Info-Table – Version 03

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IDENTIFICATION OF THE COMPONENT	
Material component code:	FR2581764
Local brand:	GLUCOVANCE
Strength(s):	250 mg/1.25 mg | 500 mg/2.5 mg | 500 mg/5 mg
TECHNICAL DATA	
Packaging site:	Merck Semoy
Technical layout ref:	PIL_510x210 [170x3]_V04
BARCODE	
Barcode type:	Code 128 A
Alpha numeric content:	FR2581764
Spotmark:	For Positioning Only
Spotmark value:	n/a
TRACEABILITY (VERSIONS)	

Vx.	Date	Designer
01	18.05.2022	Trapti Gupta
02	07.09.2022	Trapti Gupta
03	n/a	n/a

COLOURS	
Printed colour(s)	Technical information(s)
Black	Keyline

MERCK

metformin HCl + glibenclamide

Glucovance®

250 mg/1.25 mg Film-coated Tablet
500 mg/2.5 mg Film-coated Tablet
500 mg/5 mg Film-coated Tablet

Oral Hypoglycemic

Formulation

Each **metformin + glibenclamide (Glucovance) 250 mg/1.25 mg** film-coated tablet contains 250 mg Metformin hydrochloride and 1.25 mg Glibenclamide.

Each **metformin + glibenclamide (Glucovance) 500 mg/2.5 mg** film-coated tablet contains 500 mg Metformin hydrochloride and 2.5 mg Glibenclamide.

Each **metformin + glibenclamide (Glucovance) 500 mg/5 mg** film-coated tablet contains 500 mg Metformin hydrochloride and 5 mg Glibenclamide.

Pharmacological Properties

Pharmacodynamic Properties

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

Metformin may act via 3 mechanisms:

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

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

In humans, independent of its action on glycemia, metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL-cholesterol and triglyceride levels.

Glibenclamide is a sulfonylurea: it causes lowering of blood glucose by stimulating the release of insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans.

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

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

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

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

Pharmacokinetic Properties

Related to the combination

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

Bioequivalence is shown between a single 1 gram dose of metformin and 5 mg glibenclamide administered as either one tablet of 1 gram/5 mg metformin/glibenclamide or two tablets of 500 mg/2.5 mg metformin/glibenclamide under fasted and fed conditions, based on AUC and C_{max}.

Related to metformin

Absorption

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

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 mcg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 mcg/mL, even at maximum doses.

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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 (Vd) ranged from 63 to 276 L.

Metabolism

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

Elimination

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

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

Related to glibenclamide

Absorption

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

Distribution

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

Metabolism

Glibenclamide is completely metabolized 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/min. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 mL/min.

Non-clinical Safety

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

Indications

Metformin + glibenclamide (Glucovance) 250 mg/1.25 mg

Treatment of type 2 diabetes in adults as first-line therapy, when diet and exercise alone do not result in adequate glycemic control

Metformin + glibenclamide (Glucovance) 500 mg/2.5 mg, metformin + glibenclamide (Glucovance) 500 mg/5 mg

Treatment of type 2 diabetes in adults

- as second line therapy, when diet, exercise and initial treatment with metformin or glibenclamide (or another sulfonylurea) do not result in adequate glycemic control
- as replacement for previous treatment with metformin and glibenclamide in patients whose glycemia is stable and well controlled

Dosage and Administration

FOR USE IN ADULTS ONLY

Initial treatment

As first-line therapy

The initial dose is one tablet of metformin + glibenclamide (Glucovance) 250 mg/1.25 mg once a day. One tablet of metformin + glibenclamide (Glucovance) 250 mg/1.25 mg twice a day may be used if HbA1c > 9% or FPG > 2 g/L.

Metformin + glibenclamide (Glucovance) 500 mg/5 mg and metformin + glibenclamide (Glucovance) 1 gram/5 mg must not be used as initial therapy due to an increased risk of hypoglycemia.

As second-line therapy

The initial dose is one tablet of metformin + glibenclamide (Glucovance) 500 mg/2.5 mg or metformin + glibenclamide (Glucovance) 500 mg/5 mg once a day. In order to avoid hypoglycemia, the initial dose must not exceed the daily doses of glibenclamide (or equivalent dose of another sulfonylurea) or metformin already being taken.

As replacement for previous combination therapy with metformin and a sulfonylurea

The recommended initial dose must not exceed the daily dose of glibenclamide (or equivalent dose of another sulfonylurea) and metformin already being taken.

Titration

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

As first-line therapy

Dosage increase is recommended in increments of one tablet of metformin + glibenclamide (Glucovance) 250 mg/1.25 mg per day every 2 weeks or longer according to glycemia results up to the minimum effective dose to achieve adequate control of blood glucose.

