SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

Glucovance 250 mg/1.25 mg (film-coated tablet)

Glucovance 500 mg/2.5 mg (film-coated tablet)

Glucovance 500 mg/5 mg (film-coated tablet)

COMPOSITION:

Each film-coated Glucovance 250 mg/1.25 mg tablet contains 250 mg metformin hydrochloride and 1.25 mg glibenclamide.

Each film-coated Glucovance 500 mg/2.5 mg tablet contains 500 mg metformin hydrochloride and 2.5 mg glibenclamide.

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

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral hypoglycaemics

PHARMACOLOGICAL ACTION:

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

Metfomin hydrochloride is a biguanide oral anti-hyperglycaemic agent. It improves glucose tolerance, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin also increases the transport capacity of all types of membrane glucose transporters.

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 on functioning beta cells in the pancreatic islets. The mechanism of action by which glibenclamide lowers blood glucose during long term administration has not been clearly established.

Pharmacokinetics:

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.

INDICATIONS:

Glucovance is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes whose glycaemia cannot be satisfactorily managed with diet and exercise alone.

Glucovance is indicated as second-line therapy when diet and exercise, and initial treatment with a sulphonylurea or metformin do not result in adequate glycaemic control in patients with type 2 diabetes.

CONTRA-INDICATIONS:

Hypersensitivity to metformin hydrochloride, glibenclamide or other sulphonylureas and sulphonamides, or any of the excipients.

Type 1 diabetes (insulin-dependent diabetes), ketosis or ketoacidosis, diabetic pre-coma.

Renal disease or dysfunction (creatinine clearance < 60 ml/min); which may also result from conditions such as shock, dehydration, severe infection, intravascular administration of iodinated contrast agents.

Acute or chronic disease which may cause severe tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.

Major surgery

Chronic liver disease, acute alcohol intoxication, alcoholism.

Pancreatitis

Porphyria

Concomitant use with miconazole has an increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations or even coma can occur.

Lactation

WARNINGS:

Lactic acidosis:

Lactic acidosis is a rare but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure.

The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatocellular failure and any condition associated with hypoxia.

Diagnosis

Lactic acidosis is characterized by acidotic breathing, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment should be discontinued.

Lactic acidosis is a medical emergency and the patient should be hospitalized immediately.

Other warnings:

Because Glucovance contains lactose, it is not recommended in cases of congenital galactosemia, glucose and galactose malabsorption syndrome or in case of lactase deficiency.

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

The administration of oral hypoglycaemics may be associated with an increased risk of cardiovascular mortality as compared to treatment with diet alone or diet with insulin although controversy exists concerning interpretation of these findings.

INTERACTIONS:

Glibenclamide related:

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.

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.

Miconazole (systemic route, oromucosal gel) increases the hypoglycaemic effect of glibenclamide with possible onset of hypoglycaemic manifestations or even coma. Therefore, miconazole must not be combined with Glucovance (see Contra-indications).

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.

Cases of hypoglycaemia have been reported when the following products were used in combination with glibenclamide: antibacterial sulphonamides, fluoroquinolones, warfarin, MAOI's, chloramphenicol, lipid-lowering agents such as fenofibrate, pentoxifyllin, disopyramide, clofibrate, cyclophosphamide, salicylate, propranolol and other betablockers.

All beta-blockers, clonidine, reserpine, guanethidine and sympathomimetics mask some of the symptoms of hypoglycaemia i.e. palpitations and tachycardia. Beta-blockers may increase the incidence and severity of hypoglycaemia, decrease the body response to hypoglycaemia. Warn the patient and step-up blood glucose self-monitoring, especially at the start of treatment.

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

Metformin related:

Depending on the renal function, Glucovance must be discontinued 48 hours before or at the time of intravascular administration of iodinated contrast media (see Special precautions).

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

Combination related:

There is an increased risk of lactic acidosis in acute alcohol intoxication, particularly in cases of:

- fasting or malnutrition
- hepatic insufficiency

There is a risk of increase in the hypoglycaemic reaction that may even lead to hypoglycaemic coma. Patients should avoid consumption of alcohol and alcohol-containing medications. (See Contra-indications)

Related to all antidiabetic agents:

Glucocorticosteroids, beta-2-agonists, chlorpromazine at high doses (100 mg per day) and diuretics have intrinsic hyperglycaemic activity. Frequent blood glucose monitoring must be performed if used concomitantly with Glucovance, especially at the beginning of the treatment. If necessary, adjust the Glucovance dosage during therapy with the respective medicinal product and upon its discontinuation.

