GLIBENCLAMIDE
METFORMIN HYDROCHLORIDE

GLYNOVA

5 mg/500 mg Tablet
ORAL HYPOGLYCEMIC

PRODUCT DESCRIPTION:
White to off white, smooth capsule shaped, biconvex, uncoated tablet having break line on one side and plain on other side.

FORMULATION:
Each tablet contains:
Metformin (as hydrochloride) …… 500 mg
Glibenclamide ……5 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics
Mechanism of Action
Combination of glyburide and metformin hydrochloride, 2 antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes. Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide 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. Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Pharmacokinetics
Absorption and Bioavailability
Glyburide
Single-dose studies with Micronase® tablets in normal subjects demonstrate significant absorption of glyburide within 1-hour, peak drug levels at about 4 hours, and low but detectable levels at 24 hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Bioequivalence has not been established between glibenclamide + metformin and single ingredient glyburide products.
Metformin
Hydrochloride The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and a 25% lower AUC in plasma and a 35-minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.
Distribution
Glyburide
Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. In vitro, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs, such as phenylbutazone, warfarin, and salicylates, displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding results in fewer drug-drug interactions with glyburide tablets in clinical use.
Metformin Hydrochloride
The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally < 1 mcg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.
Metabolism and Elimination
Glyburide
The decrease of glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. The major metabolite of glyburide is the 4-transhydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400 and 1/40 as active, respectively, as glyburide) in rabbits. Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.
Metformin Hydrochloride
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 1) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

INDICATIONS:
Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE AND MODE OF ADMINISTRATION:
Posology
Oral route.
For use in adults only.
General:
As for all hypoglycaemic agents, the dosage should be adapted according to the individual metabolic response (glycaemia, HbA1c).
Metformin hydrochloride + Glibenclamide 500 mg/5 mg should preferably be used in patients who cannot be sufficiently controlled with 500mg / 2.5 mg.
Initiation of treatment:
Treatment should be initiated with a dose of the combination product equivalent to previous individual doses of metformin and glibenclamide; the dose being gradually increased depending on results on glycaemic parameters.
Dose titration:
The dosage should be adjusted every 2 weeks or longer, by increments of 1 tablet, depending on glycaemia results. A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.
Maximum daily recommended dose:
The maximum daily recommended dose is 3 tablets.
In exceptional cases, an increase up to 4 tablets may be recommended.

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

Elderly subjects:
The dosage of metformin/glibenclamide should be adjusted depending on renal function parameters (start with 1 tablet of 500 mg/2.5 mg); regular checks on the renal function are necessary. Patients aged 65 years and older: starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia. Treatment should be started with the lowest available dose and increased gradually if necessary.

CONTRAINDICATIONS:
This medicinal product must never be used in case of:
- hypersensitivity to the active substances, to other sulphonylurea(s) and sulphonamide(s) or to any of the excipients
- type 1 diabetes (insulin-dependent diabetes), ketoacidosis, diabetic pre-coma;
- renal failure or renal dysfunction (creatinine clearance < 60 ml/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock;
- acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock;
- hepatic insufficiency, acute alcohol intoxication, alcoholism;
- porphyria;
- lactation;
- in association with miconazole

WARNINGS AND PRECAUTIONS:
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 also other associated risk factors, such as poorly-controlled diabetes, ketosis, prolonged fasting, alcoholism, hepatic insufficiency and any condition associated with hypoxia.
Hypoglycaemia
As the medicinal product contains a sulphonylurea (glibenclamide), it exposes the patient to a risk of onset of hypoglycaemic episodes. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment should only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important that carbohydrate intake is regular since the risk of hypoglycaemia is increased by a late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycaemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol intake or during the administration of a combination of hypoglycaemic agents.
Management of hypoglycaemia: Moderate hypoglycaemic symptoms without loss of consciousness or neurological manifestations should be corrected by the immediate intake of sugar. An adjustment to the dosage and/or changes to meal patterns should be ensured. Severe hypoglycaemic reactions with coma, seizures or other neurological signs are also possible and constitute a medical emergency requiring immediate treatment with intravenous glucose once the cause is diagnosed or suspected, prior to prompt hospitalisation of the patient. The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycaemic episodes. If the patient encounters repeated episodes of hypoglycaemia, which are either severe or associated with unawareness of the situation, antidiabetic treatment options other than glibenclamide + metformin should be taken into consideration.
Renal and hepatic failure:
The pharmacokinetics and/or pharmacodynamics of metformin + glibenclamide may be modified in patients with hepatic failure or severe renal failure. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated.
Elderly patients:
Age 65 years and older has been identified as a risk factor for hypoglycemia in patients treated with sulfonylureas. Hypoglycemia can be difficult to recognize in the elderly. Starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia.
Patient information:
The risks of hypoglycaemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family.

