GLIMEPIRIDE + METFORMIN HCl

PERGLIM M-1

1 mg / 500 mg Tablet
Oral Hypoglycemic Agent

PERGLIM M-2

2 mg / 500 mg Tablet
Oral Hypoglycemic Agent

FORMULATION:

PERGLIM M-1

Each uncoated bi-layered tablet contains:
Glimepiride ..... 1 mg
Metformin HCl (in sustained-release form) ..... 500 mg

PERGLIM M-2

Each uncoated bi-layered tablet contains:
Glimepiride ..... 2 mg
Metformin HCl (in sustained-release form) 500mg

INDICATIONS:

Indicated as an adjunct to diet and exercise in type 2 diabetes mellitus patients, in case when monotherapy with Glimepiride or Metformin does not result in adequate glycemic control.

CONTRAINDICATIONS:

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

It must not be used in patients with sensitivity 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 & trauma), before x-ray examinations with iodinated contrast materials;

Liver damage;

Alcoholism;

Deficiencies 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)

SPECIAL WARNINGS & PRECAUTIONS:

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 lifestyle changes.

Symptoms of hypoglycemia may be milder or absent in those situations where hypoglycemia 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 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 a minimum of 20 grams of glucose with them at all times. They may require assistance of other persons to avoid complication. Artificial sweeteners are ineffective in controlling hypoglycemia.

Continued close observation is necessary. Severe hypoglycemia requires 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 machinery.

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 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 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.

Drug Interactions

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 anti-hyperglycemic effect. Hence, the patients treated with metformin should preferably avoid alcohol, and alcoholism is a definite contraindication.

Other Interactions: Studies with furosemide and nifedipine suggest that 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, azaproprazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, tetracylines, tritoqualine, trofofamide.

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 protracted use), nicotinic acid (in high doses), estrogens and progestogens, phenothiazines, 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.

Pregnancy

Pregnancy is generally regarded as a contraindication, 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.

Elderly Patients

Caution is advised in elderly patients. Frequent monitoring of serum creatinine and dose reduction is recommended in this age group.

DOSAGE & ADMINISTRATION:

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

Glimepiride 2mg/Metformin hydrochloride 500mg : 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 2000mg and glimepiride is 8mg 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 hemoglobin levels to normal by using the lowest effective dose of the drug.

ADVERSE REACTIONS:

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, possibly resulting in liver failure.

Blood: Rarely thrombocytopenia and in isolated cases, leucopenia, hemolytic anemia,

erythrocytopenia, granulocytopenia, agranulocytosis and pancytopenia (e.g. due to myelosuppression) may develop.

Other adverse reactions: Allergic or pseudoallergic reactions like itching, urticaria 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 urticaria 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.

OVERDOSAGE:

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

STORAGE CONDITION:

Store at temperatures not exceeding 30^0C, in a dry place.

AVAILABILITY:

Alu/Clear PVC/PVDC Blister Pack x 20's in an individual box x 20's (Box of 100's)

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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