SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

Product Name : PERGLIM M-2 Forte [Glimepiride 2 mg and Metformin Hydrochloride Sustained Release 1000 mg Tablets]

Strength : Glimepiride 2 mg & Metformin Hydrochloride 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 2 mg and Metformin Hydrochloride SR 1000 mg

Each uncoated bilayered tablet contains:

Glimepiride USP 2mg

Metformin Hydrochloride BP 1000 mg (in sustained Release form)

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Description: Oval shaped uncoated bi-convex bilayered tablet plain on both sides, with one-layer (i.e. Metformin) white in colour and the other layer (i.e. Glimepiride) yellow in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycemic control.

4.2 Posology and method of administration

Dosing

In principle the dosage of Perglim M-2 Forte is governed by the desired blood glucose level. The dosage of Perglim M-2 Forte must be the lowest which is sufficient to achieve the desired metabolic control. During treatment with Perglim M-2 Forte glucose levels in blood must be measured regularly. Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose. Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or situations where a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand. As

an improvement in control of diabetes, is, in itself, associated with higher insulin sensitivity, glimepiride requirements may fail as treatment proceeds. To avoid hyperglycemia timely dose reduction or cessation of Perglim M-2 Forte Therapy musttherefore be considered. Perglim M-2 Forte is to be administered once per day during breakfast or the first main meal.. Due to sustained release formulation Perglim M-2 Forte must be swallowed whole and not crushed or chewed.

The highest recommended dose per day should be 8mg of glimepiride and 2000mg of metformin.

Daily doses of glimepiride of more than 6mg are more effective only in a minority of patients. In order to avoid hypoglycemia the starting dose of Perglim M-2 Forte 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, Perglim M-2 Forte should be administered on the basis of dosage currently being taken.

Duration of Therapy

Treatment with Perglim M-2 Forte is normally long term therapy.

4.3 Contraindications

For Glimepiride:

In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients of Perglim M-2 Forte

In pregnant women

In breastfeeding women

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of hepatic function, change over to insulin is indicated, not least to achieve optimal metabolic control.

For Metformin:

Hypersensitivity to metformin or any of excipients.

Diabetic ketoacidosis, diabetic pre-coma.

Renal failure or renal dysfunction (e.g. serum creatine levels > 135umol/L in maland >110umol/L in females).

Acute conditions with the potential to alter renal function such as:

- Dehydration

- severe infection
- shock
-lntravascular administration of iodinated contrast agents (see Precautions)
- 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.
- Lactation.

4.4 Special warnings and precautions for use

For Glimepiride:

In exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

For Metformin:

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, and excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis

Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.

PRECAUTIONS

For Glimepiride:

In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring. Factors favouring hypoglycaemia include:

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

• undernourishment, irregular mealtimes or skipped meals.

• imbalance between physical exertion and carbohydrate intake.

• alterations of diet.

• consumption of alcohol, especially in combination with skipped meals.

• impaired renal function.

• severe impairment of liver function.

• overdosage with glimepiride.

• certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter egulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).

• concurrent administration of certain other medicines (see interactions).

• treatment with glimepiride in the absence of any indication.

If such risk factors for hypoglycaemia 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. Those symptoms of hypoglycaemia which reflect the body's adrenergic counter regulation (see Adverse Reactions) may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar). It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.Patients must, therefore, remain under close observation. Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

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.

For Metformin:

Renal Function: As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

• Atleast annually in patients with normal renal function,

• Atleast two or four times a year in patients with serum creatinine levels at the 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 an NSAID.

Administration of iodinated contrast agent: As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of rest and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery: Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

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.

• The usual laboratory tests for diabetes monitoring should be performed regularly.

• Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas.

4.5 Interaction with other medicinal products and other forms of interaction

For Glimepiride:

Based on 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 co-administered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP2C9. Potentiation of the blood-glucose-lowering effect and, thus, in

some instances hypoglycaemia may occur when one of the following drugs is taken, for example; insulin and other oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones; chloram-phenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; infosfamide; MAO inhibitors; miconazole; fluconazole; para- aminosalicyclic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid; quinolones; salicylates;sulfinpyrazone; clarithromycin; sulfonamide antibiotics; tetracyclines; 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 (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones.

H_2 receptor antagonists, beta blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose-lowering effect.

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

Both acute and chronic alcohol intake may potentiate or weaken the blood glucose-lowering action of glimepiride in an unpredictable fashion. The effect of coumarin derivatives may be potentiated or weakened

For Metformin:

Inadvisable 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: lntravascular 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.

