PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

ZORYL-M 1/M 2

Glimepiride(1/2 mg) and Metformin HCl (500 mg) ER Tablets

COMPOSITION

Each film coated tablet contains:
Glimepiride USP……1 mg
Metformin Hydrochloride BP…….....500 mg
(In extended release form)
Each film coated tablet contains:
Glimepiride USP……2 mg
Metformin Hydrochloride BP…….500 mg
(In extended release form)

Description:

This tablet is combination of oral anti diabetic drugs glimepiride, sulphonylurea and metformin, biguanide class. Glimepiride increases secretion of insulin from pancreas and Metformin decrease hepatic glucose production.

Pharmacodynamic properties:

Glimepiride:

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. This effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. Glimepiride seems to have pronounced extrapancreatic effects also.

Mechanism of action:

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

Extrapancreatic effects:

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

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 inhibits the glucose production in the liver by increasing the intracellular concentration of fructose- 2_{16}-bisphosphate, which in its turn inhibits the gluconeogenesis.

Metformin:

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) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) and delay of 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).

Clinical efficacy: The UKPDS study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure. It showed a significant reduction of the absolute risk of any diabetes-related complication in the metformin group versus diet alone, a significant reduction of the absolute risk of diabetes-related mortality, a significant reduction of the absolute risk of overall mortality, a significant reduction in the absolute risk of myocardial infarction.

Pharmacokinetic properties:

Glimepiride:

Absorption: The absorption of glimepiride after oral administration is complete. Food intake has no influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approx. 2.5 hours after oral intake and there is a linear relationship between dose and both C_{max} and AUC.

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.

Metabolism: Glimepiride is mainly metabolized in liver. Two metabolites 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.

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.

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

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients.

Elimination: 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.

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. 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 2000 mg of metformin sustained release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of metformin sustained 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).

Metformin absorption from the sustained release formulation is not altered by meal composition.

Distribution: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

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. 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 of metformin in plasma.

Therapeutic indications:

Glimepiride plus metformin tablet is recommended for treatment of non insulin dependent diabetes mellitus, as an adjunct to diet and exercise, when diabetes is not controlled with monotherapy.

Dosage & administration:

General Dosage should be individualized on the basis of both effectiveness and tolerance. The combination should be given once daily with meals and should be started at a low dose. The initial recommended dose is one tablet once daily with breakfast or first main meal of the day.

Starting dose for patients inadequately controlled on metformin monotherapy

Based on the usual starting dose of glimepiride (1-2 mg daily), glimepiride (1 mg) plus metformin (500 mg) or glimepiride (2 mg) plus metformin (500 mg) may be initiated once daily, and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients who initially responded to glimepiride monotherapy and require additional glycaemic control

Based on the usual starting doses of metformin extended release (500 mg once daily), glimepiride (1 mg) plus metformin (500mg) or glimepiride (2 mg) plus metformin (500 mg) may be initiated once daily, and gradually titrated after assessing adequacy of therapeutic response .

Starting dose for patients switching from combination therapy of glimepiride plus metformin as separate tablets

glimepiride (1 mg) plus metformin (500 mg) or glimepiride (2 mg) plus metformin (500 mg) may be initiated based on the dose of glimepiride and metformin already being taken.

Maximum Recommended Dose The maximum recommended dose for glimepiride is 8 mg daily. The maximum recommended daily dose for metformin is 2550 mg in adults.

Contraindications:

Glimepiride (1 mg) plus metformin is contraindicated in patients with hypersensitivity to any of the excipients in the tablet and in pregnancy and lactation.

Other contraindications according to the component drugs are:

Glimepiride: Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides. In case of severe renal or hepatic function disorders, a change over to insulin is required.

Metformin: Hypersensitivity to metformin hydrochloride, diabetic 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, intravascular administration of iodinated contrast agents. 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 and lactation.

	Checked by				Approved by
Department	PMQC	RA	Packing Dev.	Q.A.	Head Q.A.
Signature					
Date					

Product Name : Zoryl-M
Size : 140 x 210 (mm)
Folding Size : 140 x 26.5 (mm)
No. of Col. : 1
Date : 21/05/16

File name : 80 1503 0 8611154-Zoryl-M-PIL
Col. Shade No. : Pantone Black

Special warnings and precautions for use:

Glimepiride: When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycaemia.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Treatment with glimepiride 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.

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

Renal function: As metformin is excreted by the kidney, creatinine clearance and/or serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least annually in patients with normal renal function, at least two to four times a year in patients with creatinine clearance 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 the test 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.

Drug Interactions:

Glimepiride: If glimepiride is taken simultaneously with certain other medicines, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP 2C9.

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

Potentiation of the blood-glucose-lowering effect may occur when one of the following drugs is taken, for example: phenylbutazone, azapropazon and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetic products, certain long acting sulphonamides, tetracyclines, salicylates and p-amino-salicylic acid, MAOinhibitors, anabolic steroids and male sex hormones, quinolone antibiotics, chloramphenicol, probenecid, coumarin anticoagulants, miconazol, fenfluramine, pentoxifylline (high dose parenteral),fibrates, tritoqualine,ACE inhibitors, fluconazole.

fluoxetine,allopurinol,sympatholytics,cyclo-, tro-and iphosphamides,

Weakening of the blood-glucose-lowering effect may occur when one of the following drugs is taken, for example: oestrogens and progestagens, 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,acetozolamide.H_2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation 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.

Metformin:

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.

Pregnancy and lactation:

Glimepiride:

Pregnancy: Glimepiride is contra-indicated during pregnancy.

Lactation: Because sulphonylurea-derivatives like glimepiride pass into the breast milk, glimepiride must not be taken by breast-feeding women.

Metformin:

Pregnancy: To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fœtal 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 foetal malformations associated with abnormal blood glucose levels.

Lactation: 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.

Undesirable effects:

Glimepiride:

Hypoglycemia may occur with glimepiride. In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases. Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur. These are in general reversible upon discontinuation of medication.

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels. Gastrointestinal complaints like nausea, vomiting and diarrhoea, pressure or a feeling of fullness in the stomach and abdominal pain are very rare and seldom lead to discontinuation of therapy. Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure. Hypersensitivity reactions of the skin may occur as itching, rash and urticaria. In very rare cases hypersensitivity to light may occur. In very rare cases, a decrease in the sodium serum concentrations may occur.

Metformin:

Very common:> 1/10: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Common >1/100, <1/10: Taste disturbance

Very rare <1/10,000 and isolated reports: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Lactic acidosis, Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.Skin reactions such as erythema, pruritus, urticaria

Overdose:

Glimepiride: After ingestion of an over dosage 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.

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.

Metformin: Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

Storage:

Store in a cool, dry & dark place.

Presentation:

ZORYL-M 1/M 2 is available in blister of 10 tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Selaqui, Dehradun-248 197. INDIA

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	Checked by				Approved by
Department	PMQC	RA	Packing Dev.	Q.A.	Head Q.A.
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