SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

GLUCONORM 500 (500 mg film-coated tablets)

GLUCONORM 850 (850 mg, film-coated, tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

GLUCONORM 500

Each GLUCONORM 500 film-coated tablet contains 500 mg of metformin hydrochloride equivalent to 390 mg metformin.

Sugar free.

GLUCONORM 850

Each GLUCONORM 850 film-coated tablet contains 850 mg of metformin hydrochloride equivalent to 663 mg metformin.

Sugar free.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

GLUCONORM 500

White, biconvex, circular shaped film-coated tablets, with “A” debossed on one side and “60” debossed on the other side.

GLUCONORM 850

White, biconvex, circular shaped film-coated tablets, with “A” debossed on one side and “61” debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLUCONORM is indicated for:

Type II diabetes mellitus when diet and exercise has failed and especially if the patient is overweight. In adults GLUCONORM can be given alone as initial therapy or can be administered in combination with other oral antidiabetic medicines or insulin.

In children over 12 years of age and adolescents with type 2 diabetes mellitus, GLUCONORM may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin hydrochloride immediate-release as first-line therapy after diet failure.

4.2 Posology and method of administration

Posology

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

Adults:

Initially, one 500 mg tablet three times a day, with or after food.

After 10 to 15 days the dose should be adjusted, or increased to 850 mg or 1000 mg twice daily.

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 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 **GLUCONORM.**

In patients receiving a high GLUCONORM dose (2000 to 3000 mg per day), it is possible to replace two GLUCONORM 500 mg film-coated tablets with one GLUCONORM 1000 mg film-coated tablet.

The maximum recommended dose of GLUCONORM is 3000 mg daily, taken as 3 divided doses.

If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate GLUCONORM at the dose indicated above.

Combination with insulin

GLUCONORM and insulin may be used in combination therapy to achieve better blood glucose control. GLUCONORM is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Paediatric patients

GLUCONORM can be used in children from 12 years of age and adolescents as monotherapy or in combination with insulin.

• The usual starting dose is 500 mg or 850 mg 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 GLUCONORM is 2 000 mg daily, taken as 2 or 3 divided doses.

Patients with 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.

GLUCONORM may be used in patients with moderate renal impairment stage 3 (i.e creatinine clearance [CrCl] between 30 and 59 mL/min or estimated glomerular filtration rate [eGFR] between 30 – 59 ml/min/1.73m2) only in the absence of other conditions that may increase the risk of lactic acidosis (see section 4.4) and with the following dose adjustments:

The starting dose is 500 mg or 850 mg GLUCONORM. The maximum daily dose is 1000 mg.

The renal function should be closely monitored:

• Every 3-6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m2.

• Every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m2.

If CrCl or eGFR fall below 30 mL/min or 30 mL/min/1.73m2 respectively, GLUCONORM must be discontinued immediately.

GFR (mL/min)	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60- 89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45 – 59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30 – 44	1000 mg	
< 30	-	Metformin is contraindicated

Elderly

Due to the potential for decreased renal function in elderly subjects, it is recommended that the GLUCONORM dose be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older (see section 5.1) GLUCONORM initiation is therefore not recommended in these patients (see section 4.4).

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis), diabetic pre-coma, or the history thereof.
- Severe renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1.73m2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection or shock.
- Pancreatitis.
- Chronic liver disease.
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.
- Cardiac failure and recent myocardial infarction.
- Conditions associated with hypoxia such as unstable congestive heart failure, respiratory failure or shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Pregnancy and lactation
-

4.4 Special warnings and precautions for use

Lactic acidosis:

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

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, severe infection and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs), (see also section 5).
Special caution should therefore be paid to situations where renal function may become acutely impaired, for example in case of dehydration (severe or prolonged diarrhoea or vomiting) or when initiating medications which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs).

Diagnosis:

Non-specific symptoms that could be signs of lactic acidosis are muscle cramps, digestive disorders such as abdominal pain and asthenia.
Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.

Medical practitioners must alert the patients on the risk and on the symptoms of lactic acidosis and patients should be instructed to immediately seek medical attention and to stop taking GLUCONORM, at least temporarily, until the situation is clarified. Reintroduction should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.

Renal function:

As **GLUCONORM** is excreted by the 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 (CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m^2) and in elderly subjects.
- At least every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2.

In case CrCl is below 30 mL/min or eGFR is below 30 mL/min/1.73m2 respectively, GLUCONORM is contraindicated (see section 4.3).

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 due to dehydration (severe or prolonged diarrhoea or vomiting) or when initiating antihypertensive or diuretic therapy and when starting therapy with a NSAID.

In the acute conditions listed, treatment with GLUCONORM must be immediately and temporarily discontinued. In these cases, it is also recommended to check renal function before re-initiating treatment with GLUCONORM.

The administration of **GLUCONORM** may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Administration of iodinated contrast agent:

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

Surgery:

GLUCONORM should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

Paediatric patients

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with GLUCONORM is initiated. No effect has been reported on growth and puberty during controlled clinical studies of one-year duration with the active ingredient contained in GLUCONORM, however, no long-term data on these specific points are available. A careful follow-up of the effect of GLUCONORM on these parameters in children is therefore recommended, especially in pre-pubescent children.

