SCHEDULING STATUS: **S3**

PROPRIETARY NAME (and dosage form):

GLUCOPHAGE® 500mg TABLETS

GLUCOPHAGE® 850mg TABLETS

GLUCOPHAGE® 1000mg TABLETS

COMPOSITION;

Each Glucophage® 500mg Tablet contains 500 mg Metformin Hydrochloride.

Each Glucophage® 850mg Tablet contains 850 mg Metformin Hydrochloride.

Each Glucophage® 1000mg Tablet contains 1000mg Metformin Hydrochloride.

PHARMACOGICAL CLASSIFICATION:

A 21.2 Oral Hypoglycaemic

PHARMACOLOGICAL ACTION:

Metformin is a biguanide with antihyperglycaemic 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 utilization.

(3) Delay of intestinal glucose absorption.

Absorption:

After an oral dose of metformin, Tmax is reached in 2.5 hours. 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 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 1µg/ml. In controlled clinical trails, maximum metformin plasma levels (Cmax) did not exceed 4µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

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.

Paediatrics:

Single dose study: After single doses of metformin 500mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

INDICATIONS:

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Glucophage® film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children over 12 years of age and adolescents with type 2 diabetes, Glucophage® film-coated tablets may be used as monotherapy or in combination with insulin.

CONTRA-INDICATIONS:

- Hypersensitivity to metformin hydrochloride or to any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females or creatinine clearance < 60ml/min)
- Acute conditions with the potential to alter renal function such as:
    - Dehydration,
    - Severe infection,
    - Shock,
    - Intravascular administration of iodinated contrast agents (see

Special Warnings and Special Precautions for use).

- Acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure,
    - recent myocardial infarction,
    - shock
    - pancreatitis
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Pregnancy and 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 Glucophage® accumulation. Reported cases of lactic acidosis in patients on Glucophage® have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

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

Renal function:

As Glucophage® is excreted by kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

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

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

Administration of iodinated contrast agent

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

Surgery

Glucophage® should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents:

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with Glucophage® is initiated.

No effect of Glucophage® on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of Glucophage® on these parameters in Glucophage® treated children, especially pre-pubescent children, is recommended.

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.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Glucophage® alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas.
- As Vitamin B_{12} deficiency and megaloblastic anaemia may develop

with Glucophage use, Vitamin B_{12} levels should be assessed at least annually (see Side Effects and Special Precautions).

INTERACTIONS:

Inadvisable combinations

Alcohol:

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in Glucophage® accumulation and a risk of lactic acidosis.

Glucophage® should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Reduced renal clearance of Glucophage® has been reported during cimetidine therapy, so a dose reduction should be considered. An interaction between Glucophage® and anticoagulants is a possibility and dosage of the latter may need adjustment.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established in humans. However, animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with Glucophage® but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

DOSAGE AND DIRECTIONS FOR USE:

It is important that Glucophage® tablets be taken in divided doses with meals.

Adults: Initially, one 500 mg tablet three times a day, or one 850mg or 1000mg tablet twice a day, with or after food. After 10 to 15 days the dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastro-intestinal tolerability. Good diabetic control may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks. If control is incomplete a cautious increase in dosage to a maximum of 2550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of Glucophage®.

Children and adolescents: Glucophage® can be used in children from 12 years of age and adolescents. The usual starting dose is 500mg or 850mg once daily, given during meals or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 2000mg daily, taken as 2 or 3 divided doses.

Elderly: Glucophage® dose in the elderly should be adjusted based on renal function.

Combination therapy: see "Special Precautions"

SIDE-EFFECTS & SPECIAL PRECAUTIONS

The following side-effects may occur with Glucophage®. Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1000,

<1/100; rare ≥1/10000, <1/1000; very rare <1/10000, including isolated reports.

Metabolism and nutrition disorders:

Very rare: Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of Glucophage®. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Very rare: Lactic acidosis (see precautions below).