Iodinated contrast agents: lntravascular 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-2-agonists and diuretics have intrinsic hyperglycaemia 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

For Glimepiride:

Glimepiride must not be taken during pregnancy. Otherwise there is a risk of harm to the child.

The patient must change over to insulin during pregnancy. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

For Metformin:

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

LACTATION

For Glimepiride:

To prevent possible ingestion with breast milk and possible harm to the child, glimepiride must not be taken by breast feeding women. If necessary the patient must change over to insulin, or must stop breastfeeding.

For Metformin:

Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

For Glimepiride:

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, for example, affect the ability to drive or to operate machinery.

For Metformin:

Metformin 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 metformin is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

4.8 Undesirable effects

For Glimepiride and Metformin

The use of a combination of both compounds, either as a free combination or as a fixed combination, is associated with the same safety characteristics as the use of each compound separately.

For Glimepiride:

• ***Metabolism and nutrition disorders***

As a result of the blood-glucose-lowering action of glimepiride, hypoglycaemia may occur, which may also be prolonged.

Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, 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.
The symptoms nearly always subside when hypoglycaemia is corrected.

• Eye disorders

Especially at the start of treatment, there may be temporary visual impairment due to 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.

• Gastrointestinal disorders

Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life threatening liver failure but can regress after withdrawal ofglimepiride.

• Blood and lymphatic system disorders

Changes in the blood picture may occur: Rarely thrombopeniaand, in isolated cases, leucopenia, haemolytic anaemia, erthrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop.

• General disorders

Occasionally, allergic, or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious reactions with dyspnea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately. In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.

For Metformin:

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite (> 10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

• Metallic taste (3%) is common.

• Mild erythema has been reported in some hypersensitive individuals the incidence of such effects is regarded as very rare (<0.01%).

• A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long term with metformin and appears generally to be without clinical significance (<0.01%).

• Lactic acidosis (0.03 cases/1000 patient years) is very rare (See Warnings).

4.9 Overdose

For Glimepiride:

Signs and symptoms:

Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life threatening hypoglycaemia.

Management:

As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose. Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia may recur after initial recovery.

Admission to hospital may sometimes be necessary- even as a precautionary measure.

In particular, significant overdoses and severe reactions with signs such as loss of consciousness, or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital. If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40ml of 20% solution, for example).

Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1mg i.v.,s.c. or i.m. may be considered. In particular when treating hypoglycaemia due, to accidental intake of glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose.

Patients who have ingested life-threatening amounts of glimepiride require detoxification (e.g.by gastric lavage and medicinal charcoal).

After acute glucose replacement has been seen completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia

does not recur. The patient's blood glucose level should be carefully monitored for at least 24hours. In severe cases with a protracted course, hypoglycaemia, may persist for several days.

For Metformin:

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Mechanism of action:

Sulfonylureas and biguanides act complementary to each other. Both compounds have an additive antihyper- glycaemic effect without increasing the adverse effects of either pharmacological class.

Glimepiride acts via stimulating beta cells of pancreas to release insulin and also increases peripheral sensitivity of insulin.

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

Glimepiride

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 g/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, isabout 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.

Metformin

Absorption

After an oral dose of the sustained release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin sustained release tablet is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intra subject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the sustained release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of upto 2000mg of metformin as prolonged release tablets.

Following a single oral administration in the fed state of one tablet of metformin SR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin SR 1000 mg was shown to be bioequivalent to Metformin SR 500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

When the 1000 mg sustained release tablet is administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax is slightly prolonged by about 1hour).

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood eel Is most likely represent a secondary compartment of distribution. The mean Vd ranged between 63276L.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels ofmetformin in plasma.

5.3 Preclinical safety data

Metformin

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

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 pharmacodynamics 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose BP, Sodium Starch Glycolate BP, Ferric oxide (yellow) USP-NF, Microcrystalline Cellulose BP, Pregelatinized Starch BP, Povidone BP/Ph. Eur., Magnesium Stearate BP, Purified Water BP, Hypromellose BP, Carboxy-methylcellulose Sodium USP, Methacrylic acid copolymer dispersion USP, Macrogol BP, lsopropyl alcohol 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

Swallow whole, do not chew or crush the tablet

6.5 Nature and contents of container

Available as blister pack of 3X 10's.

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 Pvt Ltd,

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

Ambernath (East), Thane 421506

Maharashtra State, India.

9. NAFDAC REGISTRATION NUMBER

B4-7365