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.

PREGNANCY AND LACTATION:

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.

The use of Glucovance during lactation is contra-indicated.

DOSAGE AND DIRECTIONS FOR USE:

The dosage must be adjusted to each individual case. 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.

Initiation of therapy:

When diet and exercise alone do not result in adequate glycaemic control:

1 tablet daily of Glucovance 250 mg/1.25 mg.

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

In patients inadequately controlled by monotherapy:

1 tablet daily of Glucovance 500 mg/2.5 mg.

The initial dose must not exceed the daily doses of sulphonylurea or metformin already being taken.

In substitution from combination-therapy with metformin and a sulphonylurea:
1 – 2 tablets daily of Glucovance 500 mg/2.5 mg or Glucovance 500 mg/5 mg to be adjusted according to the previous dose of each component.
The recommended initial dose must not exceed the daily dose of glibenclamide (or equivalent dose of another sulphonylurea) and metformin already being taken.

Titration:

A gradual increase in the dosage may aid gastro-intestinal tolerance and prevent the onset of hypoglycaemia. The dosage can be adjusted every 1 – 2 weeks, depending on the results.

Maximum dose:

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

Elderly subjects:

In the elderly, it is recommended to initiate treatment with one tablet daily of Glucovance 250 mg/1.25 mg. The dose should then be adjusted according to results obtained and depending on renal function parameters.

Paediatric patients:

Glucovance is not recommended for use in children.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

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, < 1/1000; very rare: < 1/10 000 and isolated reports.

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 “Special precautions” below)

Uncommon: crises of hepatic porphyria and porphyria cutanea.

Very rare: lactic acidosis (see “Warnings” above). 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.

Gastro-intestinal disorders:

Very common: 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 to 3 daily doses. A slow increase of the dose may also improve gastro-intestinal tolerability.

Hepato-biliary disorders:

Very rare: liver function test 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, photosensitization, urticaria evolving in shock. A cross reactivity to sulphonamide(s) and their derivatives may occur.

Investigations:

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

Very rare: hyponatraemia.

Special Precautions:

Hypoglycaemia:

Moderate or severe hyoglycaemia with loss of consciousness usually occurs in cases of:

- Unjustified administration, namely when diabetes can be controlled by diet alone.
- Accidental excessive intake, particularly in the elderly.
- Insufficient carbohydrate intake especially if combined with physical exercise.
- Potentiation of the hypoglycaemic effect by concomitant medications or by alcohol consumption, especially when combined with fasting.
- Liver or kidney impairment – hypoglycaemia may be prolonged in such circumstances.

The dosage must be individually adapted for each patient if episodes of hypoglycaemia are to be avoided. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. Glucovance must only be prescribed if the patient adheres to a regular meal schedule (including breakfast).

Elderly, malnourished patients or patients with an alteration in general condition and those with adrenal, thyroid or pituitary insufficiency are particularly exposed to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and patients treated with beta-blockers.

The pharmacokinetics and/or pharmacodynamics of Glucovance may be modified in patients with hepatic impairment or severe renal impairment. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated (see Contra-indications).

Management of hypoglycaemia:

Moderate hypoglycaemic 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 to meal patterns must 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 hospitalization 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 must be taken into consideration.

Blood glucose imbalance:

In cases of surgical intervention or any other case of diabetes decompensation, temporary insulin based therapy must be considered as a substitute for this treatment.

Renal function:

Creatinine clearance and/or serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function;
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy; or when starting treatment with a NSAID.

Administration of iodinated contrast agents:

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, treatment should be discontinued prior to, or at the time of the test, depending on the renal function, and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Surgery:

Treatment must be discontinued 48 hours before elective major surgery and should not be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

In patients with decreased level of consciousness, I.V. glucose/dextrose should be considered.

Further treatment is symptomatic and supportive.

IDENTIFICATION:

Glucovance 250 mg/1.25 mg:
Pale yellow capsule shaped, biconvex embossed film coated tablet with “1.25” engraved on one side, and “250” on the other side.

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.

PRESENTATION:

Glucovance 250 mg/1.25 mg:

30, 60 and 90 tablets in clear or opaque white PVC/Aluminium blisters.

