SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

GLUCOVANCE 500 mg/2,5 mg (film-coated tablet)

GLUCOVANCE 500 mg/5 mg (film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated Glucovance 500 mg/2,5 mg tablet contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin, and 2,5 mg glibenclamide.

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

Excipient(s) with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Glucovance 500 mg/2,5 mg: Pale orange capsule shaped, biconvex embossed film-coated tablet with “2,5” engraved on one side.

Glucovance 500 mg/5 mg: Yellow capsule shaped, biconvex embossed film-coated tablet with “5” engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of type 2 diabetes in adults:

- Glucovance is indicated as second-line therapy, when diet, exercise and initial treatment with metformin or glibenclamide (or another sulphonylurea) do not result in adequate glycaemic control.
- As replacement therapy for previous combination therapy with metformin and sulphonylurea in patients whose glycaemia is stable and well-controlled.

4.2 Posology and method of administration

The dosage of Glucovance must be individualised on the basis of both effectiveness (glycaemia, HbA1c) and tolerance.

It is recommended to initiate the treatment with a low dose, which can then be gradually increased according to results obtained. The tablets must be administered just before a meal, in one or two daily intakes in the morning and evening. Any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.

Second-line therapy

Initial dose:

The initial dose is 1 tablet of Glucovance 500 mg/2,5 mg or Glucovance 500 mg/5 mg once a day. In order to avoid hypoglycaemia, the initial dose must not exceed the daily doses of glibenclamide (or equivalent dose of another sulphonylurea) or metformin already being taken.

Titration:

Dosage increase is recommended in increments of no more than Glucovance 500 mg/5 mg per day every 2 weeks or longer according to glycaemia results up to the minimum effective dose to

achieve adequate control of blood glucose. A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.

Maximum dose:

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

Glucovance 500 mg/5 mg must not be used as initial therapy due to an increased risk of hypoglycaemia.

In substitution from combination-therapy with metformin and a sulphonylurea:

Adults with normal renal function (GFR ≥ 90 mL/min)

Initiation of treatment:

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

Dose titration:

Dosage increase is recommended in increments of no more than Glucovance 500 mg/5 mg per day every 2 weeks or longer according to glycaemia results up to the minimum effective dose to achieve adequate control of blood glucose.
A gradual increase in the dosage may aid gastro-intestinal tolerance and prevent the onset of hypoglycaemia.
Patients must be monitored closely for signs and symptoms of hypoglycaemia.

Maximum dose:

A total daily dose of 4 tablets of Glucovance 500 mg/5 mg should not be exceeded.

Combination with insulin therapy:

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

Renal impairment:

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

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

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

GFR mL/min	**Metformin**	**Glibenclamide**
60 - 89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	No dose reduction required.
45 - 59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10,5 mg.
30 - 44	Maximum daily dose is 1000 mg.	Maximum daily dose is 10,5 mg.

GFR **mL/min**	**Metformin**	**Glibenclamide**
	The starting dose is at most half of the maximum dose.	Initiation of therapy is not recommended due to the risk of hypoglycemia.
< 30	Metformin / glibenclamide are contraindicated	

Geriatric population:

The dosage of Glucovance should be adjusted depending on renal function parameters (start with 1 tablet of Glucovance 500 mg/2,5 mg); regular checks on the renal function are necessary (see section 4.4).

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

Debilitated, and malnourished patients:

It is recommended that these patients are not titrated to the maximum dose of Glucovance to avoid the risk of hypoglycaemia.

Paediatric population:

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

Method of administration

The dosage regimen depends on the individual posology:

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

- Three times a day, morning, noon and evening, for a dosage of 3, 5 or 6 tablets/day.

The tablets should be taken with meals. The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.

When Glucovance is co-administered with a bile acid sequestrant (e.g., 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 section 4.5).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

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

Hypoglycaemia

As it contains a sulphonylurea, Glucovance exposes the patient to a risk of onset of hypoglycaemic episodes. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment should only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important that carbohydrate intake is regular since the risk of hypoglycaemia is increased by a late meal, insufficient or unbalanced

carbohydrate intakes. Hypoglycaemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol intake or during the administration of a combination of hypoglycaemic agents.

Diagnosis:

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

Management of hypoglycaemia:

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

The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycaemic episodes. If the patient encounters repeated episodes of hypoglycaemia, which are either severe or associated with unawareness of the situation, antidiabetic treatment options other than Glucovance should be taken into consideration.

Factors favouring hypoglycaemia:

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

Elderly patients:

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

Renal and hepatic failure:

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

Patient information:

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

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

Blood sugar imbalance

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

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

Cardiac function

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

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

Renal function

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

Administration of iodinated contrast agents

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

Concomitant use of glibenclamide with other medicinal products

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

Surgery

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

Other precautions

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

Regular physical exercise is as necessary as taking Glucovance.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

CONTRAINDICATED COMBINATIONS

Related to Glibenclamide:

Miconazole (systemic route, oromucosal gel)

Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma.

Related to Metformin:

Iodinated contrast media

Depending on the renal function, Glucovance must be discontinued 48 hours before or from the time of intravascular administration of iodinated contrast media.

COMBINATIONS NOT RECOMMENDED

Sulphonylurea(s) related:

Phenylbutazone (systemic route)

Phenylbutazone increases the hypoglycaemic effect of sulphonylureas. It is recommended to use another anti-inflammatory agent with 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.

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, which may facilitate the onset of a hypoglycaemic coma. Avoid consumption of alcohol and alcohol-containing medications.