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.
- Although **GLUCONORM** alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulfonylureas.
- Gluconorm may reduce vitamin 12 serum levels. The risk of low vitamin B12 levels increases with increasing Gluconorm dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency.
- Gluconorm therapy should be continued for as long as it is tolerated and not conta-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines. Gluconorm alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g sulfonylureas or meglitinides)

4.5 Interaction with other medicinal products and other forms of interaction

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 **GLUCONORM** accumulation and a risk of lactic acidosis. **GLUCONORM** 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.

Glucocorticoids (systemic and local routes), beta-2-agonists, tetracosactides, danazol, chlorpromazine at high does of 100 mg per day 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.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function. When starting or frequently using such products in combination with metformin, close monitoring of renal function is necessary.

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.

Cimetidine: Reduced renal clearance of **GLUCONORM** has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: GLUCONORM has been reported to diminish the activity of warfarin, and so dose adjustments of **GLUCONORM** should be considered.

Sulphonylurea: Concomitant therapy of **GLUCONORM** with sulphonylurea may cause hypoglycaemia.

Antiretrovirals: Practitioners prescribing metformin should be aware that patients receiving certain antiretroviral medication e.g. protease inhibitors may be independently more prone to develop lactic acidosis.

Vitamins: Long-term treatment with **GLUCONORM** may cause vitamin B_{12} malabsorption in the gastro-intestinal tract, thus a dose reduction of **GLUCONORM** should be considered.

Organic cation transporters (OCT)

Metformin, as contained in GLUCONORM, is a substrate of both transporters OCT1 and OCT2. Caution is thus advised when the following medicines are co-administered with GLUCONORM:

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin

Dose adjustment should thus be considered, particularly in patients with renal impairment.

4.6 Fertility, pregnancy and lactation Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased congenital abnormalities and perinatal mortality.

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

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 GLUCONORM 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.

Lactation

GLUCONORM is excreted into milk in lactating rats.

GLUCONORM is excreted into human breast milk in very small amounts. No adverse effects were observed in breastfed newborns /infants. However, as only limited data are available, breast-feeding is not recommended during GLUCONORM treatment.

A decision on whether to discontinue breast-feeding or to discontinue GLUCONORM needs to take into account the benefit of breast-feeding, the importance of the medicinal product to the mother, and the potential risk of adverse effects in the infant.

Fertility

Fertility of male and female rats was unaffected by GLUCONORM 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.

4.7 Effects on ability to drive and use machinery

GLUCONORM monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when GLUCONORM is used in combination with other antidiabetic medicines (e.g. sulfonylureas, insulins or meglitinides).

.**4.8 Undesirable effects** During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take GLUCONORM in 2 or 3 daily doses and to increase slowly the doses.

Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less Frequent	Megaloblastic anaemia
Immune System disorders	Frequency unknown	Hypersensitivity
Metabolism and nutrition disorders	Frequent	Vitamin B_{12} decrease/deficiency (see section 4.5)
	Less Frequent	Lactic acidosis (see section 4.4), hypoglycaemia
	Frequency Unknown	Ketoacidosis
Nervous system disorders	Frequent	Metallic taste, taste disturbance
Gastrointestinal disorders	Frequent	Anorexia, nausea, diarrhoea, vomiting, abdominal pain and loss of appetite
	Frequency Unknown	Constipation
Hepato-biliary	Less Frequent	Severe cholestatic hepatitis,

Ref 1312-1 pg 12 of 17, DD

Moved into table

Ref 1312-1 pg 13 of 17, EE

Moved into table

disorders		liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Renal and urinary disorders	Frequency Unknown	Ketonuria
Skin and subcutaneous tissue disorder	Less Frequent	Skin reactions such as erythema, pruritus, urticaria

Patients on long-term treatment with **GLUCONORM** should have an annual estimation of vitamin B_{12} levels, since **GLUCONORM** may cause malabsorption of vitamin B_{12}, which may result in megaloblastic anaemia, neuropathy , mental disturbance, mouth ulcers or visual disturbances..

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Side effects must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za.

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85 g, but can occur when **GLUCONORM** 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.

Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels. The most effective method to remove lactate and GLUCONORM is haemodialysis.

Treatment of Overdosage:

There is no specific antidote for overdose with **GLUCONORM**. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 21.2 Oral Hypoglycaemic

Pharmacotherapeutic group:

Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Mechanism of action

Metformin is a biguanide oral anti-hyperglycaemic agent. Its mode of action is thought to be:

- increased peripheral glucose utilization mediated by increased insulin sensitivity
- inhibition of increased hepatic and renal gluconeogenesis.
- 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) known to date.

5.2 Pharmacokinetic properties

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 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4 µg/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 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (Kollidon 90 F)

Magnesium Stearate

Hypromellose

Macrogol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool (at or below 25°C), dry place.

Protect from light and moisture.

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

6.5 Nature and contents of containerGLUCONORM 500

100's: Printed unit cartons containing 10 blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 10 tablets each.

GLUCONORM 850

30's: Printed unit cartons containing 3 blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 10 tablets each.

60's: Printed unit cartons containing 6 blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

UNICORN PHARMACEUTICALS (PTY) LTD.

4th Floor Offices, Block A, The District

41 Sir Lowry Road,

Woodstock, Cape Town,

7925,

Republic of South Africa

enquiries@unicornpharma.co.za

8. REGISTRATION NUMBER(S)

GLUCONORM 500: 41/21.2/0071

GLUCONORM 850: 41/21.2/0072

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 2007

10. DATE OF REVISION OF THE TEXT

15 May 2026