Similarly, the risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps accompanied by digestive disorders, abdominal pain and severe asthenia, dyspnoea attributed to acidose, hypothermia and coma.
In particular, the patient should be informed of the importance of adhering to a diet, following a programme of regular physical exercise and making regular checks on glycaemia.
Blood sugar imbalance
In case of surgery or any other cause of diabetic decompensation, temporary insulin therapy should be envisaged instead of this treatment. The symptoms of hyperglycaemia are: increased urinating, raging thirst and a dry skin
Kidney function
As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinine levels 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 non-steroidal anti-inflammatory drug (NSAID).
Administration of iodinated contrast materials
The intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, metformin + glibenclamide be discontinued 48 hours before the test or at the time of the test and may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal
Concomitant use of glibenclamide with other medicinal products
The concomitant use of glibenclamide with alcohol, phenylbutazone or danazol is not recommended
Surgery
Because it contains metformin hydrochloride, treatment must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia and may not be reinstituted earlier than 48 hours following surgery or resumption of oral nutrition and only after renal function has been re-evaluated and found to be normal.
Other precautions
All patients should continue their diet, with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet. Regular physical exercise is as necessary as taking metformin + glibenclamide. The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glibenclamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

PREGNANCY AND LACTATION:
Pregnancy
No preclinical and clinical data on exposed pregnancies are available
Breast-feeding
Metformin is excreted in human breast. No adverse effects were observed in breastfed newborns/infants of mothers treated with metformin alone. However, in the absence of data concerning passage of glibenclamide into breast milk, and in view of the risk of neonatal hypoglycaemia, this medicinal product is contraindicated in the event of breast-feeding.

Effects on ability to drive and use machines
Patients should be alerted to the symptoms of hypoglycaemia and should be advised to exercise caution when driving or using machines.

INTERACTIONS:
Contraindicated combination
Related to glibenclamide
Miconazole (systemic route, oromucosal gel): Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma.
Combinations not recommended
Related to sulphonylurea(s)
Alcohol:
Antabuse effect (intolerance to alcohol), notably for chlorpropamide, 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.
Phenylbutazone (systemic route):
Increase in the hypoglycaemic effect of sulphonylurea(s) (displacement of sulphonylurea(s) from protein-binding sites and/or decrease in their elimination). Preferably use another antiinflammatory agent exhibiting fewer interactions, or else warn the patient and step up selfmonitoring; if necessary, adjust the dosage during treatment with the anti-inflammatory agent and after its withdrawal.
Related to all antidiabetic agents
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 treatment during treatment with danazol and after its withdrawal.
Related to metformin
Alcohol:
Acute alcoholic intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting or malnutrition and hepatocellular failure. Avoid drinking alcoholic beverages and taking drugs that contain alcohol.
Combinations requiring precautions
Related to all antidiabetic agents
Chlorpromazine:
At high dosages (100 mg 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 treatment during treatment with the neuroleptic and after its withdrawal.
Corticosteroids (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 selfmonitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with corticosteroids and after their withdrawal.
β2-agonists:
Elevation in blood glucose due to the β2-agonists. Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to insulin therapy.
Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril):
ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of metformin + glibenclamide during therapy with an ACE inhibitor and upon its discontinuation.
Related to metformin
Diuretics:
Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics.
Iodinated contrast materials:
Intravascular administration of iodinated contrast materials may lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, metformin + glibenclamide must be discontinued 48 hours before the test 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.
Related to glibenclamide
Beta-blockers:
All beta-blockers mask some of the symptoms of hypoglycaemia: palpitations and tachycardia; Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.
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 treatment during treatment with fluconazole and after its withdrawal.
Bosentan:
Risk of decreased hypoglycaemic effect of glibenclamide because bosentan reduces the plasma concentration of glibenclamide. An increased risk of liver enzyme elevations was reported in patients receiving glibenclamide concomitantly with bosentan. Warn the patient, set-up monitoring of glycaemia and liver enzymes and adjust the dosage of the antidiabetic treatment if necessary.
Bile acid binding agents:
Concomitant use may cause a decrease in plasma concentration of glibenclamide, which could lead to a reduced hypoglycaemic effect. This effect was not observed when glibenclamide was taken at an earlier time than the other medicinal product. It is recommended that glibenclamide/metformin is taken at least 4 hours before the intake of a bile acid agent.
Other interaction: combination to be taken into account:
Related to glibenclamide
Desmopressin:
Reduction in antidiuretic activity.

ADVERSE DRUG REACTIONS:
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 metformin + glibenclamide in 2 or 3 daily doses and to increase slowly the doses. At the start of treatment, transient visual disturbances may occur due to a decrease in glycaemia levels. The following undesirable effects may occur under treatment with metformin + glibenclamide. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) rare (≥/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Blood and lymphatic system disorders:
These are reversible upon treatment discontinuation. Rare: leukopenia, thrombocytopenia. Very rare: agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.
Metabolism and nutrition disorders:
Hypoglycaemia
Uncommon: crises of hepatic porphyria and porphyria cutanea. Very rare: lactic acidosis. Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia. Disulfiram-like reaction with alcohol intake.
Nervous system disorders:
Common: taste disturbance.
Eye disorders:
Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.
Gastrointestinal disorders:
Very common: gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment initiation and resolve spontaneously in most cases. To prevent them, it is recommended that metformin + glibenclamide be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary 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 angiitis, erythema multiforme, exfoliative

dermatitis, photosensitization, urticaria evolving to 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: hyponatremia.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

OVERDOSE AND TREATMENT:
Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea. High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis.
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.

STORAGE CONDITIONS:
Store at temperatures not exceeding 30°C.

DOSAGE FORMS & PACKAGING AVAILABLE:
Dosage form: 5 mg/500 mg Tablet
Packaging available: Alu/PVC Blister Pack x 10's (Box of 30's and 100's)

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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