SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

Product Name : PERGLIM M-2 [Glimepiride 2mg and Metformin Hydrochloride 500 mg SR Tablets]

Strength : Glimepiride USP 2 mg & Metformin Hydrochloride BP 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 2mg and Metformin Hydrochloride 500 mg SR Tablets

Each uncoated bilayered tablet contains:

Glimepiride USP 2mg

Metformin Hydrochloride BP 500 mg (in sustained Release form)

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule shaped, biconvex, bilayered, uncoated tablet, debossed with G2 on one side i.e. yellow coloured Glimepiride layer and plain on other side i.e. white coloured Metformin layer.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-insulin dependent (Type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise and weight reduction. Also, for replacement therapy in diabetic patients stabilized on Glimepiride (1 or 2mg) with Metformin (500 mg SR), indicated in patients of 18 years of age and older.

4.2 Posology and method of administration

Glimepiride 1mg/Metformin HCl 500 mg: 1-2 tablets once daily upto a maximum of 3 tablets per day or as directed by physician.

Glimepiride 2mg/Metformin HCl 500 mg: 1 tablet once daily or as directed by physician.

Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of metformin in adults is 2000 mg and Glimepiride is 8 mg once daily.

Do not crush or chew the tablet; the whole tablet to be taken with water. Start with one tablet per day. The aim should be to decrease both fasting plasma glucose and glycosylated haemoglobin levels to normal by using the lowest effective dose of the drug.

4.3 Contraindications

This combination is not suitable for the treatment of insulin-dependent (Type 1) diabetes mellitus (e.g. for the treatment of diabetics with a history of ketoacidosis), or of diabetic precoma or coma.

It must not be used in patients hypersensitive to Metformin HCl, Glimepiride, Sulfonylureas, other sulfonamides, or any of the excipients (risk of hypersensitivity reactions).

Impaired renal function

Acute complications (severe infections, major operations and trauma) before X-ray examinations with iodinated contrast materials.

Liver damage

Alcoholism

Deficinces of vitamin B12, folic acid and iron

Ketosis-prone diabetes

Severe cardiovascular or respiratory disease

General ill health (malnutrition, dehydration, etc)

Diabetes with significant late complications (nephropathy, retinopathy).

4.4 Special warnings and precautions for use

Keep out of reach of children

Glimepiride – If risk factors for hypoglycemia are present, it may be necessary to adjust the dosage of Glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life style changes.

Symptoms of hypoglycemia may be milder or absent in those situations where hypoglycaemia develops gradually, in the elderly, and in the patients with autonomic neuropathy or those receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

Hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g. in the form of sugar lumps, sugar sweetened fruit juice or sugar sweetened tea). For this purpose, patients must carry an assistance of other persons to avoid complications.

Artificial sweeteners are ineffective in controlling hypoglycemia.

Continued close observation is necessary. Sever hypoglycemia required immediate treatment and follow-up by a physician and in some circumstances, hospitalization.

In exceptional stress situations (e.g trauma, surgery, infections with fever) blood sugar control may deteriorate, and a temporary change to insulin may be necessary.

During treatment with glimepiride, glucose levels in blood and urine must be checked regularly, as should, additionally, the proportion of glycated hemoglobin.

Alertness and reactions may be impaired due to hypo-or-hyperglycemia, especially when beginning or after altering treatment, or when glimepiride is not taken regularly. This may affect the ability to operate vehicle or machines.

Metformin – Lactic acidosis: Metformin can provoke lactic acidosis; however, the reported incidence is very low. Conditions like impaired hepatic function, renal dysfunction, hypoxemia, dehydration, sepsis, excessive alcohol intake can increase the risk of lactic acidosis. The risk can be decreased by regular monitoring of renal function and by use of minimum effective dose. In a patient with lactic acidosis, who is on metformin treatment, the drug should be discontinued immediately. Supportive measures and prompt hemodialysis to be started. Impaired renal function: Caution should be exercised with concomitant therapies that may affect renal function or interfere with the disposition of metformin (e.g. cationic drugs).

Use of iodinated contrast media: The drug should be stopped at least two days before X-ray examination with iodinated contrast material and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states: Metformin therapy should be promptly discontinued when such events occur in patients.

