MERCK

GLUCOVANCE®
(Metformin HCl and Glibenclamide Tablets)

500mg/5mg

Rx only

DESCRIPTION

GLUCOVANCE® (Metformin HCl and Glibenclamide Tablets) contains two oral antihyperglycemic drugs used in the management of type 2 diabetes, metformin hydrochloride and glibenclamide.

GLUCOVANCE is available for oral administration in tablets containing 500 mg metformin hydrochloride with 5 mg glibenclamide

In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose 15cP, titanium dioxide (E171) and macrogol 4000. The tablets are film coated, which provides color differentiation.

PHARMACOLOGY

Pharmacodynamic

GLUCOVANCE combines metformin hydrochloride and glibenclamide, two antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Glibenclamide is a second generation sulphonylurea which appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets.

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.

Pharmacokinetics

Absorption and Bioavailability

Related to GLUCOVANCE

In bioavailability studies of GLUCOVANCE 500 mg/5 mg, the mean area under the plasma concentration versus time curve (AUC) for the glibenclamide component was 18% and 7%, respectively, greater than that of the Micronase® brand of glibenclamide coadministered with metformin. The glibenclamide component of GLUCOVANCE, therefore, is not bioequivalent to Micronase®. The metformin component of GLUCOVANCE is bioequivalent to metformin coadministered with glibenclamide

Following administration of a single GLUCOVANCE 500 mg/5 mg tablet with either a 20% glucose solution or a 20% glucose solution with food, there was no effect of food on the C_{max}, and a relatively small effect of food on the AUC of the glibenclamide component. The T_{max} for the glibenclamide component was shortened from 7.5 hours to 2.75 hours with food compared to the same tablet strength administered fasting with a 20% glucose solution. The clinical significance of an earlier T_{max} for glibenclamide after food is not known. The effect of food on the pharmacokinetics of the metformin component was indeterminate. The bioavailability of glibenclamide in the combination is unaffected by the ingestion of food, but the absorption speed of glibenclamide is increased by eating.

Bioequivalence is shown between a single 1000 mg dose of metformin and 5 mg glibenclamide administered as either one tablet of 1000/5mg metformin/glibenclamide or two tablets of 500/2.5 mg metformin/glibenclamide under fasted and fed conditions, based on AUC and Cmax.

Related to Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 μg/ml. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/ml, even at maximum doses. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and a 25% lower AUC in plasma and a 35

minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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

Distribution

Related to Metformin hydrochloride
The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Related to Glibenclamide
Sulfonylurea drugs are extensively bound to serum proteins.

Metabolism and Elimination

Related to Metformin hydrochloride
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

Related to Glibenclamide
The decrease of glibenclamide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. The major metabolite of glibenclamide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glibenclamide) in rabbits. Glibenclamide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Special Populations
Hepatic Insufficiency
No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either metformin or glibenclamide.

Renal Insufficiency
No information is available on the pharmacokinetics of glibenclamide in patients with renal insufficiency.
In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see WARNINGS).

Geriatrics
There is no information on the pharmacokinetics of glibenclamide in elderly patients. Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

INDICATIONS AND USAGE
GLUCOVANCE 250 mg/1.25 mg is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.
GLUCOVANCE 500 mg/2.5 mg, 500 mg/5 mg and 1000/5mg is indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes.

DOSAGE AND ADMINISTRATION
General Considerations
Oral route. For use in adults only.
Dosage of GLUCOVANCE must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 2000 mg metformin/20 mg glibenclamide. The tablets should be taken with meals. Any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response GLUCOVANCE and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c} should be measured at intervals of approximately 3 months to assess the effectiveness of therapy.

GLUCOVANCE as Initial Therapy

The starting dose of GLUCOVANCE is 250 mg/1.25 mg once a day with a meal. In patients with baseline HbA_{1c} > 9% or an FPG > 200 mg/dl, a starting dose of GLUCOVANCE 250 mg/1.25 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 250 mg/1.25 mg per day every two weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose.

GLUCOVANCE 500 mg/5 mg and Glucovance 1000mg/5mg should not be used as initial therapy due to an increased risk of hypoglycemia.

GLUCOVANCE Use in Previously Treated Patients (Second-Line Therapy)
The starting dose of GLUCOVANCE is 500 mg/2.5 mg or 500 mg/5 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of GLUCOVANCE should not exceed the daily doses of glibenclamide or metformin already being taken. The daily dose should be titrated in increments of no more than 500 mg/5 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 2000 mg/20 mg per day.

For patients previously treated with combination therapy of glibenclamide (or another sulfonylurea) plus metformin, if switched to GLUCOVANCE, the starting dose should not exceed the daily dose of glibenclamide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of GLUCOVANCE should be titrated as described above to achieve adequate control of blood glucose.

For patients already treated with Glucovance, two tablets of Glucovance 500 mg/2.5 mg can be replaced by one tablet of Glucovance 1000 mg/5 mg

When GLUCOVANCE is co-administered with a colesevelam, 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 'Drug Interactions').

Specific Patient Populations
GLUCOVANCE is not recommended for use during pregnancy or for use in children.