Related to glibenclamide:

Bosentan

There is an increased risk of hepato-toxicity if Bosentan is given with glibenclamide and it is recommended that such use be avoided.

The hypoglycaemic effect of glibenclamide may also be reduced.

Related to metformin:

Alcohol

The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided.

COMBINATIONS TO BE USED WITH CAUTION

Related to all antidiabetic agents:

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides [system 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 Glucovance dosage during therapy with the respective medicinal product and upon its discontinuation.

Related to glibenclamide:

Fluconazole

An increase in the half-life of glibenclamide with possible onset of hypoglycaemic manifestations may occur with the concomitant use with fluconazole. 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.

Beta-blocker

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 or 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.

Desmopressin

Concomitant use with desmopressin leads to a reduction in antidiuretic activity.

Bile acid sequestrants (e.g., cholestyramine, colestipol, 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 if glibenclamide is given in a certain period of time before taking the other medicine. It is recommended that Glucovance should be administered at least 4 hours prior a bile acid sequestrant (see section 4.2).

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

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

Related to metformin:

Diuretics

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function.

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Risk related to diabetes

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

Risk related to metformin (see section 5.3)

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

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

Risk related to glibenclamide (see section 5.3)

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

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

Management

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

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

Breast-feeding

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

Fertility

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

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

4.7 Effects on ability to drive and use machinery

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

4.8 Undesirable effects

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 (≥ 1/1000, < 1/100), rare (< 1/10 000), very rare (< 1/10 000)

Blood and lymphatic system disorders

These are reversible upon treatment discontinuation.

Rare:

- Leucopenia, thrombocytopenia.

Very rare:

- Agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.

Metabolism and nutrition disorders:

Hypoglycaemia (See section 6).

Uncommon:

- Crises of hepatic porphyria and porphyria cutanea.

Very rare:

- Lactic acidosis (See section 6).
- Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
- Disulfiram-like reaction with alcohol intake.

Nervous system disorders:

Common:

- Taste disturbance.

Eye disorders:

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

Gastrointestinal disorders:

Very common:

- Gastrointestinal disorders such as nausea & vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that Glucovance be taken in 2 or 3 daily doses during or after meals[40]. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare:

- Liver function tests abnormalities or hepatitis requiring treatment discontinuation.

Skin and subcutaneous tissue disorders:

Rare:

- Skin reactions such as pruritus, urticaria, maculopapular rash.

Very rare:

- Cutaneous or visceral allergic agniitis, erythema multiforme, exfoliative dermatitis, photosensitisation, urticaria evolving to shock.

A cross reactivity to sulphonamides and their derivatives may occur.

Investigations

Uncommon:

- Average to moderate elevations in serum urea and creatinine concentrations.

Very rare:

- Hyponatraemia.

4.9 Overdose

High overdose or the existence of risk factors may lead to lactic acidosis due to the presence of metformin. Lactic acidosis must be treated in hospital and is a medical emergency. Lactate and metformin can be removed by haemodialysis. Overdose may precipitate hypoglycaemia due to the presence of glibenclamide.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A 21.2 Oral hypoglycaemics.

Pharmacodynamic properties:

Mechanism of action

Glucovance is a combination of metformin hydrochloride and glibenclamide, two anti-hyperglycaemic agents with complementary mechanisms of action.

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose.

It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of 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 (GLUTs).

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

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

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

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

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

Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with metformin or glibenclamide

combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation.

5.2 Pharmacokinetic Properties

Related to the combination

The bioavailability of the combination is comparable 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, however, the rate of absorption of glibenclamide is increased by eating.

Related to metformin

Absorption

After an oral dose of metformin, maximum plasma concentration (C_{max}) is reached in approximately 2,5 hours (t_{max}). Absolute bioavailability of a 500 or 850 mg metformin tablet is approximately 50 - 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 - 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 µg/ml, even at maximum doses.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Volume of Distribution

ranged between 63 - 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 metabolised in the liver to two metabolites. Hepatocellular failure decreases glibenclamide metabolism and appreciably slows down its excretion.

Elimination

Glibenclamide is excreted in the form of metabolites via biliary route (60 %) and urine (40 %),

elimination being complete within 45 to 72 hours. Its terminal elimination half-life is 4 to 11 hours,

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

Paediatrics:

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose, sodium croscarmellose, povidone, magnesium stearate.

Film-coating

Opadry (orange) [lactose monohydrate, hypromellose, titanium dioxide, macrogol, iron oxide].

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

30 or 60 tablets in clear or opaque white PVC/Aluminium blisters.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein, 1645

South Africa

Name and address of the manufacturer:

Merck Santé s.a.s

Centre de Production

2 Rue du Pressoir Vert

45400 Semoy, France

8. REGISTRATION NUMBERS

Glucovance 500 mg/2,5 mg tablets: 36/21.2/0412

Glucovance 500 mg/5 mg tablets: 36/21.2/0413

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Glucovance 500 mg/2,5 mg tablets: 07/03/2003

Glucovance 500 mg/5 mg tablets: 07/03/2003

10. DATE OF REVISION OF THE TEXT

21/02/2022

Glucovance 500 mg/2.5 mg		
	Schedule	**Reg. No.:**
Namibia	NS2	04/21.2/0812
Botswana	S2	BOT08014368
Kenya	POM	16537
Tanzania	POM	TZ13H218
Uganda	POM	7810/18/12

Glucovance 500 mg/5 mg		
	Schedule	**Reg. No.:**
Namibia	NS2	04/21.2/0813
Botswana	S2	BOT08014369
Kenya	POM	16538
Tanzania	POM	TZ13H217
Uganda	POM	7829/18/12