AUSTRALIAN PRODUCT INFORMATION

GLUCOVANCE®

(metformin hydrochloride and glibenclamide) tablet

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

1 NAME OF THE MEDICINE

Metformin hydrochloride and Glibenclamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GLUCOVANCE contains metformin hydrochloride and glibenclamide combination as the active ingredients and is available in three strength combinations:

Each GLUCOVANCE 250/1.25 tablet contains 250 mg metformin hydrochloride and 1.25 mg glibenclamide.

Each GLUCOVANCE 500/2.5 tablet contains 500 mg metformin hydrochloride and 2.5 mg glibenclamide.

Each GLUCOVANCE 500/5 tablet contains 500 mg metformin hydrochloride and 5 mg glibenclamide.

Excipients with known effect: lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Oral. Film-coated tablets.

GLUCOVANCE 250/1.25	:	Yellow film-coated, capsule-shaped, biconvex tablets, engraved with "250" on one side and "1.25" on the other side
GLUCOVANCE 500/2.5	:	Pale orange film-coated, capsule-shaped, biconvex tablets, engraved with "2.5" on one side
GLUCOVANCE 500/5	:	Yellow film-coated, capsule-shaped, biconvex tablets, engraved with "5" on one side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Second line treatment of diabetes mellitus type II in adult patients whose glycaemic control is inadequate after diet and exercise alone and where combined therapy with metformin and glibenclamide is appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

As with all hypoglycaemic drugs, the dosage should be individualised according to the metabolic response of each patient (glycaemia, HbA1c). It is recommended to initiate therapy with a low dosage and to gradually increase the dose as a function of laboratory results.

GLUCOVANCE may be used instead of a previously prescribed oral antidiabetic. This transfer can generally be made without any transition period, starting for preference with a low dosage and adjusting it thereafter as a function of the metabolic response of each patient. However, if the patient was previously taking a sulfonylurea with a long half-life, a treatment-free washout period of a few days may be necessary, so as to minimise the risk of hypoglycaemia due to an additive effect of the two drugs. It is recommended that, when switching the patient to a fixed-dose combination product containing metformin, any previously prescribed individual-component products should be discontinued, to minimise the risk of accidental overdosing or dose related adverse effects. Only one strength of the fixed-dose combination product should be prescribed and used at any one time.

Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose. Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal), or in the event a dose cannot be taken at the prescribed time, must be discussed and agreed between the doctor and the patient beforehand.

Initiation of treatment

Monotherapy failure

In the event of monotherapy failure with metformin or a sulfonylurea, the usual initial dosage is 1 tablet of GLUCOVANCE 500 mg/2.5 mg daily.

Combination therapy substitution

In patients already on combination therapy with metformin and sulfonylurea, the initial dosage should be 1 to 2 tablets of GLUCOVANCE 500 mg/2.5 mg daily. It is recommended to start with a lower dose of the currently used agents in the fixed combination to reduce the risk of hypoglycaemia.

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 recommended daily 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.

Dosing frequency

The tablets should be taken at the beginning of meals. The dosage regimen depends on the daily dosage in a given patient, such as:

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

The dosing frequency should be adjusted according to the eating habits of each patient. However, **any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.**

Specific populations

Elderly

In the elderly, the dosage of GLUCOVANCE should be adjusted depending on renal function parameters (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in the elderly). It is recommended

to initiate treatment with one tablet daily of GLUCOVANCE 250 mg/1.25 mg, then adjust the doses according to laboratory test results.

Paediatric patients

GLUCOVANCE is not recommended for use in children and adolescents (see Section 5.1 PHARMACODYNAMICS - Clinical Trials, Paediatric patients).

4.3 CONTRAINDICATIONS

This medicinal product must never be used in case of:

- Hypersensitivity to metformin hydrochloride, glibenclamide or other sulfonylureas or sulfonamides or to any of the excipients
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min)
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast materials (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock, acute significant blood loss, sepsis, gangrene.
- Major surgery (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Porphyria
- Congenital galactosemia, glucose and galactose malabsorption syndrome or lactase deficiency
- Lactation
- In association with miconazole (see Section 4.5 INTERACTIONS WITH OTHER MERDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Metformin

Lactic acidosis

Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis is a medical emergency and must be treated in hospital immediately. The risk of lactic acidosis increases with the degree of renal dysfunction. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal insufficiency, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Special caution should be taken in the elderly due to the decrease of renal function with age.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient years, with approximately 0.015 fatal cases per 1,000 patient years). The onset is often subtle and accompanied by non-specific symptoms such as malaise, myalgia, respiratory distress, hypothermia,

increasing somnolence and non-specific abdominal distress. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly-controlled diabetes, ketosis, prolonged fasting, alcoholism, hepatic insufficiency and any condition associated with hypoxia.

Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 μg/mL and an increased anion gap and lactate/pyruvate ratio.

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 μg/mL are generally found (see Section 5.2 PHARMACOKINETIC PROPERTIES). Underlying renal disease, or deterioration in renal function, result in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis. The risk of lactic acidosis may therefore be significantly decreased by regular monitoring of renal function in patients taking GLUCOVANCE and those patients on concomitant diuretics. The minimum effective dose of GLUCOVANCE is recommended. In addition, GLUCOVANCE therapy should be temporarily stopped in the presence of any condition associated with hypoxaemia or dehydration, in patients suffering from serious infections or trauma (particularly if gastrointestinal disturbances are noted or acidosis is suspected) and in those undergoing surgery.

Patients with known or suspected mitochondrial diseases

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function

As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal 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.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy, and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast materials

The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. GLUCOVANCE must be discontinued either 48 hours before the test when renal function is known to be impaired or from the time of the test when renal function is known to be normal. GLUCOVANCE may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Because GLUCOVANCE contains metformin hydrochloride, GLUCOVANCE must be discontinued 48 hours before elective major surgery, and may not be reinstituted earlier than 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while taking GLUCOVANCE, due to the increase of risk of lactic acidosis particularly in case of fasting or malnutrition or hepatic insufficiency.

Pancreatitis

GLUCOVANCE must be discontinued when pancreatitis is combined with sepsis or hypoxia.

Other precautions

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 (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). It is recommended that vitamin B12 serum levels are monitored annually.

Glibenclamide

Hypoglycaemia

As it contains a sulfonylurea, GLUCOVANCE exposes the patient to a risk of onset of hypoglycaemic episodes. Severe hypoglycaemia, which may be prolonged and is potentially lethal, can be induced by all sulfonylureas. 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, after alcohol intake or during the administration of a combination of hypoglycaemic agents. The use of glibenclamide in the elderly may be associated with a higher risk of hypoglycaemia than in younger adults. Hypoglycaemia may be more severe and more prolonged in the elderly.

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.

Risk factors for hypoglycaemia should be carefully monitored:

- refusal or (more particularly in elderly patients) inability of the patient to co-operate, debilitated patients
- age 65 years or older
    - it is recommended that these patients are not titrated to the maximum dose of GLUCOVANCE to avoid the risk of hypoglycaemia
- malnutrition, irregular meals, missed meals, fasting or changes to diet
- severe and prolonged exercise, 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
- alcohol ingestion, especially combined with fasting (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER INTERACTIONS)
- concomitant administration of certain other drugs, especially other antidiabetic agents (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER INTERACTIONS).

Correction of dosage must also be considered whenever the patient's weight changes, the patient's lifestyle changes or other factors arise that cause an increased susceptibility to hypoglycaemia or hyperglycaemia.

Age 65 years and older has been identified as a risk factor for hypoglycaemia in patients treated with sulfonylureas. Hypoglycaemia 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 DOSE AND METHOD OF ADMINISTRATION).

Renal and hepatic failure

The pharmacokinetics and/or pharmacodynamics of GLUCOVANCE may be modified in patients with hepatic failure or severe renal failure. Renal or hepatic insufficiency may cause increased serum concentrations of glibenclamide and hepatic insufficiency may also diminish glyconeogenic capacity. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated.

In the presence of a genetic defect in metabolism, the elimination half-life of glibenclamide may be prolonged.

It should be borne in mind that there is a possibility of cross sensitivity to sulfonamides and their derivatives.

Other precautions

- Type I diabetes should be treated with insulin.
- GLUCOVANCE should not be used if diabetes mellitus can be regulated by diet alone.
- The usual clinical and laboratory tests for diabetes monitoring, including blood glucose determination, should be performed regularly. This allows determination of the minimum effective dosage and detection of primary failure (inadequate lowering of blood glucose concentration at the maximum recommended dosage) or secondary failure (loss of control of blood glucose concentration following an initial period of effectiveness) to the medicinal product. Glycosylated haemoglobin measurements may also be useful for monitoring the patient's response to GLUCOVANCE therapy.
- Periodic assessment of renal, hepatic and cardiovascular function are also recommended during prolonged periods of treatment with GLUCOVANCE.
- Blood sugar imbalance. In cases of surgery or unusual stress (e.g. febrile infections) or any other cause of diabetic decompensation, temporary insulin therapy should be envisaged instead of this treatment.
- Because this medicinal product contains lactose, it is contraindicated in case of congenital galactosemia, glucose and galactose malabsorption syndrome or in case of lactase deficiency.