Glucovance 500 mg/2.5 mg:

30, 60 and 90 tablets in clear or opaque white PVC/Aluminium blisters.

Glucovance 500 mg/5 mg:

30, 60 and 90 tablets in clear or opaque white PVC/Aluminium blisters.

STORAGE INSTRUCTIONS:

KEEP OUT OF REACH OF CHILDREN.

Store at or below 25 °C.

REGISTRATION NUMBER:

Glucovance 250 mg/1.25 mg tablets:	36/21.2/0411
Glucovance 500 mg/2.5 mg tablets:	36/21.2/0412
Glucovance 500 mg/5 mg tablets:	36/21.2/0413

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein 1645

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 July 2010

	Schedule	Reg. No.:
Glucovance 250 mg/1.25 mg:		
Namibia	NS2	04/21.2/0811
Botswana	S2	BOT08014367
Glucovance 500 mg/2.5 mg:		
Namibia	NS2	04/21.2/0812
Botswana	S2	BOT08014368
Glucovance 500 mg/5 mg:		
Namibia	NS2	04/21.2/0813
Botswana	S2	BOT08014369

F71292 P08/13

PATIENT INFORMATION LEAFLET

Read this entire leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have more questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not share it with other people. It may harm them, even if their symptoms are the same as yours.

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

GLUCOVANCE 250 mg/1.25 mg Film-coated Tablets

GLUCOVANCE 500 mg/2.5 mg Film-coated Tablets

GLUCOVANCE 500 mg/5 mg Film-coated Tablets

1. WHAT GLUCOVANCE CONTAINS:

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

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

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

The other ingredients are croscarmellose sodium, magnesium stearate, microcrystalline cellulose, opadry, povidone, purified water and talc.

2. WHAT GLUCOVANCE IS AND WHAT IT IS USED FOR

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

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

Glucovance is used for the oral treatment (via the mouth) of type 2 diabetes mellitus in adult patients, whose blood glucose levels (glycaemia) cannot be satisfactorily managed with diet and exercise alone.

Glucovance is also indicated as second-line therapy when diet and exercise, and initial treatment with a sulphonylurea or metformin do not result in adequate blood glucose level control in patients with type 2 diabetes.

3. BEFORE YOU TAKE GLUCOVANCE

Do not take Glucovance

- if you are allergic (hypersensitive) to metformin hydrochloride, glibenclamide or other sulphonamides or any of the other ingredients of Glucovance
- if you have kidney or liver function problems
- if you suffer from type 1 diabetes mellitus (i.e. insulin-dependent) or if you have severe loss of diabetes control with either pre-coma or ketosis (a condition caused by substances called 'ketone bodies' accumulating in the blood; you may notice that your breath has an unusual, fruity odour)
- if you have a severe infection (for example an infection of the air passages or an urinary tract infection)
- if you are dehydrated (for example due to persistent or severe diarrhoea, recurrent vomiting)
- if you are treated for heart problems, have recently had a heart attack, have severe circulatory problems or breathing difficulties

- if you suffer from porphyria (a rare, hereditary disease due to an enzyme deficiency causing the body to produce and excrete too much porphyrin, a component used to make the part of blood pigment that carries oxygen)
- if you use miconazole (a medicine to treat certain yeast infections) even for local use
- if you drink alcohol excessively (either every day or only from time to time)
- if you are breast-feeding.

Make sure you ask your doctor for advice,

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

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

Take special care with Glucovance

- if you experience symptoms of a condition called lactic acidosis, i.e. vomiting, bellyache with muscle cramps and a general feeling of discomfort with severe fatigue and difficulty in breathing (see, "Very rare side-effects"). **If these symptoms occur, STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away.**

- if you experience symptoms of low blood sugar (hypoglycaemia). The warning signs may occur suddenly and can include cold sweat, cold and pale skin, dizziness, headache, rapid heart beat, feeling sick, feeling very hungry, temporary changes in vision, drowsiness, unusual tiredness and weakness, nervousness or tremor, feeling anxious, feeling confused, difficulty in concentrating.
  If you notice any of these signs:
  - first eat glucose tablets or a high sugar snack (honey, sweets, biscuits, fruit juice),
  - **STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away** as you may need to be hospitalised to bring your blood glucose back under control,
  - then rest.

  General advice: Inform your family, friends and colleagues to turn you on your side and get medical aid straight away if you become unconscious. They should not give you any food or drink when you are unconscious. It could choke you.