Surgical procedures – The drug should be temporarily discontinued and restarted only when the patient resumes oral intake and has normal renal function.

Alcohol intake: Patients to be warned against excessive alcohol intake, acute or chronic while receiving metformin.

Impaired hepatic function: The drug should be generally avoided in patients with hepatic disease.

Hypoglycemia: Does not normally occur when the drug is given alone but has been observed when given in combination with sulfonylureas and/or alcohol.

Deficiencies of folic acid, iron and Vitamin B12: Serum Vitamin B12 concentrations should be measured annually during long-term treatment.

Laboratory tests: Monitoring of response to therapy to be done periodically through measurement of fasting blood glucose and glycosylated hemoglobin levels. During initial dose titration, fasting glucose can be used to determine the response. Subsequently, both glucose and glycosylated hemoglobin must be monitored, which may be useful in evaluating long-term control.

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine: Metformin interacts with cimetidine. Therefore, the dose of metformin should be reduced if cimetidine is co-prescribed.

Hyperglycemic agents: Drugs with hyperglycemic potential (e.g. thiazides, corticosteroids and others may partly offset the anti-hyperglycemic action of metformin and in such cases the glycemic control should be closely monitored.

Alcohol: Alcohol potentiates the action of metformin on lactate metabolism as well as the antihyperglycemic effect. Hence, patients treated with metformin should preferably avoid alcohol and alcoholism is a definite contraindication.

Other interactions: Studies with furosemide and nifedipine suggest a possible interaction by Increasing plasma metformin levels. However no such changes were found with propranolol and ibuprofen.

The absorption of metformin may be reduced by acarbose and guar gum.

Hypoglycemia due to interaction with glimepiride may occur when one of the following medicines is taken, for example: insulin and other oral antidiabetics, ACE inhibitors, allopurinol, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, ifsofamide, MAO inhibitors, miconazole, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, tetracyclines, tritoqualine, trofosfamide.

Hyperglycemia due to interaction with glimepiride may occur when one of the following medicines is taken, for example: acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) and other sympathomimetic agents, glucagons, laxatives

(after protacted use), nicotinic acid (in high doses), oestrogens and progestogens, phenothiazones, phenytoin, rifampicin, thyroid hormones. H2 receptor antagonists, clonidine and reserpine may lead to either potentiation or weakening of the blood sugar lowering effect. Beta-blockers may increase the tendency to hypoglycemia.
The effect of coumarin derivatives may be potentiated or weakened.

4.6 Pregnancy and lactation

Pregnancy: Pregnancy is generally regarded as a contra-indication and insulin should be used in all pregnant diabetic women.
Nursing mothers: The ingredients in the combination may enter breast milk and is best avoided in nursing mothers.

4.7 Effects on ability to drive and use machines

Glimepiride- 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.
Metformin HCl- Metformin hydrochloride monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when meformin hydrochloride is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

4.8 Undesirable effects

Hypoglycemia: As a result of the blood-sugar lowering action of Glimepiride, hypoglycemia may occur and may also be prolonged.
Eyes: Especially at the start of treatment, temporary visual impairment may occur due to the change in blood sugar levels.

Digestive tract: occasionally nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur in isolated cases, liver enzyme levels may increase, and impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis may develop, possible resulting in liver failure.

Blood: Rarely thrombocytopenia and in isolated cases, leucopenia, hemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis and pancytopenia (e.g. due to myelosuppression) may develop.

Other adverse reactions: Allergic or pseudoallergic reactions like itching, urticarial or rashes may occur. Such reactions are mild, but may become more serious and be accompanied by dyspnea and a fall in blood pressure, sometimes progressing to shock. If urticarial occurs, a physician must be notified immediately. In isolated cases allergic vasculitis, hypersensitivity of the skin to light and a decrease in serum sodium may occur.

4.9 Overdose

Hemodialysis may be useful for removal of accumulated metformin from patients in whom overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Glimepiride

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives ATC code: A10BB12

Metformin HCl

Pharmacotherapeutic group: Blood Glucose lowering drugs, excl. Insulins, Biguanides.

