TAB. METOREG 500-G5

(Metformin and Glibenclamide Tablets)

Manufacturer:-

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Summary of product characteristics

1. Name of the Medicinal Product

(a) Product Name : Tab. Metoreg 500-G5(Metformin and Glibenclamide Tablets)
(b) Strength : Metformin 500mg, Glibenclamide 5mg
(c) Pharmaceutical Dosage Form : Tablet

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN.

Each uncoated tablet contains:
Metformin BP.....500mg
Glibenclamide BP.....5mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Sr. No.	Name of the Materials	Specification	Label Claim	Qty/tablet
1	Metformin	BP	500mg	500mg
2	Glibenclamide	BP	5mg	5mg

QUALITATIVE AND QUANTITATIVE FORMULA

METOREG 500-G5 TABLETS

(METFORMIN AND GLIBENCLAMIDE TABLETS)

S.No.	Name of Ingredients	Function of ingredients	Quantity required per tablet	Over age (%)	Total quantity required per tablet
Active					
1.	Metformin	Active Ingredient	500mg	Nil	500mg
2	Glibenclamide	Active Ingredient	5mg	Nil	5mg
Inactive					
1.	Polyvinyl Pyrrolidine K-30 BP	Binder	9.926 mg	Nil	9.926 mg
2.	Gelatin BP	Binder	5.672 mg	Nil	5.672 mg

3.	Talcum BP	Lubricant	21.270 mg	Nil	21.270 mg
4.	Magnesium Stearate BP	Lubricant	7.090 mg	Nil	7.090 mg
5.	Sodium starch Glycolate BP	Disintegrant	21.270 mg	Nil	21.270 mg
6.	Dibasic calcium phosphate BP	Diluent	113.442 mg	Nil	113.442 mg
7.	Starch BP	Binder	215.830 mg	Nil	215.830 mg
8.	Methyl Paraben sodium BP	Preservative	0.425 mg	Nil	0.425 mg
9.	Propyl paraben sodium BP	Preservative	0.212 mg	Nil	0.212 mg

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g: Blister strip containing White uncoated oval tablet having having scored on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications:

For the management of type II diabetes mellitus when diet, exercise and single drug therapy do not result in adequate glycemic control. Tablet works by decreasing the amount of glucose and controls the amount of glucose in the blood; stimulating the release of insulin from the pancreas.

4.2 Posology and method of administration

In principle, the dosage of Metoreg 500 G5 is governed by the desired blood glucose level. The dosage of Metoreg 500 G5 must be the lowest which is sufficient to achieve the desired metabolic control. During treatment with Metoreg 500 G5 glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determination of the proportion of glycated hemoglobin be carried out. 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. For the use only of a Registered

Medical Practitioner or hospital or a laboratory This package insert is continually updated: Please read carefully before using a new pack As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity Glibenclamide requirements may fall as treatment proceeds. To avoid hypoglycemia timely dose reduction or cessation of Metoreg 500 G5 therapy must therefore be considered. Initial dose: One Metoreg 500 G5 tablet should be administered as once daily with meals. Maximum Dosing: For once daily administration maximum 2 tablets of Metoreg 500 G5 can be given. For higher doses it may be necessary to divide the administration into 2 doses. Up to 4 tablets of Metoreg 500 G5 can be given per day .

4.3 Contraindications

• in patients with known hypersensitivity to Glibenclamide or metformin or any excipients

• in patients with insulin-dependent (type 1) diabetes mellitus.

• any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma or coma)

• acute conditions with the potential to alter renal function such as dehydration, severe infection, shock)

• disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.

• in patients with severe renal failure

• in patients with serious hepatic dysfunction • alcoholism (acute, chronic)

• in pregnant women

• in breast feeding women

4.4 Special warning and precautions for use

Due to Glibenclamide: Glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated hemoglobin be carried out. As is necessary during treatment with any blood-glucose-lowering drug, the patient and the physician must be aware of the risk of hypo glycaemia. Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in

the elderly. The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

Epidemiological studies suggest that the administration of Glibenclamide is associated with an increased risk of cardiovascular mortality, when compared to treatment with metformin or gliclazide. This risk was especially observed in patients with diagnosed coronary diseases. The patient should be trained to recognize the first signs of hyperglycemia (intense thirst, dry mouth, dry skin, frequent urination) so as to be able to inform your doctor in good time. 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. Persons allergic to other sulfonamide derivatives may develop an allergic reaction to Glibenclamide as well.

Due to Metformin: Metformin alone never causes hypo glycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics. Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism. Long-term treatment with metformin has been associated with a decrease in vitamin B12 serum levels which may cause peripheral neuropathy. Monitoring of the vitamin B12 level is recommended.

