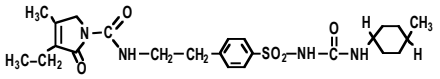
Getformin™

1mg+500mg
2mg+500mg
Tablets
(Glimepiride+Metformin HCl)

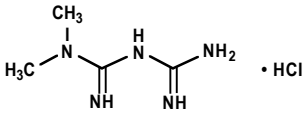
گیٹفورمن

DESCRIPTION
GETFORMIN combines glimepiride and metformin hydrochloride,two antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes. Chemically glimepiride is known as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]-sulfonyl]-3-(trans-4-methylcyclohexyl) urea having a molecular formula of $C_{24}H_{34}N_4O_5S$ and a structural formula of:



Glimepiride

Chemically metformin HCl is known as 1,1-dimethyl biguanide hydrochloride having a molecular formula of $C_4H_{11}N_5.HCl$ and a structural formula of:



Metformin HCl

QUALITATIVE & QUANTITATIVE COMPOSITION
GETFORMIN (Glimepiride + Metformin HCl) is available for oral administration as:

1. GETFORMIN Tablets 1mg+500mg
   Each film-coated tablet contains:
   Glimepiride USP…1mg
   Metformin HCl USP... 500mg

2. GETFORMIN Tablets 2mg+500mg
   Each film-coated tablet contains:
   Glimepiride USP... 2mg
   Metformin HCl USP... 500mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Glimepiride:
Glimepiride is a third generation sulphonylurea. The primary mechanism of action of glimepiride appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.
In addition, extrapancreatic effects (e.g. reduction of basal hepatic glucose production and increased peripheral tissue sensitivity to insulin and glucose uptake) may also play role in the activity of glimepiride.

Metformin HCl:
Metformin hydrochloride is a biguanide anti-diabetic, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its mode of action is thought to be multifactoral and includes delayed uptake of glucose from the intestinal tract, increased peripheral glucose utilization mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

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

Pharmacokinetics
Glimepiride:
After oral administration glimepiride is completely absorbed from the GI tract. The oral bioavailability is approximately 100%. Peak plasma concentrations occur in 2-3 hours. More than 99% of the drug is bound to plasma proteins. Glimepiride is completely metabolized by oxidative biotransformation into two main metabolites, a hydroxy derivative and a carboxy derivative.
The half-life after multiple doses is about 9 hours. Approximately 60% of dose is eliminated in the urine and 40% in the feces.

Metformin HCl:
Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract. The absolute bioavailability of a single 500mg dose is reported to be about 50% to 60%, although this is reduced somewhat if taken with food. Once absorbed plasma protein binding is negligible. It is excreted unchanged in urine. The plasma elimination half-life is reported to range from about 2-6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

Special Populations
Renal Impairment
Glimepiride
Glimepiride serum levels decreased as renal function decreased. However, metabolites serum levels (mean AUC values) increased. The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for metabolites increased as renal function decreased. Mean urinary excretion of metabolites as percent of dose, however, decreased.

Metformin HCl
In patients with impaired renal function, 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
GETFORMIN (Glimepiride + Metformin HCl) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes whose diabetes is not adequately controlled with glimepiride or metformin HCl alone, or for those patients who have initially responded to glimepiride or metformin HCl alone and require additional glycemic control.

DOSAGE & ADMINISTRATION
Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose. The maximum daily dose of metformin is 2000mg and of glimepiride is 8mg. The tablets should be swallowed whole and not crushed or chewed. The tablet is taken once daily with meals to a maximum of 4 tablets/day or as directed by the physician.

ADVERSE REACTIONS
Diarrhea, vomiting, metallic taste, rash, isolated transaminase elevations, cholestatic jaundice, allergic skin reactions, photosensitivity reactions, leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia and blurred vision. Glimepiride appears to be associated with a low incidence of hypoglycemia. It has also been found to have low propensity to cause adverse cardio vascular effects. Impaired gastrointestinal absorption of vitamin B_{12} and folic acid has been associated with long term metformin therapy. Rarely, metformin administration has resulted in lactic acidosis.

CONTRAINDICATIONS
Glimepiride + Metformin HCl combination is contraindicated in:
- Patients with known hypersensitivity to sulfonylurea or biguanide or any component of the drug.
- Insulin-dependent diabetes mellitus.
- Renal or hepatic failure.
- Alcoholism.
- NIDDM complicated by severe ketosis and acidosis.
- Diabetic pre-coma and coma.
- Patients undergoing surgery, after severe trauma or during infections.
- Chronic obstructive pulmonary disease.
- Coronary heart disease, cardiac failure.

- Peripheral vascular disease.
- Pregnancy and lactation.

PRECAUTIONS

General

- Hypoglycemia may occur if the patient's dietary intake is reduced or after accidental or deliberate overdose or after severe exercise, trauma and stress. Hypoglycemic symptoms can be reduced by prescribing a diabetic meal plan. Immediate intervention should be done if signs and symptoms of hypoglycemia occur.
  Adjust dose of drug according to blood and urinary glucose levels during the first few months.
- The patient's fasting blood glucose and HbA1c must be measured periodically to determine the minimum effective dose for the patient. After an initial period of effectiveness glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

Lactic acidosis

Lactic acidosis is rare, but serious metabolic complication that can occur due to metformin accumulation. 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, serum creatinine levels should be determined before initiating treatment and regularly thereafter.

Pediatric use

Safety and effectiveness of the drug in children have not been established.

Drug Interactions

Glimepiride:

- The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors and beta adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.
- Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control.
- Glimepiride is metabolised by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers, inhibitors or substrates of CYP2C9 (e.g. rifampicin, fluconazole, amiodarone, tolbutamide, diclofenac, ibuprofen, naproxen).
- H_2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.
- Acute and chronic alcohol intake may either potentiate or attenuate the activity of glimepiride in an unpredictable fashion.

Metformin HCl:

- Drug interactions of metformin is seen with phenprocoumon, hyperglycemic agent (e.g. - thiazides, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, cal cium channel blocking drugs and isoniazid), alcohol, furosemide, nifedipine and cationic drugs (amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and cimetidine, vancomycin). The absorption of metformin may be reduced by acarbose and guar gum.
- 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 untill 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

OVERDOSE

Glimepiride:

An overdosage of Glimepiride can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

Metformin HCl:

A large overdose of Metformin HCl may lead to lactic acidosis. Hemodialysis may be useful for removal of accumulated Metformin HCl from patients in whom Metformin HCl overdosage is suspected.

STORAGE

Store at 25°C (Excursions permitted between 15°C-30°C).
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

GETFORMIN (Glimepiride + Metformin HCl) Tablets 1mg+500mg are available in blister pack of 30's.

GETFORMIN (Glimepiride + Metformin HCl) Tablets 2mg+500mg are available in blister pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is contin ually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

200007821