GLUCOMIN-G 500MG/2.5MG TABLET
GLUCOMIN-G 500MG/5MG TABLET

COMPOSITION:
GLUCOMIN-G 500MG/2.5MG
Each film coated tablet contains 500mg of Metformin Hydrochloride and 2.5mg Glibenclamide.

GLUCOMIN-G 500MG/5MG
Each film coated tablet contains 500mg of Metformin Hydrochloride and 5mg Glibenclamide

PRODUCT DESCRIPTION:
GLUCOMIN-G 500MG/2.5MG: A beige coloured oblong shaped film coated tablet
GLUCOMIN-G 500MG/5MG: A yellow coloured oblong shaped film coated tablet

PHARMACODYNAMIC:
Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.
Metformin may act via 3 mechanisms:

- By reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; in muscle,
- By increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- By delaying intestinal glucose absorption.

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

Glibenclamide is a second generation sulfonylurea with a short 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 β-cells in the islets of Langerhans. The mechanism by which Glibenclamide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with type 2 diabetes, the blood glucose-lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extra pancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

PHARMACOKINETICS:
Absorbtion:
Metformin HCl: Metformin absorbtion is saturable and incomplete after the oral administration. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1µg/ml.
Glibenclamide: After an oral administration, Glibenclamide is very readily absorbed (>95%) and the peak plasma concentration is reached in about 4 hours.

Distribution:
Metformin HCl: Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. The red blood cells most likely represent a secondary compartment of distribution.
Glibenclamide: Glibenclamides are extensively bound to serum proteins. Displacement from protein-binding sites by other drugs may lead to enhanced hypoglycemic action.

Metabolism
Metformin HCl: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) .
Glibenclamide: The major metabolite of glibenclamide is the 4-trans-hydroxy derivative. Glibenclamide is completely metabolized in the liver to two metabolites;4-trans-hydroxy derivate and the 3-cis-hydroxy

derivative. Hepatocellular failure decreases glibenclamide metabolism and appreciably slows down its excretion.

Elimination
Metformin HCl: Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hrs, with a plasma elimination half-life of approximately 6.2 hrs. In blood, the elimination half-life is approximately 17.6 hrs, suggesting that the erythrocyte mass may be a compartment of distribution.
Glibenclamide: Glibenclamide is excreted as metabolites via biliary route (60%) and urine (40%), elimination being complete within 45 to 75 hours. Its terminal elimination half life is 4 to 11 hours. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine. Biliary excretion of metabolites increases in cases of renal insufficiency, according to the severity of renal impairment until a creatinine clearance at 30ml/min. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30ml/min.

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

DOSAGE & ADMINISTRATION:
General Consideration:
Dosage of GLUCOMIN-G must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 2000 mg metformin/20 mg glibenclamide. GLUCOMIN-G should be given with meals with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episode. GLUCOMIN-G should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glibenclamide), reduce GI side effects (largely due to metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to GLUCOMIN-G and to identify the minimum effective dose for the patient. Thereafter, $HbA1_c$(glycosylated hemoglobin), should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA1c to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using $HbA1_c$ which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to GLUCOMIN-G therapy in patients taking concomitant glybenclamide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

GLUCOMIN-G use in previously treated patients (Second line Therapy)
Recommended Starting Dose: 500mg/2.5 mg or 500mg/5 mg twice daily with meals.
For patients not adequately controlled on either glibenclamide (or another sulfonylurea) or metformin alone, the recommended starting dose of GLUCOMIN-G is 500 mg/2.5mg or 500 mg/5mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of GLUCOMIN-G should not exceed the daily doses of glibenclamide or metformin already being taken. The daily dose should be titrated in increments of no more than 500 mg/5mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 2000 mg/20 mg per day.

For patients previously treated with combination therapy of glibenclamide (or another sulfonylurea) plus metformin, if switched to GLUCOMIN-G, the starting dose should not exceed the daily dose of glibenclamide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be

monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of GLUCOMIN-G should be titrated as described above to achieve adequate control of blood glucose.

Specific Patient Populations

GLUCOMIN-G is not recommended for use during pregnancy. The initial and maintenance dosing of GLUCOMIN-G should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of GLUCOMIN-G to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

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 should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

GFR mL/min	Metformin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.
<30	Metformin is contraindicated

ROUTE OF ADMINISTRATION
Oral Administration

CONTRAINDICATIONS:

- Patients with renal disease or dysfunction (creatinine clearance <60ml/min)
- Acute or chronic disease which may also cause tissue hypoxia such as cardiovascular collapse (shock), acute myocardial infarction and septicemia
- Type-1 diabetes (insulin-dependent diabetes), acute or chronic metabolic acidosis, including diabetic ketoacidosis, pre-coma.
- Known hypersensitivity to metformin HCl or glibenclamide or other sulphonylurea(s) and sulphonamide(s) or to any of the excipients.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, dehydration and severe infection shock because it may result in acute alteration of renal function
- major surgery
- Hepatic insuffiency, acute alcohol intoxication, alcoholism.
- pophyria
- lactation
- In association with miconazole
- Severely reduced kidney function (GFR <30 mL/min)

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

WARNING AND PRECAUTIONS:

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.