Lactic acidosis Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors associated lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis . Patients and/or care-givers should be informed of the risk of lactic acidosis. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Cardiac function: Patients with heart failure are at higher risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal functions. For patients with acute or unstable heart failure, metformin is contraindicated

Administration of iodinated contrast agents: Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been reevaluated and found to be stable.

Surgery: Metformin must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

4.5 Interaction with other medicinal products and other forms of interactions:

Due to Glibenclamide: Association contraindicated

Bosentan: An increased incidence of elevated liver enzymes was observed in patients receiving Glibenclamide concomitantly with bosentan. Both Glibenclamide and bosentan inhibit the bile salt export pump, leading to intracellular accumulation of cytotoxic bile salts. Therefore this combination should not be used.

Patients who take or discontinue taking certain other medicines while undergoing treatment with Metoreg 500 G5 may experience changes in blood glucose control. Glibenclamide is mainly metabolized by CYP 2C9 and to a lesser extent by CYP 3A4. This should be taken into account when Glibenclamide is coadministered with inducers or inhibitors of CYP 2C9. Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypo glycaemia may occur when taking other drugs, including: insulin and other, oral antidiabetics, ACE inhibitors, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide,

disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, ifosfamide, MAO inhibitors, miconazole, paraaminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, sympatholytic agents such as beta-blockers and guanethidine, clarithromycin, tetracyclines, tritoqualine, trofosfamide. Weakening of the blood-glucose-lowering effect and, thus, raised blood glucose levels may occur when taking other drugs, including: 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, thyroid hormones, rifampicin. H2-receptor antagonists, 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 hypo glycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood glucose lowering action of Glibenclamide in an unpredictable fashion. Glibenclamide may either potentiate or weaken the effect of coumarin derivatives. Glibenclamide may increase cyclosporine plasma concentration and potentially lead to its increased toxicity. Monitoring and dosage adjustment of cyclosporin are therefore recommended when both drug are coadministered. Colesevelam binds to Glibenclamide and reduces Glibenclamide absorption from the gastro-intestinal tract. No interaction was observed when Glibenclamide was taken at least 4 hours before colesevelam. Therefore, Glibenclamide should be administered at least 4 hours prior to colesevelam.

Due to Metformin

Alcohol : Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting , malnutrition or hepatic impairment.

Iodinated contrast agents: Metformin must be discontinued prior to, or at the time of the image procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Medicinal products with intrinsic hyperglycemic activity : (e.g. glucocorticoids (systemic and local routes) and sympathomimetics) More frequent blood glucose monitoring may be required.

Medicinal products affecting renal function: Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT): Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin. Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Phenprocoumon : Metformin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended.

Levothyroxine: Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if necessary.

4.6 Pregnancy and lactation:

Tablet must not be taken during pregnancy. 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.

Lactation: To prevent possible ingestion with breast milk, Metoreg 500 G5 must not be taken by breastfeeding women. If necessary, the patient must change over to insulin, or must stop breastfeeding.

4.7 Effects on ability to drive and use machine:

Alertness and reactions may be impaired by hypo- or hyperglycemic episodes, especially when beginning or after altering treatment, or when Metoreg 500 G5 is not taken regularly. This may, for example, affect the ability to drive or operate machinery.

4.8 Undesirable effects:

ADRs common to both Glibenclamide and metformin

Gastrointestinal disorders: Nausea (common frequency for Glibenclamide or very common for metformin), Vomiting (not known frequency for Glibenclamide or very common for metformin), Abdominal pain (common frequency for Glibenclamide or very common for metformin) Diarrhea (common frequency for Glibenclamide or very common for metformin) These ADRs often occur during initiation of therapy and resolve spontaneously in most cases the treatment.

Skin and subcutaneous disorders: Itching (not known frequency for Glibenclamide) Rashes (common frequency for Glibenclamide) Erythema (very rare frequency for metformin) Pruritus (very rare frequency for metformin) Urticaria (very rare frequency for metformin) Hypersensitivity of the skin to light/skin photosensitivity (not known frequency).

Blood and lymphatic system disorders: Hemolytic anemia (not known frequency)

ADR due to Glibenclamide:

Metabolism and nutrition disorders: Hypoglycemia (very common frequency), sometimes prolonged and even life-threatening, may occur as a result of the blood-glucose-lowering action of Glibenclamide. This happens when there is imbalance between Glibenclamide dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism. Possible symptoms of hypo glycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, 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 hypoglycemic attack (very common frequency) may resemble that of a stroke. The symptoms of hypo glycaemia nearly always subside when hypo glycaemia is corrected. In isolated cases, sodium concentration in the serum may decrease (not known frequency).

Eye disorders: Especially at the start of treatment, there may be temporary visual impairment (not known frequency) due to 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.

Gastrointestinal disorders: Sensations of pressure or fullness in the epigastrium (uncommon frequency) may occur.

