adult patients**.

It is used to replace the combination of the two active substances of Glucovance (metformin hydrochloride and glibenclamide) given separately in patients previously treated with this combination, if the combination was effective in controlling the patients' glucose level in the blood.

**2. What you need to know before you take Glucovance**

**Do not take Glucovance**

- if you are allergic (hypersensitive) to metformin hydrochloride, glibenclamide or other sulphonamides or any of the other ingredients of Glucovance (listed in section 6)
- if you have severely reduced kidney function
- if you have liver function problems
- if you suffer from type 1 diabetes mellitus (i.e. insulin-dependent)
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, 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

stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

- if you have a severe infection (for example an infection of the air passages or an urinary tract infection)
- if you are dehydrated (for example due to persistent or severe diarrhoea, recurrent vomiting)
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if 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)
- if you use miconazole (a medicine to treat certain yeast infections) even for local use
- if you drink alcohol excessively (either every day or only from time to time)
- if you are breast-feeding.

#### **Make sure you ask your doctor for advice,**

- if you need to have an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your bloodstream
- if you need to have a surgery under general, spinal or peridural anaesthesia

You must stop taking Glucovance for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor's instructions precisely.

#### **Warnings and precautions**

Talk to your doctor before taking Glucovance.

#### **Risk of lactic acidosis**

Glucovance 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 problems and any medical conditions in which a part of the body has reduced supply of oxygen (such as acute severe heart disease).

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

**Stop taking Glucovance 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 fluid than normal. Talk to your doctor for further instructions.

**Stop taking Glucovance 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
- stomach ache (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.

If you need to have major surgery you must stop taking Glucovance during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Glucovance.

## **Risk of Hypoglycaemia**

- if you experience symptoms of low blood sugar (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.
- Patients aged 65 years and older are particularly sensitive to hypoglycemic action of glibenclamide and are therefore more at risk of hypoglycaemia. In the elderly, low blood sugar may be somewhat difficult to recognise. The initial dose and the maintenance dose of glibenclamide, must be set by your doctor carefully in order to avoid hypoglycemic reactions.

If you notice any of these signs:

- first eat glucose tablets or a high sugar snack (honey, sweets, biscuits, fruit juice),
- **STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away** as you may need to be hospitalised to bring your blood glucose back under control, then rest.

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 low blood sugar level might occur if:

- you eat too little or miss a meal
- your diet contains insufficient or unbalanced levels of sugar
- you drink alcohol
- you exercise more than usual
- you have liver, kidney or certain hormone problems
- the dosage of your medicine is too high
- you are an elderly person
- you are taking certain medicines and Glucovance at the same time (see section 2, “Other medicines and Glucovance”).

Discuss with your doctor whether Glucovance is the appropriate treatment for your diabetes if you often experience severe symptoms of low blood sugar or if you find it hard to recognise them.

- if you suffer from any infectious illnesses such as flu, infection of the air passages or urinary tract infection.
- if you have an inherited condition where your red blood cells don't produce enough of the enzyme G6PD (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
- Continue to follow any dietary advice your doctor has given you and get some regular exercise while you are taking this medicine.
- Consult your doctor regularly to test your blood sugar levels and your kidney function.

Consult your doctor, if any of the above-mentioned situations applies to you and if you feel unsure about using this medicine.

During treatment with Glucovance, 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.

## **Other medicines and Glucovance**

*While taking Glucovance, you must not use any of the following medicines:*

- miconazole even for local use (see section 2, “Do not take Glucovance”)
- If you need to have an injection of contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Glucovance before or at



the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Glucovance.

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 Glucovance. It is especially important to mention the following:

- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID 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)
- beta-blockers (used to treat a variety of cardiovascular conditions, such as high blood pressure, and some other diseases)
- beta-2 agonists (used to treat asthma, such as ritodrine, salbutamol or terbutaline)
- bosentan (used to treat pulmonary hypertension)
- corticosteroids and tetracosactide (a class of hormones used to treat a variety of conditions, e.g. severe inflammation of the skin or in asthma)
- fluconazole (used to treat certain yeast infections)
- chlorpromazine (a neuroleptic medicine, which affects how your brain works)
- desmopressin (generally used to reduce urine production)
- danazol (used to treat endometriosis, a condition where the tissue lining of the uterus is found outside the uterus)
- bile acid sequestrants (cholesterol-lowering medicines used to reduce the amount of cholesterol in the blood)
- medicines that may change the amount of Glucovance in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

Special precautions may include self-monitoring of blood glucose, blood tests and modification of dosage.

### **Glucovance with alcohol**

Avoid excessive alcohol intake while taking Glucovance since this may increase the risk of lactic acidosis (see section “Warnings and precautions”).

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. 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.

### **Driving and using 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 low blood sugar begin to appear.

### **Important information about some of the ingredients of Glucovance**

Each Glucovance tablet contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

### 3. How to take Glucovance

#### Dosage

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Only adults may take this medicine.

Your doctor will adapt the dosage of your treatment depending on its effect on your blood tests.

Continue to follow any dietary advice your doctor has given you. Glucovance cannot replace the benefits of a healthy lifestyle.

Have a regular meal schedule with a sufficient and balanced sugar intake. This will decrease the risk of low blood sugar.

The usual starting dose is equivalent to the individual doses of metformin hydrochloride and glibenclamide you received before being treated with Glucovance. If you are an elderly person, the usual starting dose is one tablet of Glucovance 500 mg/2.5 mg per day.