Patients and/or care-givers 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.

Hypoglycemia:

GLUCOMIN-G in which contains a sulphonylurea, it is capable of producing hypoglycemia or hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycemia likely to occur in case when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents or ethanol and energy restricted diet. The symptoms are headache, nausea, hunger, vomiting, extreme tiredness, sleep disorder restlessness, aggression, impaired concentration and reactions, depression, confusion, speech impediment, visual disturbance, trembling, paralysis and paraesthesia, dizziness, delirium, convulsions, somnolence, unconsciousness, superficial breathing and bradycardia. Due to a counterregulation caused by the hypoglycemia sweating, fear, tachycardia, hypertension, palpitations, angina and arrhythmia can occur. These latter symptoms can be absent when the hypoglycemia is developed slowly, in case of autonomic neuropathy or the patient takes beta-blocking agents, clonidine, reserpine, guanethidine or sympathomimetics

Management of hypoglycaemia:

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

The careful selection of patient and dosage and adequate instructionfor the patients are important to reduce the risk of hypoglycaemia episodes. If the severe associated with unawareness of the situation, antidiabetic treatment option other than GLUCOMIN-G should be taken into consideration.

Factors favouring hypoglycaemia: concomitant administration of alcohol, especially combined with fasting, refusal or (more particularly in elderly patient) 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 GLUCOMIN-G, certain endocrine disturbances: thyroid insufficiency, pituitary and adrenal gland insufficiency and concomitant administration of certain other drugs (see Interaction with other medicaments)

Renal function
GFR should be assessed before treatment initiation and regularly there after [See Section Recommended Dosage]. 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 Contraindications].

***Use of Concomitant Medications that may Affect Renal Function or Metformin Disposition*:**
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin eg, cationic drugs that are eliminated by renal tubular secretion (see Interactions), should be used with caution.

***Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (eg, IV urogram, IV cholangiography, angiography and computed topography (CT) scans with intravascular contrast materials)*:**
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with the lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, GLUCOMIN-G should be temporarily discontinued at the time of or prior to procedure, and withheld for 48 hrs subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Surgical Procedures:
GLUCOMIN-G therapy should be temporarily suspended (48 hour) before any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted (48 hour) afterwards until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake:
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOMIN-G. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired Hepatic Function:
Since impaired hepatic function and renal failure have been associated with some cases of lactic acidosis, GLUCOMIN-G should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. If hyperglycaemiaoccurs in such patients, it may be prolonged and appropriate treatment must be initiated.
Information for Patients:
Patients should be informed of the potential risks, symptoms and treatment of GLUCOMIN-G and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hemoglobin parameters.
The risks of lactic acidosis associated with metformin therapy, its symptoms, and conditions that predispose to its development, as noted in the Warnings and Precautions sections, should be explained to patients.

Other precautions:
All patient 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 GLUCOMIN-G. The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly. This is because, this medicinal product contains lactose, it is contraindicated incase of congenital galactosemia, glucose and galactose malabsorbtion syndrome or in case of lactase deficiency.

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin 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 anemia 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. Metformin therapy should be continued for as long as it is tolerated and not

contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

EFFECTS ON THE ABILITY TO DRIVE OR OPERATE MACHINERY:
Patients should be alerted to the symptoms of hypoglycemia and should be advised to exercise caution when driving or using machines.

SIDE EFFECTS:
The following undesirable effects may occur under treatment with GLUCOMIN-G

	Side effects
Investigations	- Average to moderate elevations in serum urea and creatinine concentration. - Hyponatremia
Blood and lymphatic system disorder	- Leukopenia, thrombocytopenia - Agranulocytosis, haemolytic anemia, bone marrow aplasia and pancytopenia
Nervous system disorders	- taste disturbance
Eye disorders	- Transient visual disturbance may occur at the start of treatment due to a decrease in glycaemia levels.
Gastrointestinal disorders	- nausea, vomiting, diarrhoe, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment initiation resolve spontaneously in most cases. To prevent them, it is recommended that GLUCOMIN-G be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.
Skin and subcutaneous tissue disorder	- skin reactions such as pruritus, urticaria, maculopapular rash. - Cutaneous or visceral allergic angiitis, erythema multiforme, exfoliative dermatis photosensitization, urticaria evolving to shock. - A cross reactivity to sulphonamides and their derivatives may occur.
Metabolism and nutrition disorder	- Hypoglycaemia - Crises of Hepatic porphyria and porphyria cutanea - Lactic acidosis - Decrease of Vitamin B12 absorbtion with decrease of serum level 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.
Hepatobiliary disorder	Liver function test abnormalities or hepatitis requiring treatment discontinuation.

