GLIMTROL M2

(**Glimepride 2mg and Metformin 500mgTablets**)

COMPOSITION:
Each film coated tablet contains:
Metformin hydrochloride 500mg
Glimepride 2mg

PHARMACOKINETICS:
Absorption:
After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.
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:
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 cells most likely represent a secondary compartment of distribution. The mean volume of distribution Vd ranged from 63 to 276 l.
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:
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. 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.
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.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Pharmacotherapeutic group: Metformin and sulfonamides. ATC code: A10BD02.
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin may act via 3 mechanisms: (1) by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) and by delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

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.

INDICATIONS:
Treatment of type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glimepride in patients whose glycaemia is stable and well-controlled.
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CONTRAINDICATIONS:
This medicinal product must never be used in case of:
- hypersensitivity to the active substances, to other sulphonylurea(s) and sulphonamide(s) or to any of the excipients;
- type 1 diabetes (insulin-dependent diabetes), ketoacidosis, diabetic pre-coma;
- renal failure or renal dysfunction (creatinine clearance < 60 ml/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock;
- 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;
- porphyria;
- lactation;
- in association with miconazole.

POSOLOGY & ADMINISTRATIONS:
Posology Oral route. For use in adults only.
Initiation of treatment: Treatment should be initiated with a dose of the combination product equivalent to previous individual doses of metformin and glimepride; the dose being gradually increased depending on results on glycaemic parameters.
Dose titration: The dosage should be adjusted every 2 weeks or longer, by increments of 1 tablet, depending on glycaemia results. A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.
Maximum daily recommended dose: The maximum daily recommended dose is 3 tablets.
Dosage regimen: The dosage regimen depends on the individual posology:
- Once a day, in the morning at breakfast, for a dosage of 1 tablet/day,
- Twice a day, morning and evening, for a dosage of 2 or 4 tablets/day,
- Three times a day, morning, noon and evening, for a dosage of 3, 5 or 6 tablets/day or for a dosage 3 tablets/day.

The tablets should be taken with meals. The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.
Combination with insulin therapy: No clinical data are available on the concomitant use of this product with insulin therapy.
Elderly subjects: The dosage of metformin/glimepride should be adjusted depending on renal function parameters; regular checks on the renal function are necessary. Patients aged 65 years and older: starting and maintenance doses of glimepride must be carefully adjusted to reduce the risk of hypoglycaemia. Treatment should be started with the lowest available dose and increased gradually if necessary.
Paediatric patients: It is s not recommended for use in children.
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WARNINGS & PRECAUTIOns
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, alcoholism hepatic insufficiency and any condition associated with hypoxia.
Hypoglycaemia

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.

Administration of iodinated contrast materials
The intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, must be discontinued 48 hours before the test or at the time of the test and may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Concomitant use of glimepride with other medicinal products
The concomitant use of glimepride with alcohol, phenylbutazone or danazol is not recommended.
Surgery
Because contains metformin hydrochloride, treatment must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia and may not be reinstituted earlier than 48 hours following surgery or resumption of oral nutrition and only after renal function has been re-evaluated and found to be normal.
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. Regular physical exercise is as necessary as taking [Nationally completed name]. The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly.

DRUG INTERACTIONS:
Related to metformin Diuretics: Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics.
Iodinated contrast materials:
Intravascular administration of iodinated contrast materials may lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, must be discontinued 48 hours before the test 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.
Related to Glimepride
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

ADVERSE REACTIONS:
During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take in 2 or 3 daily doses and to increase slowly the doses. At the start of treatment, transient visual disturbances may occur due to a decrease in glycaemia levels.

PREGNANCY & LACTATION:
No preclinical and clinical data on exposed pregnancies are available.
When uncontrolled, diabetes (gestational or permanent) gives rise to an increase in congenital abnormalities and perinatal mortality. Diabetes must be controlled as far as possible during the period of conception in order to reduce the risk of congenital abnormalities.
Management: Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. must not be used for the treatment of diabetes during pregnancy. It is imperative that insulin be used to achieve adequate blood glucose control. It is recommended that the patient be transferred from oral antidiabetic therapy to insulin as soon as she plans to become pregnant or if pregnancy is exposed to this medicinal product. Neonatal blood glucose monitoring is recommended.
Breast-feeding: Metformin is excreted in human breast. No adverse effects were observed in breastfed newborns/infants of mothers treated with metformin alone. 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.

OVERDOSE:
Symptoms
Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis.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.

STORAGE: Store below 30°C. Protect from light and moisture.

SHELF LIFE: 36 months

PRESENTATION:
GLIMTROL M2 : PVC Blister Pack of 10×10 tablets..

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