Elderly patients:
GLUCOVANCE should not be used in patients with advanced age.
The initial and maintenance dosing of GLUCOVANCE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. (See WARNINGS.)

CONTRAINDICATIONS
- Known hypersensitivity to metformin hydrochloride,glibenclamide or other sulphonylurea and sulphonamide or to any of the excipients
- Type I diabetes (insulin-dependent diabetes), diabetic pre-coma
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Renal disease or renal dysfunction (creatinine clearance < 60 mL/min) which may also result from conditions such as dehydration, severe infection and cardiovascular collapse (shock)
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock
- Acute or chronic diseases which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Porphyria
- Lactation
- In association with miconazole

GLUCOVANCE must be discontinued 48 hours prior to elective major surgical interventions and may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

WARNINGS
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 CONTRAINDICATIONS and DRUG INTERACTIONS).

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.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes 19 (Suppl. 2):747-830,1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5g per day) had a rate of cardio-vascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of glibenclamide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included In this study, it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

GLUCOVANCE

Hypoglycemia

GLUCOVANCE is capable of producing hypoglycemia or hypoglycemic symptoms, therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both glibenclamide and metformin hydrochloride and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. 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.

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.

Glibenclamide

Haemolytic anemia

Treatment of patients with glucose-6-phosphate-dehydrogenase 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.

Metformin hydrochloride

Renal function

As metformin hydrochloride is substantially excreted by the kidney, it is recommended that CrCl or eGFR should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with CrCl above 60 mL/min or eGFR above 60 mL/min/1.73m^2.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution is needed in situations where renal function may become acutely impaired, due to dehydration (severe or prolonged diarrhoea or vomiting), or when initiating drugs which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs). In the acute conditions listed, metformin must be immediately and temporarily discontinued.

In these cases, it is also recommended to check renal function before initiating treatment with GLUCOVANCE.

Use of concomitant medications that may affect renal function or metformin disposition
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see PRECAUTIONS: Drug Interactions), should be used with caution.

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 DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS.

Hypoxic states
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur in patients on GLUCOVANCE therapy, the drug should be promptly discontinued.

Surgery
Because Glucovance contains metformin, 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.

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 dry skin.

Alcohol intake
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOVANCE. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired hepatic function
Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOVANCE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels
In controlled clinical trials with metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia (see ADVERSE REACTIONS) and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation.

It is recommended that vitamin B12 serum levels are monitored annually. 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 ADVERSE REACTIONS).

Change in clinical status of patients with previously controlled type 2 diabetes
A patient with type 2 diabetes previously well controlled on metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, GLUCOVANCE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Other precautions
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 Patients
GLUCOVANCE
Patients should be informed of the potential risks and benefits of GLUCOVANCE (Metformin HCl and Glibenclamide Tablets) and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis associated with metformin therapy, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue GLUCOVANCE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOVANCE, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving GLUCOVANCE.

Laboratory Tests
Periodic fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) measurements should be performed to monitor therapeutic response.

Initial and periodic monitoring of hematologic parameters (e.g. hemoglobin/hematocrit and red blood cell indices) and renal function (creatinine clearance, this can be estimated using the Cockcroft-Gault formula, and/or serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Drug Interactions

GLUCOVANCE
Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOVANCE, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUCOVANCE, the patient should be observed closely for hypoglycemia. Metformin is negligibly bound to plasma proteins and is, therefore less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

Glibenclamide
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving GLUCOVANCE, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving GLUCOVANCE, the patient should be observed closely for loss of blood glucose control.

A possible interaction between glibenclamide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glibenclamide. The mechanism for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Metformin hydrochloride
Furosemide
A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max}, by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31 % and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

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

Cationic drugs
In addition to the interaction with the OCT substrates/inhibitors/inducers (see DRUG INTERACTIONS), other cationic drugs (such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are

eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.

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 'Contraindication').

Combinations not recommended
Related to sulphonylurea(s)
Alcohol
An antabuse syndrome (intolerance to alcohol) has occurred very rarely following the concomitant use of alcohol and glibenclamide. This effect has also been reported with chlorpropamide, glipizide and tolbutamide. Alcohol ingestion may 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.

Phenylbutazone (systemic route)
Increase in the hypoglycaemic effect of sulphonylureas (displacement of sulphonylureas 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 glibenclamide

Bosentan
There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and it is recommended that such use to be avoided; the hypoglycaemic effect of glibenclamide may also be reduced.

Related to metformin
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting or 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 DOSAGE AND ADMINISTRATION and PRECAUTIONS.

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 to be used with caution
Related to all antidiabetic agents
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides [systemic and local routes], beta-2-agonists, and chlorpromazine at high dosages of 100 mg per day, diuretics)
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

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.

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, trimethoprime, 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, and a 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 such as 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.

Clonidine, reserpine, guanethidine and sympathomimetics

These substances may mask the warning symptoms of a hypoglycaemic attack. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.

Fluconazole

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

Desmopressin

Reduction in antidiuretic activity.