  A low blood sugar level might occur if:
  - you eat too little or miss a meal
  - your diet contains insufficient or unbalanced levels of sugar
  - you drink alcohol
  - you exercise more than usual
  - you have liver, kidney or certain hormone problems
  - the dosage of your medicine is too high
  - you are an elderly person
  - you are taking certain medicines and Glucovance at the same time (see section,

"Taking other medicines").

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

- if you suffer from any infectious illnesses such as flu, infection of the air passages or urinary tract infection.
- Continue to follow any dietary advice your doctor has given you and get some regular exercise while you are taking this medicine.
- Consult your doctor regularly to test your blood sugar levels and your kidney function.

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

Taking other medicines

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

- miconazole even for local use (see section 3, "Do not take Glucovance")
- iodinated contrast agents (see section 3, "Do not take Glucovance")

Special precautions may be required if you take Glucovance and any of the following medicines at the same time:

- angiotensin-converting enzyme inhibitors (used to treat a variety of cardiovascular conditions, such as high blood pressure, and some other diseases)

- diuretics (used to remove water from the body by increasing urine production)
- beta-blockers, clonidine, reserpine, guanethidine or sympathicomimetics (used to treat a variety of cardiovascular conditions, such as high blood pressure, and some other diseases)
- beta-2 agonists (used to treat asthma, such as ritodrine, salbutamol or terbutaline)
- bosentan (used to treat pulmonary hypertension)
- corticosteroids and tetracosactide (a class of hormones used to treat a variety of conditions, e.g. severe inflammation of the skin or in asthma)
- certain painkillers (i.e. non-steroidal anti-inflammatory drugs, such as phenylbutazone)
- fluconazole (used to treat certain yeast infections)
- chlorpromazine (a neuroleptic medicine, which affects how your brain works)
- desmopressin (generally used to reduce urine production)
- danazol (used to treat endometriosis, a condition where the tissue lining of the uterus is found outside the uterus)

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

Avoid medicines containing alcohol (see section “Taking Glucovance with food and drink”).

If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of Glucovance with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.

Taking Glucovance with food and drink:

Avoid alcohol when you take this medicine as alcohol can increase certain side-effects such as lactic acidosis and a low blood sugar level (see section "Possible side-effects"). This also applies to medicines containing alcohol.

Pregnancy

Tell your doctor if you are, you think you might be or are planning to become pregnant. During pregnancy, diabetes should be treated with insulin. If you find out that you are pregnant while taking Glucovance, consult your doctor so that he/she may change your treatment.

Breast-feeding

You must not take Glucovance, if you are breast-feeding or if you are planning to breast-feed your baby.

Driving and using machines

Do not drive or use machines:

- if your vision is blurred. This may happen at the beginning of the treatment because of a lower level of sugar in your blood.
- if you feel that symptoms of low blood sugar begin to appear.

Important information about some of the ingredients of Glucovance:

Each Glucovance tablet contains lactose. If your doctor has told you that you have an intolerance to certain sugars, contact your doctor before taking this medicine.

4. HOW TO TAKE GLUCOVANCE

Dosage

Always take Glucovance exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Only adults may take this medicine.

Your doctor will adapt the dosage of your treatment depending on its effect on your blood tests. Continue to follow any dietary advice your doctor has given you. Glucovance cannot replace the benefits of a healthy lifestyle.
Have a regular meal schedule with a sufficient and balanced sugar intake. This will decrease the risk of low blood sugar.

If you have the impression that the effect of Glucovance is too strong or too weak, talk to your doctor or pharmacist.

Initial treatment:

As first-line therapy

The initial dose is 1 tablet of Glucovance 250 mg/ 1.25 mg once a day.
Glucovance 500 mg / 5 mg must not be used as initial therapy due to an increased risk of hypoglycaemia.

In patients inadequately controlled by monotherapy

1 tablet daily of Glucovance 500 mg/2.5 mg.

The initial dose must not exceed the daily doses of sulphonylurea or metformin already taken.

In substitution from combination-therapy with metformin and a sulphonylurea

1 – 2 tablets daily of Glucovance 500 mg/2.5 mg or Glucovance 500 mg/5 mg to be adjusted according to the previous dose of each component.

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

Titration:

A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia. The dosage can be adjusted every 1 – 2 weeks, depending on the results.

