1.3.1 Summary of Product Characteristics (SmPC)

PRODUCT INFORMATION FOR HEALTH PROFESSIONALS

1. NAME OF MEDICINAL PRODUCT:

Mepiryl 2mg Tablet (Glimepiride 2mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablets contains;

Glimepiride	2.06mg
Lactose Monohydrate	117.00mg
Microcrystalline cellulose	38.00mg
Sodium Starch glycolate	9.00mg
Iron Oxide Yellow	0.10mg
Indigo Carmine Lake	0.10mg
Povidone K30	0.10mg
Purified Water	Q.S
Magnesium Stearate	0.50mg

3. PHARMACEUTICAL FORM:

Tablet

4. CLINICAL PARTICULARS:

4.1 THERAPEUTIC INDICATIONS:

It is indicated as an adjunct to diet and exercise to lower blood glucose in patients with non-insulin dependent (type 2) diabetes mellitus (NIDDM) whose hyperglcaemia cannot be controlled by diet and exercise alone

4.2 DOSAGE AND ADMINSTRATION

The desired blood glucose level determines the dosage of Mepiryl®. The dosage must be the lowest that is sufficient to achieve the desired metabolic control. If necessary, the daily dose can be increased. It is recommended that the increase be guided by regular blood glucose monitoring, and that the dose can be increased gradually i.e. at intervals of one to weeks and according to the following dose steps; 1mg – 2mg – 3mg – 4mg- 6mg. Daily doses of more than 6mg are more effective only in a minority of patients, A maximum of 8mg per day may not be exceeded. Normally a single daily dose of Mepiryl® is sufficient to provide metabolic control over 24 hours. It is recommended that this dose be taken immediately before a substantial breakfast or, if none is taken, immediately before the first main meal.

4.3 CONTRA-INDICATION

Mepiryl® must not be used in patients hypersensitive to Glimepiride, other sulphonyureas, other sulfonamides, or any of the excipients (risk of hypersensitivity reactions), in pregnant or breast-feeding women as safety has not been shown, impaired liver function and moderate to more severe impaired renal function and children.

Mepiryl® is not suitable for the treatment of insulin-dependent (Type1) diabetes mellitus.

4.4 SPECIAL WARNING AND PRECAUTION FOR USE

Glimepiride must be taken shortly before or during a meal. When meals are taken at irregular hours or skipped altogether, treatment with ”Glimepiride Tablets” may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.

The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.

Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate

- undernutrition, irregular mealtimes or missed meals or periods of fasting

- alterations in diet

- imbalance between physical exertion and carbohydrate intake

- consumption of alcohol, especially in combination with skipped meals

- impaired renal function

- serious liver dysfunction

- overdosage with Glimepiride Tablets

- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency)

- concurrent administration of certain other medicinal products (see section 4.5)

Treatment with glimepiride tablets requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride tablets

In stress-situations (e.g. accidents, acute operations, infections with fever etc) a temporary switch to insulin may be indicated.

No experience has been gained concerning the use of glimepiride tablets in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. 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.

Glimepiride Tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Fertility, pregnancy and lactation

Pregnancy

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride

There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride (see section 5.3).

Consequently, glimepiride should not be used during the whole pregnancy. In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Lactation

The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

4.5 DRUG INTERACTION:

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulfonylureas, the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus in some instances hypoglycaemia may occur when one of the following medicinal products is taken, for example:

- phenylbutazone, azapropazone and oxyfenbutazone,

- insulin and oral antidiabetic products, such as metformin,

- salicylates and p-amino-salicylic acid,

- anabolic steroids and male sex hormones,

- chloramphenicol, certain long acting sulfonamides, tetracyclines, quinolone antibiotics and clarithromycin,

- coumarin anticoagulants,

- fenfluramine,

- disopyramide,

- fibrates,

- ACE inhibitors,

- fluoxetine, MAO-inhibitors,

- allopurinol, probenecid sulfinpyrazone,

- sympatholytics,

- cyclophosphamide, trophosphamide and iphosphamides,

- miconazole, fluconazole,

- pentoxifylline (high dose parenteral),

- tritoqualine

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken for example:

- oestrogens and progestogens

- saluretics, thiazide diuretics

- thyroid stimulating agents, glucocorticoids

- phenothiazine derivatives, chlorpromazine

- adrenaline and sympathicomimetics

- nicotinic acid (high dosages) and nicotinic acid derivatives

- laxatives (long term use)

- phenytoin, diazoxide

- glucagon, barbiturates and rifampicin

- acetazolamide

H2 antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6 EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

No studies on the effects on the ability to drive and use machines have been performed.