Colesevelam

When co-administered simultaneously the plasma concentration of glibenclamide is reduced which may lead to a reduced hypoglycaemic effect. This effect was not observed when glibenclamide is given in time lag. It is recommended that GLUCOVANCE should be administered at least 4 hours prior colesevelam.

Pregnancy and lactation

Pregnancy

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.

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, GLUCOVANCE should not be used during pregnancy unless clearly needed. (See below.)

There are no adequate and well-controlled studies in pregnant women with GLUCOVANCE (Metformin HCl and Glibenclamide Tablets) or its individual components. No animal studies have been conducted with the combined products in GLUCOVANCE. The following data are based on findings in studies performed with the individual products.

Risk related to glibenclamide

Reproduction studies were performed in rats and rabbits at doses up to 500 times the maximum recommended human daily dose of 20 mg of the glibenclamide component of GLUCOVANCE based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to glibenclamide.

Risk related to metformin

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg of the metformin component of GLUCOVANCE based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Non-teratogenic effects

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that GLUCOVANCE be used during pregnancy. However, if it is used, GLUCOVANCE should be discontinued at least two weeks before the expected delivery date. (See Pregnancy; Teratogenic Effects: Pregnancy Category B.)

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.

Nursing Mothers
Studies in lactating rats show that metformin is excreted into milk. In humans, in the absence of data concerning passage of GLUCOVANCE into breast milk, and in view of the risk of neonatal hypoglycaemia, this medicinal product is contraindicated in the event of breast-feeding.

Effects on ability to drive and use machines
Patients must be alerted to the symptoms of hypoglycaemia and must be advised to exercise caution when driving or using machines.

ADVERSE REACTIONS
GLUCOVANCE in Clinical Trials
In double-blind clinical trials involving GLUCOVANCE, 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. GLUCOVANCE's Most Common Clinical Adverse Events (>5%) when Compared to Placebo, by Primary Term, in Double-Blind Clinical Studies

Adverse Event	Number (%) of Patients			
	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)
Diarrhea	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)

Disulfiram-like reactions have very rarely been reported in patients treated with glibenclamide tablets.

Hypoglycemia
In controlled clinical trials of GLUCOVANCE (Metformin HCl and Glibenclamide Tablets) there were no hypoglycemic episodes requiring medical intervention and/or pharmacologic therapy: all events were managed by the patients. The incidence of reported symptoms of hypoglycemia (such as dizziness, shakiness, sweating, and hunger), in the initial therapy trial of GLUCOVANCE are summarized in Table 2. The frequency of hypoglycemic symptoms in patients treated with GLUCOVANCE 250 mg/1.25 mg was highest in patients with a baseline HbA_{1c} <7%, lower in those with a baseline HbA_{1c} of between 7 and 8%, and was comparable to placebo and metformin in those with a baseline HbA_{1c} >8%. For patients with a baseline HbA_{1c} between 8% and 11 % treated with GLUCOVANCE 500mg/2.5 mg as initial therapy, the frequency of hypoglycemic symptoms was 30-35%. As second-line therapy in patients inadequately controlled on sulfonylurea alone, approximately 6.8% of all patients treated with GLUCOVANCE experienced hypoglycemic symptoms. (See PRECAUTIONS section)

Gastrointestinal Reactions
The incidence of GI side effects (diarrhea, nausea/vomiting, and abdominal pain) in the initial therapy trial are summarized in Table 2. Across all GLUCOVANCE trials, GI 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 GI adverse events.

Table 2. Treatment Emergent Symptoms of Hypoglycemia or Gastrointestinal Adverse Events in placebo- and Active-Controlled Trial of GLUCOVANCE as Initial Therapy

Variable	Placebo N=161	Glibenclamide Tablets N=160	Metformin Tablets N=159	GLUCOVANCE 250mg/1.25mg Tablets N=158	GLUCOVANCE 500mg/2.5mg Tablets N=162
Mean Final Dose	0mg	5.3mg	1317mg	557/2.78mgmg	824/4.1mg
Number (%) of patients with symptoms of hypoglycemia	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)

Post Marketing Surveillance

The following undesirable effects may occur under treatment with GLUCOVANCE. Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon: ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000 not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations
Uncommon: Average to moderate elevations in serum urea and creatinine concentrations.
Very rare: Hyponatremia.

Blood and lymphatic system disorders
These are reversible upon treatment discontinuation.
Rare: Leukopenia, thrombocytopenia.
Very rare: Agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.

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

Metabolism and nutrition disorders
Hypoglycaemia (see PRECAUTIONS section).
Common: Vitamin B12 deficiency, consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see PRECAUTIONS section). Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

Uncommon: Crises of hepatic porphyria and porphyria cutanea.
Very rare: Lactic acidosis (see WARNINGS section).
Disulfiram-like reaction with alcohol intake.

Hepatobiliary disorders

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

OVERDOSAGE
Overdosage of sulfonylureas, including glibenclamide tablets, can produce hypoglycemia (see Precautions). Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

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

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.

STORAGE
Store at or below 30°C; Protect from light.

PRESENTATIONS & PACK SIZE
500 mg/5 mg – 30's; 120's

Not all presentations & pack size may be available locally.

Manufactured by:

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or

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