As second-line therapy

Dosage increase is recommended in increments of no more than metformin + glibenclamide (Glucovance) 500 mg/5 mg per day every 2 weeks or longer according to glycemia results up to the minimum effective dose to achieve adequate control of blood glucose. Patients must be monitored closely for signs and symptoms of hypoglycemia.

As replacement for previous combination therapy with metformin and a sulfonylurea

Dosage increase is recommended in increments of no more than metformin + glibenclamide (Glucovance) 500 mg/5 mg per day every 2 weeks or longer according to glycemia results up to the minimum effective dose to achieve adequate control of blood glucose. Patients must be monitored closely for signs and symptoms of hypoglycemia.

Maximum Dose

The maximum recommended dose is 2000 mg metformin hydrochloride/20 mg glibenclamide per day.

Elderly

Patients aged 65 years and older: Starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycemia. Treatment should be started with the lowest available dose and increased gradually if necessary. It is recommended that these patients are not titrated to the maximum dose of metformin + glibenclamide (Glucovance) to avoid the risk of hypoglycemia. Regular assessment of renal function is necessary (see Special Warnings and Precautions).

Debilitated and malnourished patients

It is recommended that these patients are not titrated to the maximum dose of metformin + glibenclamide (Glucovance) to avoid the risk of hypoglycemia.

Children

Neither safety nor efficacy has been established in children.

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Patients with renal impairment

Metformin + glibenclamide (Glucovance) may be used in patients with moderate renal impairment, stage 3 (creatinine clearance [CrCl] between 30 and 59 mL/min or estimated glomerular filtration rate [eGFR] between 30 and 59 mL/min/1.73m²) only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:

- Patients with CrCl between 30 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m²: The maximum dose of metformin is 1000 mg daily. The renal function should be closely monitored every 3 - 6 months.
- Patients with CrCl between 30 and 59 mL/min or eGFR between 30 and 44 mL/min/1.73m²: It is not recommended to initiate metformin + glibenclamide (Glucovance) but metformin + glibenclamide (Glucovance) can be maintained in patients already treated, provided that the maximum daily dose of metformin is not higher than 1000 mg. The renal function should be closely monitored every 3 months.

If CrCl or eGFR fall below 30 mL/min or below 30 mL/min/1.73m² respectively, metformin + glibenclamide (Glucovance) must be discontinued immediately.

Use with insulin

No clinical data are available on the concomitant use of metformin + glibenclamide (Glucovance) with insulin therapy.

Administration

The tablets should be taken with meals

- Once a day, in the morning (breakfast) if the dosage is one tablet per day.
- Twice a day, in the morning (breakfast) and evening (dinner) if the dosage is two or four tablets per day.
- Three times a day, in the morning (breakfast), noon (lunch) and evening (dinner), if the dosage is three, five or six tablets per day

The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent hypoglycemia. Patients should avoid alcohol when taking metformin + glibenclamide (Glucovance).

When metformin + glibenclamide (Glucovance) is co-administered with colesevelam, it is recommended that metformin + glibenclamide (Glucovance) should be administered at least 4 hours prior to colesevelam in order to minimize the risk of reduced absorption.

Missed dose

Patients must not take a double dose to make up for a forgotten dose. The next dose should be taken at the usual time.

Contraindications

Metformin + glibenclamide (Glucovance) must **never** be used in case of:

- Hypersensitivity to metformin hydrochloride, glibenclamide or other sulfonylureas and sulfonamides or to any of the excipients
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Sever renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1.73m²)
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, cardiovascular collapse (shock)
- Disease (especially acute disease, or worsening of chronic diseases) which may cause tissue hypoxia such as unstable congestive heart failure, respiratory failure, recent myocardial infarction, cardiovascular collapse or shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Porphyria (a rare hereditary disease due to an enzyme deficiency causing the body to produce and excrete too much porphyrin, a component used to make the part of blood pigment that carries oxygen)
- Lactation
- In association with miconazole even for local use (see Interactions)

Intravascular administration of iodinated contrast materials may lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, metformin + glibenclamide (Glucovance) must be discontinued 48 hours before or from the time of intravascular administration of iodinated contrast media and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Metformin + glibenclamide (Glucovance) must be discontinued 48 hours before an elective major surgery and may not be reinstituted until 48 hours afterwards, and only after kidney function has been re-evaluated and found to be normal.

Special Warnings and Precautions

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment) metabolic complication. Risk factors include poorly-controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, severe infection, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs), (see also Contraindications).

Lactic acidosis can occur due to metformin accumulation. Reported cases of lactic acidosis in patients treated with metformin have occurred primarily in diabetic patients with acute renal failure or acute worsening of renal function.

Special caution should therefore be paid to situations where renal function may become acutely impaired (see also Contraindications), for example in case of dehydration (severe or prolonged diarrhea 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.