Nervous system disorders:

Common: Taste disturbance.

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 Glucophage® be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepato-biliary disorders:

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorder:

Very rare: Skin reactions such as erythema, pruritus, urticaria.

In published and post marketing data and in controlled clinical studies in a limited

paediatric population aged 10 – 16 years during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Special precautions

Lactic acidosis has occurred to a greater extent in patients with contraindications to therapy. In patients with a metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia) lactic acidosis should be suspected and Glucophage® therapy stopped. Lactic acidosis is a medical emergency which must be treated in hospital.

Glucophage® is excreted by the kidney and regular monitoring of renal function is advised in all diabetics.

Glucophage® therapy should be stopped 2-3 days before surgery and clinical investigations such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained.

The use of Glucophage® is not advised in conditions which may cause dehydration or in patients suffering from serious infections, trauma or on low calorie intake.

Patients receiving continuous Glucophage® therapy should have an annual estimation of Vitamin B12 levels because of reports of decreased Vitamin B12 and folic acid absorption.

During concomitant therapy with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with Glucophage® and insulin may be necessary to be carried out in hospital because of the possibility of hypoglycaemia until the correct ratio

of the two drugs has been obtained.

Contra-indications should be carefully observed.

KNOWM SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Hypoglycaemia can occur when Glucophage® is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and Glucophage® is haemodialysis. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

IDENTIFICATION:

Glucophage® 500mg Tablets – White, round, biconvex, film-coated tablets.

Glucophage® 850mg Tablets – White, round, convex, film-coated tablets.

Glucophage® 1000mg Tablets – White, oval, biconvex, bisected, film-coated tablets with “1000” embossed on one side.

PRESENTATION:

Glucophage® 500mg Tablets – 100’s and 500's in white HDPE Securitainers or 90’s in transparent/colourless PVC/aluminium blisters.

Glucophage® 850mg Tablets – 60’s and 300's in white HDPE Securitainers or 60’s in transparent/colourless PVC/aluminium blisters.

Glucophage® 1000mg Tablets – 60’s and 300’s in white HDPE Securitainers or in transparent/colourless PVC/aluminium blisters.

STORAGE INSTRUCTIONS:

Store at or below 25°C.

Protect from light and moisture.

Keep out of reach of children.

The blister should not be removed from the carton until required for use.

REGISTRATION NUMBER / APPLICATION NUMBER:

Glucophage® 500mg Tablets – G3244 (Act 101/1965)

Glucophage® 850mg Tablets – F/21.2/145

Glucophage® 1000mg Tablets – 37/21.2/0272

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:

17 April 2009

Read all of this leaflet carefully before you start taking GLUCOPHAGE tablets

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

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

GLUCOPHAGE® 500mg TABLETS

GLUCOPHAGE® 850mg TABLETS

GLUCOPHAGE® 1000mg TABLETS

1. WHAT GLUCOPHAGE CONTAINS

Each Glucophage® 500mg Tablet contains 500 mg Metformin Hydrochloride.

Each Glucophage® 850mg Tablet contains 850 mg Metformin Hydrochloride.

Each Glucophage® 1000mg Tablet contains 1000mg Metformin Hydrochloride.

The other inactive ingredients are:

Povidone K30

Magnesium stearate

Purified water

Methocel E5.

2. WHAT GLUCOPHAGE IS USED FOR

GLUCOPHAGE is used to treat type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Glucophage® film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children over 12 years of age and adolescents with type 2 diabetes, Glucophage® film-coated tablets may be used as monotherapy or in combination with insulin.