Information for the prescriber

It is recommended that, when switching the patient to a metformin/glibenclamide fixed-dose combination product, any previously prescribed individual-component products should be discontinued, to minimise the

risk of accidental overdosing or dose related adverse effects. Only one strength of the metformin/glibenclamide fixed-dose combination product should be prescribed and used at any one time.

Information for the patient

The risks of hypoglycaemia and hyperglycaemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family. Symptoms of hyperglycaemia include severe thirst, dry mouth, frequent micturition, dry skin; while symptoms of hypoglycaemia include intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep or transient neurological disorders. 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. In particular, the patient should be informed of the importance of adhering to a diet with a regular distribution of carbohydrate intake during the day, following a programme of regular physical exercise and making regular checks on glycaemia. Overweight patients should continue their energy-restricted diet.

Use in the Elderly

In the elderly, decreased renal function is frequent and asymptomatic. Therefore, it is recommended that creatinine and/or serum creatinine levels be determined before initiating treatment and regularly thereafter at least two to four times a year in elderly subjects. The dosage of GLUCOVANCE should be adjusted depending on renal function parameters.

Age 65 years and older has been identified as a risk factor for hypoglycaemia in patients treated with sulfonylureas. Hypoglycaemia 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 DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

GLUCOVANCE should not be administered to children.

Effects on Laboratory Tests

No information regarding the effect of metformin or glibenclamide on laboratory tests is available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Contraindicated combinations

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 CONTRAINDICATIONS).

Related to metformin

Iodinated contrast materials:

GLUCOVANCE must be discontinued either 48 hours before the test when renal function is known to be impaired, or from the time of the test when renal function is known to be normal (see Section 4.3 CONTRAINDICATIONS).

Inadvisable combinations

Related to glibenclamide

Bosentan:

There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide. Such use should be avoided. The hypoglycaemic effect of glibenclamide may also be reduced.

Related to sulfonylureas

Phenylbutazone (systemic route):

Increase in the hypoglycaemic effect of sulfonylureas (displacement of sulfonylureas 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.

Combinations requiring precautions

Related to metformin

Cimetidine:

Reduced clearance of metformin has been reported during cimetidine pharmacokinetic interaction study.

Anticoagulants:

Metformin increases the elimination rate of vitamin K antagonists during pharmacokinetics interaction study.

Nifedipine:

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

Organic cation transporters (OCT):

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with:

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) may decrease the renal elimination of metformin and thus lead to an increase metformin plasma concentration.

Carbonic anhydrase inhibitors:

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Metformin hydrochloride tablet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

NSAID:

May increase the risk of lactic acidosis and adversely affect renal function.

Therefore, caution is advised when these drugs are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

Related to glibenclamide

Fluconazole:

Increase in the half-life of sulfonylurea with possible onset of hypoglycaemic manifestations. Warn the patient and step up blood glucose self-monitoring, and possibly adjust the dosage of the antidiabetic during treatment with fluconazole and after its withdrawal.

Pharmacodynamic Interactions

Inadvisable combinations

Related to metformin

Alcohol:

Increased risk of lactic acidosis during acute alcoholic intoxication, particularly in cases of fasting or malnutrition and hepatic insufficiency. Avoid drinking alcoholic beverages and taking drugs that contain alcohol.

Related to sulfonylureas

Alcohol:

In very rare cases, intolerance to alcohol may occur. Disulfiram-like reactions have occurred very rarely following the concomitant use of alcohol and glibenclamide. This disulfiram effect has been reported with other sulfonylureas, notably for chlorpropamide, glibenclamide, glipizide, tolbutamide. Excessive alcohol ingestion may dangerously increase the hypoglycaemic action (via inhibition of compensation reactions or delaying its metabolic inactivation), which may facilitate the onset of a hypoglycaemic coma. Avoid consumption of alcohol and alcohol-containing medications.

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 during treatment with danazol and after its withdrawal.

Combinations requiring precautions

Related to metformin

Diuretics:

Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics. Thiazide diuretic therapy may impair glucose tolerance. Dosage adjustment of metformin may be required.

Other calcium channel blockers may affect glucose control in diabetic patients.

Beta-blockers:

Co-administration of metformin and beta-blockers may result in a potentiation of the anti-hyperglycaemic action. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

Related to glibenclamide

Other drugs given at the same time as sulfonylureas may cause undesirable depression or elevation of the blood sugar level.