ATC code: A10BA02

Glimepiride reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. It interacts with specific receptors at the plasma membrane of the insulin releasing pancreatic beta- cells where it inhibits ATP- sensitive K+ channels resulting in depolarization of the cell membrane, opening of voltage sensitive Ca2+ channels, increase in intracellular calcium levels and subsequent insulin release1. Metformin Metformin acts as an anti hyperglycaemic agent by improving hepatic and peripheral tissue sensitivity to insulin. It also appears to have beneficial effect on serum lipid levels and so on fibrinolytic activity.

Metformin therapy is not associated with increase in body weight.2 Metformin decreases glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Rationality for combination of Glimepiride And Metformin- Sulfonylureas and biguanides act complementary to each other. Both compounds have an additive anti hyperglycaemic effect without increasing the adverse effects of either pharmacological class.

Glimepiride acts via stimulating b cells of pancreas to release insulin and also increases peripheral sensitivity of insulin. Metformin acts via enhanced peripheral glucose uptake and utilization. It also reduces hepatic glucose production, thereby metformin diminishes insulin resistance.

Glimepiride has less propensity to cause hypoglycaemia and increase in body weight as compared to other sulfonylurea. Since metformin is reported to have predominant peripheral mechanism of action, therefore it lacks the anabolic effects of sulfonylureas and does not cause weight gain.

Metformin is associated with a decrease in fasting and postprandial plasma insulin and triglyceride levels, increase in HDL-cholesterol, increase of tissue plasminogen activator, decrease in platelet aggregation.

5.2 Pharmacokinetic properties

*Glimepirid*e- Glimepiride is rapidly and completely absorbed after oral administration. The oral bioavailability is approximately 100%. Following oral administration of 1 mg single dose to healthy volunteers, peak serum concentration ((Cmax) of 103+ 34 ng/ml occurred within 2-3 hours. More than 99% of the drug is bound to plasma proteins. Glimepiride is completely biotransformed by hepatic oxidative metabolism into cyclohexylhydroxymethyl derivative(M1) which is further metabolized to form a carboxyl derivative (M2) by cytosolic enzymes. After a single dose, the elimination half life (t1/2) of glimepiride is 5 hours. The urinary excretion of metabolites accounts for 60% of dose, the remainder is found as metabolites in faeces.

Metformin - Metformin has absolute oral bioavailability of 50-60%. GIT absorption is complete within 6 hrs of ingestion within metformin is rapidly distributed in body after absorption. The renal elimination of metformin is biphasic. 95% of the absorbed metformin is eliminated during primary elimination phase having half-life of 6 hours. Rest of the 5% is eliminated during slow terminal elimination phase with mean half-life of 20 hours. Metformin is not bound to plasma

proteins, 40-60% of the dose is recovered as unchanged drug in urine with a further 30% recovered as unchanged drug in faeces.

Pharmacokinetically the two drugs appear to be compatible, as metformin is not plasma protein bound and does not get metabolized in liver. So interaction with glimepiride (having 99% plasma protein binding and metabolized via liver) does not appear to be possible. Hence the combination of glimepiride and metformin would help in treatment of NIDDM.

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 Hydrochloride - Pre clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose BP, Sodium Starch Glycolate BP, Ferric oxide (yellow) USP-NF, Titanium dioxide BP, Microcrystalline cellulose BP, Pregelatinized starch BP, Povidone K BP/Ph.Eur, Magnesium stearate BP, Hypromellose BP, Carboxymethylcellulose Sodium USP, Methacrylic acid copolymer dispersion Drug USP, Macrogol PEG 6000 BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Keep out of reach of children

Protect from light and moisture

Store below 30^{o}C in a dry place

6.5 Nature and contents of container

Blisters of 20 tablets in carton.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE F PRODUCT REGISTRATION

Mega Lifesciences Nigeria Limited

6B, Guinness Road, Ogba, Ikeja, Lagos,

8. DRUG PRODUCT MANUFACTURER

Manufactured by:

Inventia Healthcare Limited,

F1-F1/1, Additional Ambernath M.I.D.C,

Ambernath (East), Thane 421506

Maharashtra State, India.

9. NAFDAC REGISTRATION NUMBER

A4-1903