SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product
Diapride Plus-2

2. Quality and Quantitative Composition
Each uncoated bilayered tablet contains:
Glimepiride USP 2 mg
Metformin Hydrochloride BP 500mg

3. Pharmaceutical Form
Uncoated tablets

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 Diapride Plus is governed by the desired blood glucose level. The dosage of Diapiride Plus must be the lowest which is sufficient to achieve the desired metabolic control.
During treatment with Diapride Plus 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 Diapiride Plus 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.
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 Diapiride Plus is normally a long-term therapy.

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 sulfonylurea agents can lead to haemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non- sulfonylurea alternative should be considered. In postmarketing 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 reinstituted 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.

4.5 Interactions with Other Medicaments

Glimepiride:

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

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered 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 01 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; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxilylline (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 reinstituted 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 01 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, puritus, 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. The 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:
Healthcare professionals are requested to report any suspected adverse reactions to the respective National Regulatory Authority.

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 (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean T max (time to reach Cmax) was slightly increased (12%) and the mean Cmax 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; Cmax 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 Cmax 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 Cmax 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 (Vd) 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 14 C-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,
Croscarmellose Sodium,
Dibasic Calcium phosphate,
Povidone (k-30),
Purified water,
Colloidal anhydrous silica,
Talc,
Magnesium stearate,
Microcrystalline cellulose,
Lactose,
Ferric oxide (Red),
Sodium starch glycolate.

6.2 Incompatibilities:
Not applicable

6.3 Shelf life:
36 Months from the date of Manufacturing.

6.4 Special precautions for storage:
Store below 30°C. Keep all medicine away from the reach of children.

6.5 Nature and contents of container:
PVC Blister Pack of 10's.

6.6 Special precautions for disposal and other handling
No Special requirements

7. Marketing Authorization Holder:
MICRO LABS LIMITED

31 Race course
road, Bangalore-
560001

8. Marketing Authorization Numbers
H2011/CTD087/116

9. Date of first authorization
17th May, 2012

10. Date of revision of the text
September 2021