Beta-blockers, clonidine, reserpine, guanethidine and sympathomimetics:

All beta-blockers, clonidine, reserpine, guanethidine and sympathomimetics 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.

Other drugs that may potentiate the hypoglycaemic action of glibenclamide:

Anabolic steroids, bezafibrate, chloramphenicol, clofibrate, co-trimoxazole, coumarin derivatives, disopyramide, fenfluramine, fluoxetine, gemfibrozil, guanethidine, heparin, MAO-inhibitors, non-steroidal anti-inflammatory agents, pentoxifylline (oxpentifylline) (parenteral, in high doses), phenylbutazone, phosphamides, probenecid, quinolone antibiotics, salicylates, sulphinpyrazone, tetracycline compounds and certain long-acting sulfonamides.

Other drugs that may cause an attenuation of the hypoglycaemic action of glibenclamide:

Acetazolamide, calcium channel blockers, cimetidine, diazoxide, glucagon, isoniazid, nicotinic acid (high dosage), oestrogens, progestogens, phenothiazine derivatives, phenytoin, ranitidine, rifampicin, saluretics, sympathomimetic agents, thyroid hormones and large doses of laxatives.

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 during treatment with the neuroleptic and after its withdrawal.

Corticosteroids (glucocorticoids) and tetracosactide (tetracosactrin) (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_2-agonists:

Elevation in blood glucose due to the β_2 agonist. Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to insulin therapy.

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.

Other interaction - combination to be taken into account

Related to glibenclamide

Desmopressin:

Reduction in antidiuretic activity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The potential effects of the combination of metformin and glibenclamide or glibenclamide alone on fertility have not been investigated in animal studies.

Fertility of male or female rats was unaffected by metformin alone at oral doses up to 600 mg/kg/day, approximately 3 times the maximum recommended daily dose on a body surface area basis.

Use in Pregnancy

Pregnancy Category C

GLUCOVANCE must not be used for the treatment of diabetes during pregnancy. The patient should be transferred from GLUCOVANCE to insulin during pregnancy. When uncontrolled, diabetes gives rise to an increase in congenital abnormalities and perinatal mortality. It is important to achieve strict normoglycaemia during pregnancy.

There are no adequate and well-controlled studies with metformin and glibenclamide in pregnant women. No studies in pregnant animals have been conducted with the combination of metformin and glibenclamide. Metformin alone was not teratogenic in rats and rabbits at oral doses up to 600 mg/kg/day and 140 mg/kg/day, respectively, approximately 3 and 1 times the maximum recommended daily dose on a body surface area basis. Sulfonylureas such as glibenclamide may enter the foetal circulation and cause neonatal hypoglycaemia. Embryotoxicity and/or birth defects have been demonstrated in animals dosed with glibenclamide alone.

Use in Lactation

Studies on lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Although it is not known whether glibenclamide is excreted in milk, some sulfonylurea drugs are known to be excreted in human milk. In view of the potential risk of neonatal hypoglycaemia, GLUCOVANCE should not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Until optimal control is achieved, or when changing from one product to another, or when tablets are not taken regularly, the patient's alertness and capacity to react may be impaired to such an extent that they may not be fit to drive or to operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Metformin

Gastrointestinal disorders

Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite are very common (>10%): these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that this medicinal product be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.

Metabolism and nutrition disorders

Lactic acidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) is a very rare (<0.01%) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.

The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted.

Vitamin B12 deficiency is commonly reported with metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see Section 4.4 SPECIAL WARNINGS AND

PRECAUTIONS FOR USE, Other precautions). Therefore, serum B12 levels should be monitored annually or periodic parenteral B12 supplementation considered.

Hepatobiliary disorders

Very rare: liver function test abnormalities or hepatitis requiring treatment discontinuation.

Skin and subcutaneous tissue disorders

Skin reactions such as erythema, pruritus and urticaria have been reported but the incidence is very rare (<0.01%).

Nervous system disorders

Taste disturbance (3 %) is common.

Glibenclamide

Clinical experience in the use of glibenclamide has shown that side effects serious enough to compel discontinuation of therapy are uncommon, even during long-term therapy. However, if adverse effects persist, the drug should be discontinued.

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting, diarrhoea, epigastric fullness or sensation of pressure, anorexia, heartburn, dyspepsia and diarrhoea are the most common adverse reactions for glibenclamide alone, occurring in about 1 to 2% of patients. Glibenclamide induced adverse gastrointestinal effects appear to be dose related and may subside following a reduction in dosage.

