

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CO-MEPIRYL FORTE TABLET

Glimepiride and Metformin Hydrochloride

Strength:

2/1000mg

Pharmaceutical form

Tablets for oral administration

2. QUALITATIVE AND QUANTITATIVE

COMPOSITION Each uncoated bilayer tablet contains

Glimepiride USP 2mg (Immediate release)

Metformin Hydrochloride BP 1000mg (Sustained release form)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A bilayer capsule shaped tablets, light yellow colour with “MBN” on one layer, white colour and No engraving on the other layer.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications:

The combination of Glimepiride and Metformin is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes who are already treated with a combination of glimepiride and metformin or whose diabetes is not adequately controlled with Metformin alone, or for those patients who have initially responded to glimepiride alone and require additional glycaemic control.

4.2. Posology and method of administration:

In principle, the dosage of Glimepiride and Metformin Hydrochloride sustained release Tablets is governed by the desired blood glucose level. The dosage of Glimepiride and Metformin Hydrochloride sustained release Tablets must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with Glimpiride and Metformin Hydrochloride sustained release Tablets glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out.

The highest recommended dose per day should be 8 mg of glimepiride and 2000 mg of metformin. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients. In order to avoid hypoglycaemia, the starting dose of Glimpiride and Metformin Hydrochloride sustained release Tablets should not exceed the daily doses of glimepiride or metformin already being taken. When switching from combination therapy of glimepiride plus metformin as separate tablets, it should be administered on the basis of dosage currently being taken.

Pediatric: Safety and effectiveness of glimepiride and metformin combination in pediatric patients have not been established

Geriatric: Aging is associated with reduced renal function, glimepiride and metformin combination should be used with caution in the elderly.

Liver impairment: should be administered with extreme caution in patients with impaired liver function. It is advised to consult your doctor to make a suitable adjustment in dosage and/or time-interval between two dosages.

Renal failure: Metformin is known to be excreted by the kidneys, and because risk of serious adverse reactions to the drug is greater in patients with impaired renal function, glimepiride and metformin should be used only in patients with normal renal function

Titration:

The daily dose should be titrated in increments of 1 tablet only, corresponding to the lowest strength (in case various strengths are available).

Duration of treatment:

Treatment with Glimpiride and Metformin Hydrochloride sustained release Tablets is normally a long-term therapy.

Method of administration: Oral administration and tablets should be taken whole with liquid, preferably with food

4.3. Contraindications:

- ✓ Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia.
- ✓ Known hypersensitivity to metformin, glimepiride or any of the components of this product.

- ✓ Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- ✓ Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

4.4. Special warning and precautions:

Hypoglycemia: All sulphonylurea drugs are capable of producing severe hypoglycaemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Haemolytic anaemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulphonylurea agents can lead to haemolytic anemia. Since glimepiride belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulphonylurea alternative should be considered. In post marketing reports, haemolytic anaemia has been reported in patients who did not have known G6PD deficiency.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold the diabetic regime and temporarily administer insulin. The oral antidiabetic therapy may be reinstated after the acute episode is resolved.

Surgical procedures: Metformin should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted 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 metformin.

“This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.”

4.5. Interactions with Other Medicaments

Glimepiride:

Based on experience with glimepiride and on what is known of other sulphonylureas, the following interactions must be considered:

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is co-administered with inducers (e.g., rifampin) or inhibitors (e.g. fluconazole) of CYP 2C9. Potentiation of the blood-glucose-Lowering effect and, thus, in some instances hypoglycemia may occur when one of the following drugs is taken, for example insulin and other, oral Antidiabetic; ACE inhibitors; anabolic steroids and male sex hormones;

chloramphenicol; coumarin derivatives; cydophosphamide; disopyramide; fenfluramine; fenylamidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; Azapropazone; oxyphenbutazone; Probenecid; quinolones; salicylates; sulfinpyrazone; clarithromycin; sulfonamide antibiotics; tetracycline; tritoqualine; trofosfamide. Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use); nicotinic acid

Metformin

Individual 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 metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal. Associations requiring precautions for use:

Glucocorticoids (systemic and local routes), beta-z-agonists, and diuretics have intrinsic hyperglycemic 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.