The following non-specific symptoms could be signs of lactic acidosis: such as muscle cramps, digestive disorders as abdominal pain and severe asthenia.

Diagnosis

Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, and hypothermia and followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be immediately hospitalized (see Overdose).

Physicians must alert the patients on the risk and on the symptoms of lactic acidosis. Patients should be instructed to immediately seek medical attention and to stop taking metformin. Metformin + Glibenclamide (Glucovance) must be immediately discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin + glibenclamide (Glucovance) should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.

Hypoglycemia

As it contains a sulfonylurea, metformin + glibenclamide (Glucovance) exposes the patient to a risk of onset of hypoglycemia. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycemia. This treatment must only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important

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BARCODE	
Barcode type:	Code 128 A
Alpha numeric content:	FR2581764
Spotmark:	For Positioning Only
Spotmark value:	n/a
TRACEABILITY (VERSIONS)	

Vx.	Date	Designer
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03	n/a	n/a

that carbohydrate intake is regular since the risk of hypoglycemia is increased by a late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol is consumed, or during the administration of a combination of hypoglycemic agents

Diagnosis

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

Management of hypoglycemia

Moderate hypoglycemic symptoms without loss of consciousness or neurological manifestations must be corrected by the immediate intake of sugar. An adjustment to the dosage and/or changes in meal patterns must be ensured. Severe hypoglycemic 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 hospitalization of the patient.

The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycemic episodes. If the patient encounters repeated episodes of hypoglycemia, which are either severe or associated with unawareness of the situation, antidiabetic treatment options other than metformin + glibenclamide (Glucovance) must be taken into consideration.

Factors favoring hypoglycemia

- Concomitant administration of alcohol, especially combined with fasting
- Refusal or (more particularly in elderly patients) inability of the patient to cooperate
- Malnutrition, irregular meals, missed meals, fasting or changes to diet
- Poor balance between physical exercise and carbohydrate intake
- Renal failure
- Severe liver failure
- Overdose of metformin + glibenclamide (Glucovance)
- Certain endocrine disturbances: thyroid insufficiency, pituitary and adrenal gland insufficiency
- Concomitant administration of certain other medicines

Renal and hepatic impairment

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

Elderly patients

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

Information for the patient

The risks of hypoglycemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family. Similarly, the risk of lactic acidosis must be considered in the event of non-specific signs such as muscle

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cramps accompanied by digestive disorders, abdominal pain and severe asthenia, dyspnea attributed to acidose, hypothermia and coma.

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

Infectious diseases

The doctor should be informed if the patient is suffering from any infectious illnesses such as flu, infection of the air passages or urinary tract infection.

Blood sugar imbalance

The doctor should be informed in case of surgery or any other cause of diabetic decompensation since temporary treatment with insulin should be envisaged. The symptoms of hyperglycemia are increased urination, raging thirst and a dry skin.

Renal function

As metformin 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.
- At least every 3 to 6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m^2 and in elderly subjects.
- At least every 3 to 6 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2. In case creatinine clearance or GFR is below 45 mL/min/1.73m^2, it is not recommended to initiate metformin + glibenclamide (Glucovance).

In case CrCl or eGFR is below 30mL/min or 30 mL/min/1.73m^2 respectively, metformin+glibenclamide (Glucovance) is contraindicated (see Contraindications).

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 diarrhea or vomiting), 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 metformin + glibenclamide (Glucovance).

Cardiac function

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

For patients with acute and unstable heart failure, metformin + glibenclamide (Glucovance) is contraindicated.

Other Precautions

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

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

Treatment of patients with glucose-6-phosphate-dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glibenclamide belongs to the chemical class of sulfonylurea drugs, caution is recommended when using metformin + glibenclamide (Glucovance) in patients with G6PD deficiency and a non-sulfonylurea alternative may be considered.

Blood sugar imbalance

Lactose

Because metformin + glibenclamide (Glucovance) contains lactose, it is contraindicated in case of congenital galactosemia, glucose and galactose malabsorption syndrome or in case of lactase deficiency.

Effects on the ability to drive and use machines

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

Use in 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.

Risk related to metformin

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

Clinical studies involving a few small series have not shown evidence of fetal malformation directly related to metformin.

Risk related to glibenclamide

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

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

Management

Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. Metformin + glibenclamide (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.

Lactation

Metformin is excreted in milk in lactating rats.

Metformin is excreted into human breast milk in very small amounts. No adverse effects were observed in breastfed newborns/infants.

Although it is not known whether glibenclamide is excreted in human milk, some sulphonylureas are excreted in human milk. Because the risk of neonatal hypoglycemia may exist, metformin + glibenclamide (Glucovance) is contraindicated in the event of breastfeeding.

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Undesirable Effects

The following undesirable effects may occur under treatment with metformin + glibenclamide (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, hemolytic anemia, 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 glycemia levels.