Metabolism and nutrition disorders

Hypoglycaemia which may be not only severe, but also prolonged and fatal (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Disulfiram effect with alcohol intake.

Hepatobiliary disorders

Hepatic porphyria, increased liver enzymes (AST, ALT), abnormal liver function, cholestasis, cholestatic hepatitis, granulomatous hepatitis and bilirubinemia have been reported with sulfonylureas.

Skin and subcutaneous tissue disorders

Reactions of skin and mucous membranes: pruritus, erythema, urticaria erythematous, maculopapular rash and bullous skin eruptions or psoriasiform drug eruption occur in 1.5% of glibenclamide treated patients; if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda, pellagra-like changes have been reported with sulfonylureas. A few cases of photosensitization have been reported. In very rare cases, cutaneous or visceral allergic angiitis, exfoliative dermatitis and urticaria evolving to shock have been reported.

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

Eye disorders

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

Blood and lymphatic system disorders

Haematological disorders, reversible when treatment is stopped:

leukopenia, thrombocytopenia, thrombocytopenic purpura; more rarely: agranulocytosis, eosinophilia, haemolytic anaemia, aplastic anaemia, bone marrow aplasia, pancytopenia and coagulation disorders.

Investigations

Occasional average to moderate elevations in serum urea and creatinine concentrations.

Isolated cases of hyponatraemia.

Miscellaneous

Although a causal relationship has not been established, the following adverse effects have been reported in patients receiving:

Glibenclamide:

paraesthesia, blindness, deafness, diplopia, visual disturbances, tremor, convulsions (other than withdrawal), encephalopathy, confusion, acute psychosis, abnormal renal function, acute renal failure, ocular disturbances (accommodation changes, crystalline lens changes), lactic acidosis, alopecia/hypotrichosis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), arthralgia, arthritis, cerebrovascular disorders, headache, facial oedema, angioedema and increased sweating.

GLUCOVANCE:

dystonia, muscle contractions involuntary, disorientation, grand mal seizure, unconsciousness, unresponsiveness, myocardial infarction, tachycardia, chest pain, pulmonary hypertension, pancreatitis, cholelithiasis, acute gallstone pancreatitis, gastrointestinal haemorrhage, disseminated intravascular coagulation, haemorrhage, acute renal failure, dermatitis, overdose, dehydration, metabolic acidosis, hypoglycaemic coma and elevated blood glucose level.

Clinical Trials of GLUCOVANCE

In double-blind U.S clinical trials involving GLUCOVANCE as initial therapy or as second-line therapy, a total of 642 patients received GLUCOVANCE, 312 received metformin therapy, 324 received glibenclamide therapy, and 161 received placebo. The percent of patients reporting events and types of adverse events reported in clinical trials of GLUCOVANCE (all strengths) as initial therapy and second-line therapy are listed in Table 1.

Table 1. Most Common Clinical Adverse Events (>5 %) in Double-Blind US Clinical Studies of GLUCOVANCE Used as Initial or Second-Line Therapy

	Number (%) of Patients			
Adverse Event	Placebo N = 161	Glibenclamide N = 324	Metformin N = 312	GLUCOVANCE N = 642
Upper respiratory infection	22 (13.7)	57 (17.6)	51 (16.3)	111 (17.3)
Diarrhoea	9 (5.6)	20 (6.2)	64 (20.5)	109 (17.0)
Headache	17 (10.6)	37 (11.4)	29 (9.3)	57 (8.9)
Nausea/vomiting	10 (6.2)	17 (5.2)	38 (12.2)	49 (7.6)
Abdominal pain	6 (3.7)	10 (3.1)	25 (8.0)	44 (6.9)
Dizziness	7 (4.3)	18 (5.6)	12 (3.8)	35 (5.5)

Hypoglycaemia

In controlled clinical trials of GLUCOVANCE there were no hypoglycaemic episodes classified as Serious Adverse Event. The incidence of reported symptoms of hypoglycaemia (such as dizziness, shakiness, sweating, and hunger), in the initial therapy trial of GLUCOVANCE are summarised in Table 2. The frequency of hypoglycaemic symptoms in patients treated with GLUCOVANCE 250 mg/1.25 mg was highest in patients with a baseline HbA1c<7%, lower in those with a baseline HbA1c of between 7 and 8%, and was

comparable to placebo and metformin in those with a baseline HbA1c >8%. For patients with a baseline HbA1c of between 8% and 11% treated with GLUCOVANCE 500 mg/2.5 mg as initial therapy, the frequency of hypoglycaemic symptoms was 30-35%. As second-line therapy in patients inadequately controlled on sulfonylurea or metformin alone, approximately 6.8% and 12.3% respectively of all patients treated with GLUCOVANCE experienced hypoglycaemic symptoms.