#### Maximum daily dose

For Glucovance 500 mg/2.5 mg: 6 tablets.

For Glucovance 500 mg/5 mg: 3 tablets. In exceptional cases, your doctor may prescribe 4 tablets.

#### Dosage adjustment in elderly patients

Take special care if you are an elderly person. The dose of Glucovance will be carefully increased depending on your blood sugar levels and your kidney function. Make sure that you consult your doctor regularly.

#### Dosage adjustment in patients with reduced kidney function

If you have reduced kidney function, your doctor may prescribe a lower dose.

#### Administration

Take the tablets with a meal. Swallow each tablet whole with a glass of water. Do not crush or chew them before swallowing.

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, 5 or 6 tablets per day.

Your doctor will tell you how to take Glucovance if you have to take it in combination with a cholesterol-lowering medicine (bile acid sequestrant). Glucovance must be taken at least 4 hours prior to a cholesterol-lowering medicine (bile acid sequestrant).

#### If you take more Glucovance than you should

If you have taken more Glucovance tablets than you should have, you may experience lactic acidosis or low blood sugar (for symptoms of lactic acidosis and low blood sugar, see section 2, "Warnings and precautions"). **TALK to your DOCTOR IMMEDIATELY.**

#### If you forget to take Glucovance

Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time.

#### If you stop taking Glucovance

There are usually no side effects when you stop taking this medicine. However, as your diabetes is not treated any more, complications due to a lack of treatment can occur.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects were observed in clinical studies or in routine patient management.

Glucovance may cause a very rare (may affect up to 1 user in 10,000), but very serious side effect called lactic acidosis (see section “Warnings and precautions”). If this happens you must **stop taking Glucovance and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Vision disorders: When you start taking this medicine, it may disturb your vision due to a lower level of sugar in your blood. However, this reaction usually disappears after a while.

Low blood sugar: For symptoms of low blood sugar, see section 2, “Warnings and precautions”.

##### **Very common side effects** (may affect more than 1 in 10 people)

- gastrointestinal disorders such as nausea, vomiting, diarrhoea, bellyache and loss of appetite. These side effects occur most frequently after starting therapy. It helps if you spread the doses over the day and if you take the tablets with a meal. **Should these symptoms continue, STOP taking this medicine and CONSULT your DOCTOR.**

##### **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 (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

##### **Uncommon side effects** (may affect up to 1 in 100 people)

- abnormal urea and creatinine levels in the blood, which show changes in the way the kidneys are working.
- a crisis of certain forms of porphyria (porphyria hepatica or porphyria cutanea; for an explanation of porphyria, see section 2, “Do not take Glucovance”) may occur in patients with certain enzyme deficiency.

##### **Rare side effects** (may affect up to 1 in 1.000 people)

- reduction in the number of white blood cells, which makes infections more likely
- reduction in blood platelets which increases risk of bleeding or bruising
- skin reactions including itching, hives, skin rash

##### **Very rare side effects** (may affect up to 1 in 10.000 people)

- lactic acidosis (see section “Warning and precautions”)
- severe reduction in the number of white blood cells (agranulocytosis), anaemia due to a too extensive breakdown of the red blood cells (haemolytic anaemia), lack or insufficient number of new blood cells produced by the bone marrow (bone marrow aplasia) and very severe reduction in the number of blood cells (pancytopenia; this can make the skin look pale, can cause weakness or breathlessness, can increase the risk of bleeding or bruising or make infections more likely)
- abnormalities in liver function tests or inflammation of the liver (hepatitis; this can cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, **stop taking Glucovance and talk to your doctor.**
- excessive skin sensitivity to sun, serious allergic reactions of the skin or blood vessels
- intolerance to alcohol (with symptoms such as general feeling of discomfort, redness of face, rapid heart beat)

- low level of sodium, which can cause tiredness and confusion, muscle twitching, fits or coma

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Glucovance**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## **6. Contents of the pack and other information**

### **What Glucovance contains**

- The active substances are metformin hydrochloride and glibenclamide.
- One film-coated tablet of Glucovance 500 mg/2.5 mg contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base and 2.5 mg glibenclamide.
- One film-coated tablet of Glucovance 500 mg/5 mg contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base and 5 mg glibenclamide.
- The other ingredients are microcrystalline cellulose, sodium croscarmellose, povidone K 30, magnesium stearate and Opadry OY-L-24808 (orange) [lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)] in Glucovance 500 mg/2.5 mg or Opadry 31-F-22700 (yellow) [lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol, yellow iron oxide (E172), red iron oxide (E172), Quinoline Yellow Lake (E104)] in Glucovance 500 mg/5 mg.

### **What Glucovance looks like and contents of the pack**

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.

The tablets are supplied in clear or opaque blister packs containing 20, 28, 30, 50, 56, 60, 84, 90, 100, 120, 180 or 600 tablets (PVC/Aluminium). Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

[To be completed nationally]

### **Manufacturer**

Merck Santé / SEMOY  
2 rue du Pressoir Vert  
F-45400 Semoy, France

or

Merck, S.L.  
Poligono Merck  
Mollet Del Valles, 08100 Barcelona  
Spain

**This medicine is authorised in the Member States of the European Economic Area under the following names:**

France, Netherlands, Portugal,: GLUCOVANCE 500 mg/5 mg

**This leaflet was last revised in .....**