3. BEFORE YOU TAKE GLUCOPHAGE

Do not take GLUCOPHAGE:

- If you are hypersensitive (allergic) to metformin or any of the other ingredients of GLUCOPHAGE.
- If you suffer from diabetic ketoacidosis, diabetic pre-coma.
- If you suffer from renal failure or renal disease or conditions which may alter renal function such as:
  - Dehydration,
  - Severe infection,
  - Shock,
  - Intravascular administration of iodinated contrast agents (see Special Warnings and Special Precautions for use).
- Acute or chronic disease which may cause tissue a shortage of oxygen such as:
  - cardiac or respiratory failure,
  - recent heart disease,
  - shock
  - infection of the pancreas
- Liver disease, acute alcohol intoxication, alcoholism
- If you are pregnant or breast feeding your baby.

Take special care with GLUCOPHAGE

- Tell your doctor if you have received a contrast media before a radiological examination.
- If you are due for surgery tell your doctor you are taking GLUCOPHAGE.
- You should continue your 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.

Pregnancy and Breast-feeding

If you are pregnant or breast feeding your baby while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

Special warnings:

A serious, but rare condition, lactic acidosis may occur due to GLUCOPHAGE accumulation, usually in patients with renal disease. The symptoms of this condition are difficulty in breathing, stomach pain and low temperature followed by coma. If you suspect you suffer from the condition, contact your doctor immediately.

Taking other medicines with GLUCOPHAGE

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

Tell you doctor or pharmacist if you are taking/using any of the following medicines:

- Iodinated contrast agents
- Glucocorticoids (systemic and local routes)
- Medicines used to treat high blood pressure such as beta-2-agonists,

ACE-inhibitors and diuretics

- Medicines used to treat stomach ulcers such as cimetidine
- Medicines used to treat clotting (anticoagulants)

4. HOW TO TAKE GLUCOPHAGE

Always take GLUCOPHAGE exactly as your doctor has instructed you. Your doctor will decide which dose is applicable to you. You should check with your doctor or pharmacist if you are unsure.

It is important that GLUCOPHAGE tablets be taken in divided doses with meals.

Adults: Initially, one 500 mg tablet three times a day, or one 850mg or 1000mg tablet twice a day, with or after food. After 10 to 15 days the dose may be changed according to blood glucose measurements. You will feel better within a few days, but it is not unusual for the full effect to be delayed for up to two weeks.

Children and adolescents: GLUCOPHAGE can be used in children from 12 years of age and adolescents. The usual starting dose is 500mg or 850mg once daily, given during meals or after meals. After 10 to 15 days the dose may be adjusted on the basis of blood glucose measurements.

Elderly: GLUCOPHAGE dose in the elderly should be adjusted based on renal function.

Swallow the tablet whole with a drink of water.

Try to take your tablet at the same time each day.

If you have the impression that the effect of GLUCOPHAGE is too strong or too weak, talk to your doctor or pharmacist, who may wish to change your treatment.

If you take more GLUCOPHAGE than you should:

If you take more tablets than your normal dose, contact your doctor or nearest hospital 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 a dose:

Take the last missed dose as soon as you remember. Do not take a double dose.

5. POSSIBLE SIDE EFFECTS

GLUCOPHAGE can have side effects. The following side-effects may occur more frequently:

- Taste disturbance
- 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 Glucophage® be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

The following side-effects may occur less frequently:

- Liver function tests abnormalities or hepatitis
- Skin reactions such as swelling, redness, itching, hives.

Tell you doctor if you suffer from a blood disease that is caused by a deficiency of vitamin B12 and folic acid.

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.

'If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist'.

6. STORING AND DISPOSING OF GLUCOPHAGE

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

Store below 25°C. Protect from light and moisture.

Keep your tablets in the container they came in.

Do not use after the expiry date stated on the carton

Return all unused medicine to your pharmacist.

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

7. PRESENTATION OF GLUCOPHAGE

Glucophage® 500mg Tablets – 100's and 500's in white HDPE Securitainers or 90's in transparent/colourless PVC/aluminium blisters.

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10. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTATION:

MERCK (PTY) LTD

1 Friesland Drive,

Longmeadow Business Estate South,

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11. DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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