Gastrointestinal Reactions

The incidence of gastrointestinal side effects (diarrhoea, nausea/vomiting and abdominal pain) in the initial therapy trial are summarised in Table 2. Across all GLUCOVANCE trials, gastrointestinal symptoms were the most common adverse events with GLUCOVANCE and were more frequent at higher dose levels. In controlled trials, <2% of patients discontinued GLUCOVANCE therapy due to gastrointestinal adverse events.

Table 2. Treatment Emergent Symptoms of Hypoglycaemia or Gastrointestinal Adverse Events in a Placebo – and Active- Controlled Trial of GLUCOVANCE as Initial Therapy

Variable	Placebo N = 161	Glibenclamide tablets N = 160	Metformin tablets N = 159	GLUCOVANCE 250 mg/1.25 mg tablets N = 158	GLUCOVANCE 500 mg/2.5 mg tablets N = 162
Mean Final Dose	0 mg	5.3 mg	1317 mg	2.78 mg/557 mg	4.1 mg/824 mg
Number (%) of patients with symptoms of hypoglycaemia	5 (3.1)	34 (21.3)	5 (3.1)	18 (11.4)	61 (37.7)
Number (%) of patients with gastrointestinal adverse events	39 (24.2)	38 (23.8)	69 (43.3)	50 (31.6)	62 (38.3)

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Overdose may also precipitate hypoglycaemia due to the presence of the sulfonylurea (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Since hypoglycaemia and its clinical symptoms may recur after apparent clinical recovery (even after several days), close and continued medical supervision and possibly referral to a hospital are indicated. In particular, significant overdosage and severe reactions, e.g. with unconsciousness or other neurological dysfunction, are emergency cases and require immediate care and hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, administer glucagon (adults: 0.5 to 1 mg) intravenously, subcutaneously or intramuscularly; or an intravenous infusion of a 20% glucose solution (adults: 40 to 100 ml) until the patient recovers consciousness. In infants, glucose must be dosed very carefully, accompanied by close monitoring of blood glucose, taking into account the risk of potentially severe hyperglycaemia. Other symptomatic therapies (e.g. anticonvulsants) should be administered as necessary.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It increases insulin sensitivity but does not stimulate insulin secretion. Metformin reduces blood glucose levels probably via:

1. reducing hepatic glucose production by inhibiting gluconeogenesis
2. increasing the transport capacity of membrane glucose transporters (GLUT) and thus improving peripheral glucose uptake and utilisation in skeletal muscles, and
3. delaying intestinal glucose absorption.

Metformin also increases glycogen synthase activity and stimulates intracellular glycogen synthesis.

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 and long-term clinical studies: metformin reduces total cholesterol, LDL-cholesterol and triglyceride levels.

Glibenclamide

Glibenclamide is a second generation sulfonylurea 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 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

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 II 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.

Clinical Trials

Second Line Therapy

In a 16-week, double-blind, active-controlled U.S. clinical trial, a total of 639 patients with type II diabetes not adequately controlled (mean baseline HbA1c 9.5%, mean baseline FPG 11.8 mmol/L) while being treated with at least one-half the maximum dose of a sulfonylurea (e.g., glibenclamide 10 mg, glipizide 20 mg) were randomized to receive glibenclamide (fixed dose, 20 mg), metformin (500 mg), GLUCOVANCE 500 mg/2.5 mg, or GLUCOVANCE 500 mg/5 mg. The doses of metformin and GLUCOVANCE were titrated

to a maximum of four tablets daily as needed to achieve FPG<7.8 mmol/L. Trial data at 16 weeks are summarised in Table 3.

Table 3. GLUCOVANCE as Second-Line Therapy in Patients Not Adequately Controlled with Sulfonylurea: Summary of Trial Data at 16 Weeks

Mean Final Dose	20 mg	1840 mg	8.8 mg/1760 mg	17 mg/1740 mg
Haemoglobin A1c	N=158	N=142	N=154	N=159
Baseline Mean (%)	9.6	9.5	9.4	9.4
Final Mean	9.6	9.8	7.9	7.9
Difference from Glibenclamide			-1.7[a]	-1.7[a]
Difference from Metformin			-1.9[a]	-1.9[a]
Fasting Plasma Glucose	N=163	N=152	N=160	N=160
Baseline Mean (mmol/L)	12.1	11.8	11.8	11.7
Final Mean	12.3	13	9.4	8.9
Difference from Glibenclamide			-2.8[a]	-3.3[a]
Difference from Metformin			-3.6[a]	-4[a]
Body Weight Mean Change from Baseline	+0.4 kg	-2.8 kg	+0.8 kg	+0.5 kg
Final HBA1c Distribution	N=158	N=142	N=154	N=159
<7%	2.5%	2.8%	24.7%	22.6%
≥7%	97.5%	97.2%	75.3%	77.4%

