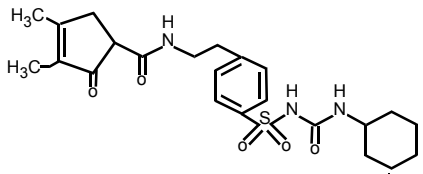
Glimepiride

Getryl®

1mg, 2mg, 3mg, 4mg Tablet
Oral Hypoglycemic

DESCRIPTION
Glimepiride (Getryl®) is an oral blood glucose lowering drug of the sulfonylurea class. Chemically glimepiride is 1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]-sulphonyl]-3-(trans-4-methylcyclohexyl)urea. The molecular formula is $C_{24}H_{34}N_4O_5S$ and the structural formula is:



Glimepiride

FORMULATION
Glimepiride (Getryl®) is available for oral administration as:

1. Glimepiride (Getryl®) Tablets 1mg
   Each tablet contains:
   Glimepiride…1mg

2. Glimepiride (Getryl®) Tablets 2mg
   Each tablet contains:
   Glimepiride…2mg

3. Glimepiride (Getryl®) Tablets 3mg
   Each tablet contains:
   Glimepiride…3mg

4. Glimepiride (Getryl®) Tablets 4mg
   Each tablet contains:
   Glimepiride…4mg

CLINICAL PHARMACOLOGY
Mechanism of Action
The primary mechanism of action of glimepiride appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra-pancreatic effects (e.g. reduction of basal hepatic glucose production and increased peripheral tissue sensitivity to insulin and glucose uptake) may also play a role in the activity of glimepiride. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacokinetics
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 elimination half-life ($t_{1/2}$) after multiple doses is about 5-8 hours. Approximately 60% of dose is eliminated in the urine and 40% in the feces.

Special populations
Renal Insufficiency
A single-dose clinical study glimepiride showed that glimepiride serum levels decreased as renal function decreased. However, metabolite 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.

INDICATIONS
Glimepiride (Getryl®) is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

Glimepiride (Getryl®) may be used concomitantly with metformin when diet, exercise, and Glimepiride (Getryl®) or metformin alone do not result in adequate glycemic control.

Glimepiride (Getryl®) is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent.

DOSAGE & ADMINISTRATION
In initiating treatment for noninsulin-dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. There is no fixed dosage regimen for the management of diabetes mellitus with Glimepiride (Getryl®) or any other hypoglycemic agent. The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient. Short-term administration of Glimepiride (Getryl®) may be sufficient during periods of transient loss of control in patients usually well controlled on diet and exercise.

Usual Starting Dose
The usual starting dose of Glimepiride (Getryl®) as initial therapy is 1-2mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1mg once daily, and should be titrated carefully. The maximum starting dose of Glimepiride (Getryl®) should be not more than 2mg.

Usual Maintenance Dose
The usual maintenance dose of Glimepiride (Getryl®) is 1 to 4mg once daily. The maximum recommended dose is 8mg once daily. After reaching a dose of 2mg, dose increases should be made in increments of no more than 2mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA_{1c} levels, for example, every 3 to 6 months.

Glimepiride (Getryl®) – Metformin Combination Therapy
If patients do not respond adequately to the maximal dose of Glimepiride (Getryl®) monotherapy, addition of metformin may be considered. With concomitant Glimepiride (Getryl®) and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

Glimepiride (Getryl®) – Insulin Combination Therapy
Combination therapy with Glimepiride (Getryl®) and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150mg/dL in plasma or serum depending on the patient. The recommended Glimepiride (Getryl®) dose is 8mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose.

Special populations
In elderly, debilitated, or malnourished patients, or in patients with hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Renal impaired patients
In patients with mild to moderate renal impairment, a starting dose of 1mg once daily must not be exceeded. The dose may then be carefully titrated upwards if necessary based on fasting blood glucose levels in increments of 1mg at intervals of one to two weeks.

ADVERSE REACTIONS
Glimepiride is generally well tolerated. However following are the side effects reported during treatment with glimepiride.
Hypoglycemia: Hypoglycemia is the greatest potential risk with all sulfonylureas.
Visual reactions: There may be temporary visual impairment (e.g., changes in accommodation and/or blurred vision) due to the change in

blood glucose levels, especially at the start of treatment.
Gastrointestinal reactions: Occasionally gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur.
Hematologic reactions: Rarely, thrombocytopenia and in isolated cases, leukopenia may develop. In isolated instances, thrombocytopenic purpura, agranulocytosis, pancytopenia due to myelosuppression, eosinophilia, hemolytic anemia, aplastic anaemia, erythrocytopenia and granulocytopenia may occur.
Dermatologic reactions: Occasionally, allergic or pseudo-allergic skin reactions (e.g., pruritus, erythema, urticaria, erythematous and maculo-papular and bullous skin eruptions or psoriasiform drug eruption) may occur in patients treated with sulfonylureas.
Hepatic reactions: Increased liver enzymes (AST, ALT), abnormal liver function, cholestasis, cholestatic hepatitis, granulomatous hepatitis, bilirubinemia aernia and liver failure have been reported with sulfonylureas in isolated cases.
Electrolyte disturbance: In isolated cases, hyponatremia has been reported in patients receiving glimepiride and other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or to increase release of anti-diuretic hormone.
Others: Isolated cases of allergic vasculitis have been reported with sulfonylureas.

CONTRAINDICATIONS
- Glimepiride is contraindicated in patients with known hypersensitivity to the drug.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

PRECAUTIONS
The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response. After an initial period of effectiveness glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

Hypoglycemia
All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.
Debilitated patients, malnourished patients and patients with adrenal, pituitary, renal or hepatic insufficiency are particularly susceptible to the hypoglycemic action of sulfonylureas and should therefore be carefully monitored. The dosage of glimepiride should be carefully adjusted in these patients.
Hepatic insufficiency may cause increased serum concentrations of glimepiride and may diminish gluconeogenic capacity, both of which increase the risk of severe hypoglycemic reactions.
Alcohol ingestion, severe or prolonged exercise, deficient caloric intake or use of more than one antidiabetic agent may predispose patients to the development of hypoglycemia.

Loss of control of blood glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with glimepiride or even use insulin monotherapy.

Pregnancy
Glimepiride is not recommended for use during pregnancy.

Nursing mothers
It is not known whether glimepiride is distributed into human breast milk. However, some sulfonylureas are distributed into human breast milk. Because of its potential to cause hypoglycemia in nursing infants, glimepiride is not recommended for use by nursing mothers.

Pediatric use
Glimepiride is not recommended for use in children.

Drug Interactions
- 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 co-administered 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.
- Concomitant treatment with a beta-receptor blocker, clonidine, guanethidine or reserpine may mask the warning symptoms of a hypoglycemic attack.
- Acute and chronic alcohol intake may either potentiate or attenuate the activity of glimepiride in an unpredictable fashion.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight and moisture.

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

AVAILABILITY
Glimepiride (Getryl®) Tablets 1mg are available in blister pack of 10's (Box of 20's).

Glimepiride (Getryl®) Tablets 2mg are available in blister pack of 10's (Box of 20's).

Glimepiride (Getryl®) Tablets 3mg are available in blister pack of 10's (Box of 20's).

Glimepiride (Getryl®) Tablets 4mg are available in blister pack of 10's (Box of 20's).

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

Keep out of reach of children.

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

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PH07-200006661

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Imported by: Getz Pharma (Phils.) Inc., 2/F Tower 1, The Rockwell Business Center, Ortigas Ave., Pasig City, Philippines.