<u>Metabolism and nutrition disorders</u>
Common: Vitamin B12 decrease/deficiency

PREGNANCY & LACTATION:
Use in pregnancy: Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. Insulin should be used during pregnancy to maintain blood glucose as close to normal as possible. GLUCOMIN-G should not be used as treatment of diabetes during pregnancy. Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. It is recommended that the patient to be transferred from oral antidiabetic therapy to insulin as soon as the person plans to become pregnant or if pregnancy is exposed to this medicinal product. Neonatal blood glucose monitoring is recommended.

Use in lactation: Although it is not known whether glibenclamide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue GLUCOMIN-G, taking into account the importance of the drug to the mother. If GLUCOMIN-G is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

DRUG INTERACTION:

- *Miconazole (systemic route, oromucosal gel)*
  Increase in the hypoglycaemic manifestations, or even coma.
- Iodinated contrast materials:
  Depending on the renal function, GLUCOMIN-G must be discontinued 48 hour before the test or at the time of the test
- *Alcohol*
  Antabuse effect (intolerance to alcohol), notably for clorpropamide, glibenclamide, glipizide, tolbutamide. Increase of the hypoglycaemic reaction (inhibition of compensation reactions), which may facilitate the onset of a hypoglycaemic coma. Avoid consumption of alcohol and alcohol-containing medications.
  Increased risk of lactic acidosis during acute alcoholic intoxication particularly in cases of fasting or malnutrition and hepatocellular failure. Avoid drinking alcoholic beverages and taking drugs that contain alcohol.
- *Phenylbutazone*
  Increase in the Hypoglycaemic affect of sulphonylurea(s) (displacement sulphonylurea(s) from protein binding sites and/or decrease in the elimination). Preferably use another anti-inflammatory agent exhibiting few 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
- *Bosentan*
  There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and it is recommended that such use to be avoided; the hypoglycaemic effect of glibenclamide may also be reduced.
- *Danazol*
  If the combination cannot be avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with danazol and after its withdrawal.
- *Chlorpromazine*
  At high dosages (100mg per day of chlorpromazine), elevation in blood glucose (reduction in release of insulin) Precaution for use: warn the patient and step-up self monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with the neuroleptic and after its withdrawal.
- *Corticostroids (glucocorticoids) and tetracosactides (systemic and local routes):*
  Elevation in blood glucose, sometimes accompanied by ketosis (decreased carbohydrate tolerance with corticosteroids).
  Precaution for use: warn the patient and step-up self monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with the corticosteroids and after its withdrawal.
- *ß2-agonists*
  Elevation in blood glucose due to the ß2-agonists.
  Precaution for use: warn the patient and step-up self monitoring of blood glucose. Possibly transfer the insulin theraphy.
- *Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril)*
  ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of GLUCOMIN-G during theraphy with an ACE inhibitor and upon its discontinuation.
- *Diuretics*
  Lactic acidosis due to metformin triggered by any functional renal insuffiency, related to diuretics and more particularly to loop diurectics
- *Beta-blockers, clonidine, reserpine, guanethidine and sympathomimetics*

All Beta-blockers, clonidine, reserpine, guanethidine and sympathomimetics mask some of the symptoms of hypoglycaemia: palpitation 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

- *Fluconazole*
  Increase in the half life of sulphonylurea with possible onset of hypoglycaemic manifestations
  Warn the patient and step-up blood glucose self-monitoring and possibly adjust the dosage of the antidiabetic during treatment with the flucanazole and after its withdrawal.
- *Desmopressin*
  Reduction in antidiurectic activity.

OVERDOSAGE & TREATMENT:
The presence of the sulphonylurea may produce hypoglycaemia.
The presence of metformin produce lactic acidosis under high overdose or the existence of concomitant risk factors (see Special warning and precaution for use). Lactic acidosis is a medical emergencies requiring immediate hospitalization. The most effective treatment is to remove lactate and metformin by dialysis.
The plasma clearance of glibenclimade may be prolonged in patients suffering from liver disease.
Since glibenclamide is extensively bound to proteins, it is not eliminated by dialysis.

PRESENTATION:
10 tablets per blister. Box of 10, 20, 30, 50, 60, 90, 100, 120, 180, 500, and 1000 tablets

STORAGE:
Store below 30^{o}C

MANUFACTURED BY:
Noripharma Sdn. Bhd. 200701034604 (792633-A)
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