Gastrointestinal disorders

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhea, 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 metformin + glibenclamide (Glucovance) be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability. Should these symptoms continue, the patient should stop taking metformin + glibenclamide (Glucovance) and the doctor must be consulted.

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 sulfonamide(s) and their derivatives may occur.

Metabolism and nutrition disorders

Hypoglycemia (see Warnings and Precautions)

Common: Vitamin B_{12} decrease/ deficiency

(See Warnings and Precautions)

Uncommon: Crises of hepatic porphyria and porphyria cutanea

Very rare: Lactic acidosis (See Warnings and Precautions)

Disulfiram-like reaction with alcohol intake.

Hepatobiliary disorders

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

ADR Reporting Statement

At the first sign of any adverse drug reaction, patient must seek medical attention immediately.

Report any suspected adverse drug reaction to ICSR_SEA@merckgroup.com and to the FDA: www.fda.gov.ph.

Interactions

Contraindicated combination

Related to glibenclamide

- Miconazole (systemic route, oromucosal gel): Increase in the hypoglycemic effect with possible onset of hypoglycemic manifestations, or even coma.

Related to metformin

- Iodinated contrast media: Intravascular administration of iodinated contrast materials may lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, metformin + glibenclamide (Glucovance) must be discontinued 48 hours before or from the time of intravascular administration of iodinated contrast media and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations not recommended

Related to sulfonylureas

- 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 hypoglycemic action (via inhibition of compensation reactions or delaying its metabolic rate[s]), which may facilitate the onset of a hypoglycemic coma. Avoid consumption of alcohol and alcohol-containing medications.
- Phenylbutazone (systemic route): Increase in the hypoglycemic 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.

Related to glibenclamide

- Bosentan: There is an increased risk of hepatoxicity if bosentan is given with glibenclamide and it is recommended that such be avoided; the hypoglycemic effect of glibenclamide may also be reduced.

Related to metformin

- Alcohol: Increase in risk of lactic acidosis during alcoholic intoxication, particularly in cases of fasting or malnutrition and hepatocellular failure. Avoid drinking alcoholic beverages and taking drugs that contain alcohol.

Combinations requiring precautions

Related to all antidiabetic agents

- Medicinal products with intrinsic hyperglycemic activity (e.g. glucocorticoids and tetracosactides [systemic and local routes], beta-2-agonists, danazol, 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.

Related to metformin

- Diuretics: Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics.
- Organic cation transporters (OCT): Metformin is a substance 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.

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

- Beta-blockers: All beta-blockers mask some of the symptoms of hypoglycemia such as palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycemia. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.
- Clonidine, reserpine, guanethidine or sympathomimetics: These substances may mask the warning symptoms of a hypoglycemic attack. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.
- Fluconazole: Increase in the half-life of sulfonylurea with possible onset of hypoglycemic 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.
- Desmopressin: Reduction in antidiuretic effect of desmopressin.
- Colesevelam: When co-administered simultaneously the plasma concentration of glibenclamide is reduced which may lead to a reduced hypoglycemic effect. This effect was not observed when glibenclamide is given in time lag. It is recommended that metformin + glibenclamide (Glucovance) should be administered at least 4 hours prior to colesevelam.
- Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril): ACE inhibitors may decrease the blood glucose levels. If necessary adjust the dosage of metformin + glibenclamide (Glucovance) during therapy with an ACE inhibitor and upon its discontinuation.

Overdose

Overdose may precipitate hypoglycemia due to the presence of sulfonylurea.

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 a hospital. The most effective treatment is to remove lactate and metformin by hemodialysis.

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.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Date of First Authorization

Glucovance 250 mg/1.25 mg Film-coated Tablet	05 March 2003
Glucovance 500 mg/2.5 mg Film-coated Tablet	05 March 2003
Glucovance 500 mg/5 mg Film-coated Tablet	05 March 2003

Registration Number

Glucovance 250 mg/1.25 mg Film-coated Tablet	DR-XY28383
Glucovance 500 mg/2.5 mg Film-coated Tablet	DR-XY28382
Glucovance 500 mg/5 mg Film-coated Tablet	DR-XY28255

Storage Condition

Store at temperatures not exceeding 30°C.
Do not use after the expiry date.
Keep out of the reach and sight of children.

Presentation

Glucovance 250 mg/1.25 mg Film-coated Tablet
Box of 30 film-coated tablets in blister strips

Glucovance 500 mg/2.5 mg Film-coated Tablet
Box of 30 film-coated tablets in blister strips

Glucovance 500 mg/5 mg Film-coated Tablet
Box of 30 film-coated tablets in blister strips

Manufactured by **Merck Sante s.a.s.**
2 rue du Pressoir Vert, 45400 Semoy, France

Imported by **Merck, Inc.**
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