4.6. Pregnancy and lactation

Pregnancy

Recent information suggested that abnormal blood glucose levels during pregnancy are associated with the higher incidence of congenital abnormalities. Most experts suggest insulin be used to maintain the blood glucose levels as close to normal as possible. The use of glimepiride and metformin combination is not recommended for use in pregnancy.

Lactation

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted on nursing mothers. Glimepiride should not be used by breast-feeding mothers. Hence, the use of glimepiride and metformin combination is not recommended for use in lactating mothers, and if the diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

4.7. Effects on ability to drive and use machine:

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery).

4.8. Undesirable effects:

Gastrointestinal disturbances: Nausea, diarrhoea, gastric pain, constipation, vomiting, metallic taste in mouth. These reactions are generally dose related and disappear when the dose is reduced. *Dermatological effects:* Rash, pruritus, urticaria, erythema & flushing.

Miscellaneous: Headache and dizziness.

Haematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone.

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretics) action of ADH and/or increase release of ADH.

Hypoglycaemia: Glimepiride appears to be associated with a low incidence of hypoglycaemia. Glimepiride may have the potential to produce adverse cardiovascular effects; however glimepiride has been established agent for the treatment of type 2 diabetes for a number of years without adverse cardiovascular effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medical products is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via TMDA ADR reporting tool; website: or search for TMDA adverse reactions reporting tool in the google play store.

4.9. Overdose:

Overdosage of sulfonylureas, including glimepiride, can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated

aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycaemia may recur after apparent clinical recovery.

Lactic acidosis is a rare, but serious, metabolic complication that can occur if metformin accumulates during treatment due to overdosing. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties:

Glimepiride

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulphonylureas such as glimepiride.

Metformin

Metformin is an oral antihyperglycaemic drug used in the management of type 2 diabetes. It improves glucose tolerance in patients with type 2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to sulphonylureas, thiazolidinediones, or α -glucosidase inhibitors. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption

Glimepiride

After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with NIDDM have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours. When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Metformin extended release

The absolute bioavailability of a metformin 500-mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of metformin extended release; C_{max} is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels

are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. At steady state, the AUC and C_{max} are less than dose proportional for extended release within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/ mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from extended release at a 2000 mg once daily dose is similar to the same total daily dose administered as immediate release tablets 1000 mg twice daily. After repeated administration of extended release, metformin did not accumulate in plasma. Within subject variability in C_{max} and AUC of metformin from extended release is comparable to that with immediate release. Although the extent of metformin absorption (as measured by AUC) from the extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low-fat meals had the same effect on the pharmacokinetics of extended release.

Distribution

Glimepiride

After intravenous (IV) dosing in normal subjects, the volume of distribution (V_d) was 8.8 L (113 mL/ kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metformin extended release

Distribution studies with metformin extended release have not been conducted. However, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism

Glimepiride

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Metformin extended release

Metabolism studies with metformin extended release have not been conducted. However, intravenous single-dose studies in normal subjects demonstrate that metformin immediate

release is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Elimination

Glimepiride

When ¹⁴C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faeces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Metformin

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 of metformin 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.

5.3. Preclinical safety Data:

Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

Metformin

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients:

Hypromellose
Carmellose sodium
Dibasic calcium
phosphate Povidone
Colloidal anhydrous
silicaTalc
Magnesium stearate
Lactose
Ferric Oxide (RED)
Sodium Starch Glycollate

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

3 years

6.4. Special precautions for storage:

Store below 30°C. Keep out from the reach of children.

6.5. Nature and contents of container:

Blister Pack of 3*10 tablets

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with NAFDAC requirements for Destruction.

7. MARKETING AUTHORIZATION HOLDER:

May & Baker Nigeria Plc
1 May & Baker Avenue Off Idiroko Road
Ota Ogun State.

8. MARKETING AUTHORIZATION

May & Baker Nigeria Plc

9.NAFDAC REGISTRATION NUMBER

B4-6590