[a] p<0.001

After 16 weeks, there was no significant change in the mean HbA1c in the patients randomized to glibenclamide or to metformin therapy. Treatment with GLUCOVANCE at doses up to 20 mg/2000 mg per day resulted in significant lowering of HbA1c, FPG, and PPG from baseline compared to glibenclamide or metformin alone.

In a 16-week, double-blind, active-controlled European clinical trial, a total of 411 patients with type II diabetes not adequately controlled (mean baseline HbA1c 7.9%, mean baseline FPG 10.8 mmol/L) while being treated with metformin (at least 850 mg b.i.d. or 500 mg t.i.d.) in addition to diet and exercise were randomized to receive glibenclamide 5 mg, metformin 500 mg, GLUCOVANCE 500 mg/2.5 mg, or GLUCOVANCE 500 mg/5 mg. The doses of metformin and GLUCOVANCE were titrated to a maximum of four tablets daily as needed to achieve FPG <7 mmol/L. Trial data at 16 weeks are summarised in Table 4.

Table 4. GLUCOVANCE as Second-Line Therapy in Patients Not Adequately Controlled with Metformin: Summary of Trial Data at 16 Weeks

Mean Final Dose	13.4 mg	1660 mg	6.1 mg/1225 mg	11.7mg/1170mg
Haemoglobin A1c	N=103	N=104	N=100	N=103
Baseline Mean (%)	7.9	8.1	7.9	7.6
Final Mean	7.5	7.8	6.7	6.8
Difference from Glibenclamide			-0.9[a]	-0.6[a]
Difference from Metformin			-1.0[a]	-0.7 [b]
Fasting Plasma Glucose	N=103	N=104	N=100	N=103
Baseline Mean (mmol/L)	10.4	11.0	10.7	10.6

Table 4. GLUCOVANCE as Second-Line Therapy in Patients Not Adequately Controlled with Metformin: Summary of Trial Data at 16 Weeks				
Final Mean	9.6	10.4	8.1	8.2
Difference from Glibenclamide			-1.9[a]	-1.6[a]
Difference from Metformin			-2.1[a]	-1.8[a]
Body Weight Mean Change from Baseline	+0.9 kg	-0.8 kg	+0.6 kg	+1 kg
Final HBA1c Distribution	N=103	N=104	N=100	N=103
<7%	41.9%	37.6%	75.5%	63.8%
≥7%	58.1%	62.4%	24.5%	36.2%

[a] $p<0.001$

[b] $p<0.01$

No clinical trial has been performed in type II diabetes patients already on combination therapy whose glycaemia is well controlled.

Paediatric patients

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 than either metformin hydrochloride or glibenclamide in reducing HbA1c from baseline.

5.2 PHARMACOKINETIC PROPERTIES

Metformin

Absorption

After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50 to 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces is 20 to 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 µg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 µg/mL, even at maximum doses.

Following administration of a single combination of a GLUCOVANCE 500 mg/5 mg tablet with food, there is no effect of food on the bioavailability of metformin.

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.

Metabolism

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

Excretion

Renal clearance of metformin is > 400 mL/minute, 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.

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.

Metabolism

Glibenclamide is completely metabolised in the liver to 2 metabolites. Hepatocellular failure decreases glibenclamide metabolism and appreciably slows down its excretion.

Excretion

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 of 30 mL/minute. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 mL/minute.

Metformin and Glibenclamide

The metformin component of GLUCOVANCE is strictly bio-equivalent to metformin co-administered with glibenclamide. In bioavailability studies, the glibenclamide component of GLUCOVANCE showed a higher peak plasma concentration as well as an earlier time to peak. No difference in total area under the curve was noted between GLUCOVANCE and the co-administered glibenclamide and metformin.

The bioavailability of metformin is unaffected by the ingestion of food whereas the effect of food on the glibenclamide component of GLUCOVANCE is indeterminate. Thus, GLUCOVANCE can be safely administered at the beginning of the meals.

In this setting, the magnitude of the differences in the pharmacokinetic properties between GLUCOVANCE and the reference preparations is not outside the range of differences between individuals and day-to-day variations. These slight pharmacokinetic differences are easily overcome by titration and are not expected to result in clinically relevant modifications on the long-term outcome of diabetes management.