Hepatobiliary disorders: There may be hepatitis (not known frequency), elevation of liver enzyme levels (not known frequency) and/or cholestasis (not known frequency) and jaundice (not known frequency) which may progress to life-threatening liver failure (not known frequency) but can regress after withdrawal of Metoreg 500 G5

Blood and lymphatic system disorders: Potentially life-threatening changes in the blood picture may occur. They may include mild to severe thrombopenia (e.g. presenting as purpura) (not known

frequency) and erythrocytopenia (not known frequency), leucopenia, granulocytopenia (not known frequency), agranulocytosis (not known frequency), and (e.g. due to myelosuppression) pancytopenia (not known frequency). In principle, these reactions are reversible once Metoreg 500 G5 has been withdrawn.

Immune system disorders: Hypersensitivity reactions allergic or pseudo allergic reactions(not known frequency) may occur; they may be directed against Glibenclamide itself, but may alternatively be triggered by excipients. Allergy to sulfonamide derivatives may also be responsible for an allergic reaction to Glibenclamide. Mild reactions in the form of urticaria (not known frequency) may develop into serious and even life-threatening reactions with dyspnoea and fall in blood pressure, sometimes progressing to shock (not known frequency). In the event of urticaria, a physician must therefore be notified immediately.

Skin and subcutaneous disorders: Bullous reactions (not known frequency), erythema multiforme (not known frequency), dermatitis exfoliative (not known frequency) have been observed. Allergic vasculitis (not known frequency) may arise and, in some circumstances, may be life-threatening

ADRs due to Metformin:

Metabolism and nutrition disorders: Lactic acidosis (very rare frequency) (see section Warnings) - Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin (very rare frequency). Consideration of such etiology is recommended if a patient presents with megaloblastic anemia. - Cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post marketing experience (not known frequency).

Nervous system disorders: Encephalopathy (not known frequency) .

Gastrointestinal disorders: Loss of appetite (very common frequency) - Metallic taste (common frequency).

Hepatobiliary disorders: Reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation (very rare frequency).

Investigations: Reduction of thyrotropin level in patients with hypothyroidism (not known frequency). - Hypomagnesemia in the context of diarrhea (not known frequency).

4.9 Overdose

Signs and symptoms Acute overdose as well as long-term treatment with too high a dose of Glibenclamide may lead to severe, protracted, life-threatening hypo glycaemia. Hypoglycemia has not been seen with metformin doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Pancreatitis may occur in the context of a metformin overdose.

Management As soon as an overdose of Glibenclamide 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 hypo glycaemia and its clinical signs may recur after initial recovery. Admission to hospital may sometimes be necessary - even as 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 40 ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c. or i.m., may be considered. Patients who have ingested life-threatening amounts of Metoreg 500 G5 require detoxification (e.g. by gastric lavage and medicinal charcoal). After acute glucose replacement has been completed, it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypo glycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypo glycaemia, or the danger of slipping back into hypo glycaemia, may persist for several days. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis. In addition to the treatment of any underlying disease (congestive heart failure, liver failure, nephropathy) a correction of the state of shock is required, by the infusion of insulin with glucose and sodium bicarbonate .

5 Pharmacological Properties

5.1 Pharmacodynamic Properties:

Pharmacological classification-

Anti-diabetic therapy, Glibenclamide: Antidiabetic. Sulfonylurea Metformin: Antidiabetic. Biguanide.

Pharmacological action-

Glibenclamide is an orally active hypoglycemic agent, which acts by stimulating insulin secretion.

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypo glycaemia.

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 utilization.
3. And delay of intestinal glucose absorption.

5.2 Pharmacokinetic Properties:

Glibenclamide is rapidly absorbed and is extensively bound to plasma proteins, but is not readily displaced by acidic drugs. It is excreted as metabolites in the urine and bile.

Metformin -After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and the dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1µg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4µg/ml, even at maximum doses.

5.3 Preclinical Safety Data:

Glibenclamide: Acute toxicity studies showed no specific susceptibility. The acute oral toxicity of Glibenclamide was extremely low in all species tested (LD50 greater than 4 g/kg). Chronic toxicity tests in rats and dogs at doses up to 8.0 mg/kg did not show any evidence of toxic effects. A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the maximum human dose showed no effects on fertility.

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

6 Pharmaceutical Particulars

6.1 List of excipients:

Polyvinyl Pyrrolidine K-30 BP
Gelatin BP
Talcum BP
Magnesium Stearate BP
Sodium Starch Glycolate BP
Dibasic Calcium Phosphate BP
Starch BP
Methyl Paraben Sodium BP
Propyl Paraben Sodium BP

6.2 Incompatibilities:

Not Applicable.

6.3 Shelf life: 36 Months

6.4 Special precautions for storage: Store in a dry place at temperature not exceeding 30ºC. protect from light.

6.5 Nature and contents of container: Blister strip

6.6 Special precautions for disposal and other handling

No special requirements for disposal.