Maximum dose:

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

Dosage adjustment in elderly patients

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

Administration

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

Take the tablets

- once a day, in the morning (breakfast) if you take 1 tablet per day
- twice a day, in the morning (breakfast) and evening (dinner) if you take 2 or 4 tablets per day
- three times a day, in the morning (breakfast), noon (lunch) and evening (dinner), if you take 3, 5 or 6 tablets per day.

If you take more Glucovance than you should

If you have taken more Glucovance tablets than you should have, you may experience low blood sugar (for symptoms of low blood sugar, see section, “Take special care with Glucovance”). **TALK to your DOCTOR IMMEDIATELY.**

In the event of overdosage, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control center.

If you forget to take Glucovance

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

If you stop taking Glucovance

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

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

5. POSSIBLE SIDE EFFECTS

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

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

Low blood sugar: For symptoms of low blood sugar, see section, “Take special care with Glucovance”.

Very common side effects (in more than 1 in 10 patients)

- gastrointestinal disorders such as nausea, vomiting, diarrhoea, bellyache and loss of appetite.

  These side effects occur most frequently after starting therapy. It helps if you spread the doses over the day and if you take the tablets with a meal. **Should these symptoms continue, STOP taking this medicine and CONSULT your DOCTOR.**

Common side effects (in less than 1 in 10, but more than 1 in 100 patients)

- taste disturbance

Uncommon side effects (in less than 1 in 100, but more than 1 in 1,000 patients)

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

Rare side effects (in less than 1 in 1,000, but more than 1 in 10,000 patients)

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

Very rare side effects (in less than 1 in 10,000 patients)

- lactic acidosis: a very serious complication particularly if your kidneys are not working properly, which results in vomiting, bellyache with muscle cramps and a general feeling of discomfort with severe fatigue and difficulty in breathing and which requires specific treatment. **If these symptoms occur, STOP taking this medicine IMMEDIATELY and TELL your DOCTOR straight away.**
- severe reduction in the number of white blood cells (agranulocytosis), anaemia due to a too extensive breakdown of the red blood cells (haemolytic anaemia), lack or insufficient number of new blood cells produced by the bone marrow (bone marrow aplasia) and very severe reduction in the number of blood cells (pancytopenia; this can make the skin look pale, can cause weakness or breathlessness, can increase the risk of bleeding or bruising or make infections more likely)

- abnormalities in liver function tests or inflammation of the liver (hepatitis; this can cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). In this case Glucovance must be discontinued.
- excessive skin sensitivity to sun, serious allergic reactions of the skin or blood vessels
- intolerance to alcohol (with symptoms such as general feeling of discomfort, redness of face, rapid heart beat)
- low level of sodium, which can cause tiredness and confusion, muscle twitching, fits or coma
- decreased vitamin B12 levels in the blood

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

6. STORING AND DISPOSING OF GLUCOVANCE

Keep all medicines out of the reach and sight of children.

Do not use Glucovance after the expiry date, which is stated on the carton after “EXP”.

Store at or below 25 °C.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF GLUCOVANCE

Glucovance 250 mg/1.25 mg:

30, 60 and 90 tablets in a clear or opaque white PVC/Aluminium blisters.

Glucovance 500 mg/2.5 mg:

30, 60 and 90 tablets in a clear or opaque white PVC/Aluminium blisters.

Glucovance 500 mg/5 mg:

30, 60 and 90 tablets in a clear or opaque white PVC/Aluminium blisters.

8. IDENTIFICATION OF GLUCOVANCE

Glucovance 250 mg/1.25 mg are pale yellow capsule shaped, biconvex, embossed film coated tablets with “250” engraved on one side and “1.25” on the other side

Glucovance 500 mg/2.5 mg tablets are orange capsule-shaped, biconvex, embossed film-coated tablets with “2.5” engraved on one side.

Glucovance 500 mg/5 mg tablets are yellow capsule-shaped, biconvex, embossed film-coated tablets with “5” engraved on one side.

9. REGISTRATION NUMBER

Glucovance 250 mg/1.25 mg tablets:	36/21.2/0411
Glucovance 500 mg/2.5 mg tablets:	36/21.2/0412
Glucovance 500 mg/5 mg tablets:	36/21.2/0413

10. NAME AND ADDRESS OF REGISTRATION HOLDER

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein 1645

11. DATE OF PUBLICATION

23 July 2010