Paediatric patients:

There were no differences in pharmacokinetics of glibenclamide and metformin between adolescents and weight and gender-matched healthy adults. There are no reliable data in children (12 years or younger).

5.3 PRECLINICAL SAFETY DATA

No animal studies have been conducted with the combination of metformin and glibenclamide.

Genotoxicity

Metformin

Metformin was not genotoxic in assays for gene mutations (S. typhimurium, mouse lymphoma cells) or chromosomal damage (chromosomal aberrations test in human lymphocytes or in vivo micronuclei formation test).

Glibenclamide

Glibenclamide was not genotoxic in a limited set of in vitro assays for gene mutations

(S. typhimurium) and other genotoxic effects (DNA damage/alkaline elution assay). The clastogenic potential of glibenclamide has not been investigated.

Carcinogenicity

Metformin

Long-term carcinogenicity studies with metformin alone have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at oral doses up to 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are approximately 3 to 4 times the maximum recommended daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumourigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats at 900 mg/kg/day.

Glibenclamide

A study with glibenclamide alone in a small number of rats (15/sex/group) at doses up to 300 mg/kg/day (approximately 136 times the maximum recommended daily dose on a body surface area basis) for 18 months showed no carcinogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

GLUCOVANCE 250/1.25, GLUCOVANCE 500/2.5 and GLUCOVANCE 500/5 tablets contain croscarmellose sodium, povidone, magnesium stearate, microcrystalline cellulose.

GLUCOVANCE 250/1.25 tablet also contains Opadry II complete film coating system OY-L-22903 Yellow (ID 4389).

GLUCOVANCE 500/2.5 tablet also contains Opadry II complete film coating system OY-L-24808 Pink (ID 4390).

GLUCOVANCE 500/5 tablet also contains Opadry II complete film coating system 31F22700 Yellow (ID 4391).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

GLUCOVANCE 250/1.25 : PVC/Al Blister pack 10, 30, 60, 90 and 120 tablets

GLUCOVANCE 500/2.5 : PVC/Al Blister pack 10, 30, 60, 90 and 120 tablets

GLUCOVANCE 500/5 : PVC/Al Blister pack 10, 30, 60, 90 and 120 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 96725 – GLUCOVANCE 250/1.25 metformin hydrochloride 250 mg and glibenclamide 1.25 mg tablet blister pack

AUST R 96728 – GLUCOVANCE 500/2.5 metformin hydrochloride 500 mg and glibenclamide 2.5 mg tablet blister pack

AUST R 96729 – GLUCOVANCE 500/5 metformin hydrochloride 500 mg and glibenclamide 5 mg tablet blister pack

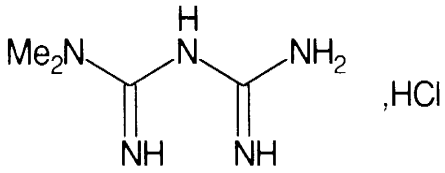
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Metformin hydrochloride



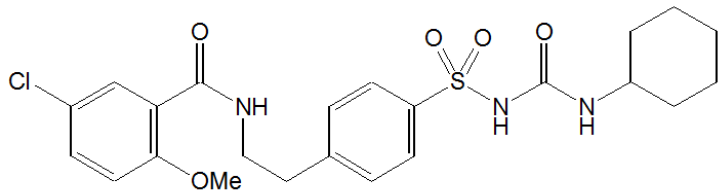
Chemical name : 1,1-dimethylbiguanide hydrochloride

Molecular formula: $C_4H_{11}N_5$, HCl

Molecular weight: 165.6

Metformin hydrochloride is a white, crystalline powder, which is odourless or almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%), and practically insoluble in chloroform and in ether.

Glibenclamide



Chemical name : 1-{4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzene-sulphonyl}-3-cyclohexylurea

Molecular formula: $C_{23}H_{28}ClN_3O_5S$

Molecular weight: 494

Glibenclamide is a white or almost white, crystalline powder; odourless or almost odourless. It is practically insoluble in water and in ether, slightly soluble in ethanol and methanol and sparingly soluble in chloroform.

CAS Number

Metformin hydrochloride	Glibenclamide
1115-70-4	10238-21-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

9/9/2008

10 DATE OF REVISION

01/07/2026

Summary Table of Changes

Section Changed	Summary of New Information
4.6	Update to information for use in pregnancy.

GLUCOVANCE® is licensed to the Viatris company group.

GLUCOVANCE_pi\Jul26/00 (CCDS 14 Feb 2025)