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).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.7 SIDE EFFECTS/ADVERSE EFFECTS

Hypoglyceamia (sometimes life-threatening) may occur as a result of the blood-glucose-lowering action of Mepiryl®. This happens when there is an imbalance between Mepiryl® dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism.

Possible symptoms of hypoglyceamia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, sleep disorders, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression confusion, speech disorders, aphasia, visual disorders, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia.

In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tarchycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias.

The clinical picture of a severe hypoglyceamia may persist if hypoglyceamia is corrected.

Eyes
Especially at the start of treatment, there may be temporary visual impairment due th the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.

Digestive tract

Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure of fullness in the epigastrium, abdominal pain and diarrhoea may occur.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions from clinical investigations were based on experience with glimepiride and other sulfonylureas, were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.

Not known: severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

Immune system disorders

Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

Not known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders

Rare: hypoglycaemia.

These hypoglycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and dosage (see further under section 4.4).

Eye disorders

Not known: visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastrointestinal disorders

Very rare*:* nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

Hepato-biliary disorders

Very rare*:* hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.

Not known: hepatic enzymes increased.

Skin and subcutaneous tissue disorders

Not known: hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

Investigations

Very rare: blood sodium decrease.

4.9 OVER DOSAGE

Symptoms

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5.0 PHARMACOLOGICAL PROPERTIES

Pharmaceutical Group: Blood glucose lowering drugs, excl. insulins: Sulfonamide, urea derivatives.

ATC Code A10BB12

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent (type 2) diabetes mellitus.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

Insulin release:

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results -by opening of calcium channels - in an increased influx of calcium into the cell. This leads to insulin release through exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylureas binding site.

Extrapancreatic activity

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C, which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether the medicinal product was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect

Combination therapy with metformin

Improved metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum daily dosage of metformin has been shown in one study.

Combination therapy with insulin

Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. In two studies, the combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

Special populations

Paediatric population:

An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both glimepiride and metformin exhibited a significant decrease from baseline in HbA_{1c} (glimepiride -0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of non-inferiority to metformin in mean change from baseline of $HbA_{1c.}$ The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.

Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

Pharmacokinetic properties

Absorption

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only the absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approx 2.5 hours after oral intake (mean 0.3 μg/ml during multiple dosing of 4 mg/daily) and there is a linear relationship between dose and both Cmax and AUC (area under the time concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres), which is roughly equal to the albumin distribution space, high protein binding (>99%) and a low clearance (approx. 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood-brain barrier is low.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites most probably resulting from hepatic metabolism (major enzyme is CYP2C9) were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra individual variability was very low. There was no relevant accumulation.

Special populations

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding.

Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Paediatric population

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean $AUC_{(0\text{-last})}$, Cmax and $t_{1/2}$similar to that previously observed in adults.

Preclinical safety data

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.

5.1 PHARMACEUTICAL PARTICULARS:

LIST OF EXCIPIENTS

Glimepiride	2.06mg
Lactose Monohydrate	117.00mg
Microcrystalline cellulose	38.00mg
Sodium Starch glycolate	9.00mg
Iron Oxide Yellow	0.10mg
Indigo Carmine Lake	0.10mg
Povidone K30	0.10mg
Purified Water	Q.S
Magnesium Stearate	0.50mg

5.2 INCOMPATIBILITIES:

Not Applicable

5.3 SHELF LIFE: 36 Months

5.4 SPECIAL PRECAUTION FOR STORAGE:

Store below 30°C

5.5 NATURE AND CONTENT OF CONTAINER:

3 X 10 Tablet, packed in blister strips along with a leaflet in a printed carton which is labelled.

5.6 SPECIAL PRECAUTION FOR DISPOSAL

To be destroyed by NAFDAC enforcement unit.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose Monohydrate

Microcrystalline Cellulose PH 102

Sodium Starch glycolate

Iron Oxide Yellow

Indigo Carmine Lake

Povidone K 30

Magnesium Stearate BP

Purified Water

6.2 INCOMPATIBILITIES

None known

6.3 Shelf life

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30° C. Protect from light

6.5 Nature and contents of container

3*10 packed in PVC/Foil.

6.6 Special precautions for disposal and other handling

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7. Manufacturer

May & Baker Nigeria Plc.

1, May & Baker Avenue off Idiroko Road

Ota

Ogun State.