Glimepiride

Norizec®

1 mg, 2 mg & 3 mg Tablet
oral hypoglycemic

℞

FORMULATION
Each tablet contains:
Glimepiride ……..... 1 mg, 2 mg or 3 mg

PRODUCT DESCRIPTION
1 mg Tablet: Pink, flat, round tablet with breakline on one side and plain on the other
2 mg Tablet: Cream, flat, round tablet with crossline on one side and plain on the other
3 mg Tablet: Green, flat, round tablet with crossline on one side and plain on the other

CLINICAL PHARMACOLOGY
Pharmacodynamics
Glimepiride is a sulfonylurea antidiabetic agent. It lowers blood glucose primarily by stimulating the release of endogenous insulin from functioning pancreatic ß-cells. Glimepiride exerts its extrapancreatic effects in two ways: by increasing rapidly the number of active glucose transport molecules in the plasma membranes of the muscle and fat cells resulting in stimulated glucose uptake and by increasing the intracellular concentration of fructose-2,6-bisphosphate, resulting in the inhibition of glucose production in the liver (gluconeogenesis).

Pharmacokinetics
Glimepiride is completely (100%) absorbed from the gastrointestinal tract after oral administration. There was no change observed in the clearance of glimepiride at a dose range of 1 to 8 mg, exhibiting linear kinetics. Peak serum concentration is reached in about 2 to 3 hours. The time to reach C_{max} (T_{max}) was slightly increased (12%) and the mean C_{max} and AUC were slightly decreased (8% and 9%, respectively) when glimepiride was given with meals.

Glimepiride has a very low volume of distribution (about 8.8 L), high protein binding (>99.5%), and low total body clearance (approximately 48 mL/min). It is likely to be only minimally removed by hemodialysis. Glimepiride is excreted in milk in animals. It is transferred to the placenta and passage of the blood-brain barrier is low. There was no relevant accumulation of glimepiride in the blood.

Glimepiride is completely metabolized by oxidative biotransformation with cyclohexyl hydroxyl methyl derivative (M1) and carboxyl derivative (M2) as major metabolites. Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1 which has one-third the pharmacologic activity of its parent compound. However, it is not clear whether the glucose-lowering effect of M1 is clinically significant.

About 60% of glimepiride is recovered in the urine within 7 days with M1 (predominant) and M2 accounting for 80-90% of that recovered. About 40% is recovered in the feces; M1 and M2 (predominant) account for 70% of that recovered in the feces. No parent drug is recovered from urine or feces. The terminal half-lives of these metabolites were 3-6 and 5-6 hours, respectively. Significant biliary excretion of glimepiride or its M1 metabolite is not observed after IV dosing.

INDICATION
Adjunct to proper dietary management, physical exercise, and weight reduction to improve glycemic control in adults with type 2 diabetes mellitus. Glimepiride may be used as monotherapy or in combination with metformin or insulin.

DOSAGE AND ADMINISTRATION

- There is usually no fixed dosage regimen with any antidiabetic agent for the management of hyperglycemia in patients with diabetes mellitus. Dosage should be individualized based on both effectiveness and patient tolerance.
- Inform patients on the potential risks and advantages of glimepiride and alternative modes of therapy. The importance of adherence to dietary instructions, regular exercise program and regular testing of blood glucose should also be advised to patients.
- During treatment initiation and dose titration, fasting plasma glucose (FPG) should be used to identify the minimum effective dose and determine the therapeutic response to glimepiride (i.e., detect primary and secondary failure). Glycosylated hemoglobin (HbA_{1c}) should be measured at intervals of approximately every three months to monitor patient's response to therapy.
- Short-term administration of glimepiride may be sufficient during periods of transient loss of control in patients usually controlled well on diet and exercise.

Usual Adult Starting Dose
As initial therapy: 1-2 mg once daily with breakfast or the first main meal

Start patients who may be more sensitive to hypoglycemic agents at 1 mg once daily and titrate dose carefully. No exact dosage relationship exists between glimepiride and other oral hypoglycemic agents.

Maximum Starting Dose: not more than 2 mg
Failure to follow an appropriate drug regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Usual Maintenance Adult Dose
Usual Maintenance Adult Dose: 1-4 mg once daily
Maximum Recommended Dose: 8 mg once daily
After reaching a dose of 2 mg, increase dosage in increments of not more than 2 mg at 1-2 week intervals based on the patient's glucose response.

Glimepiride-Metformin Combination Therapy
- If patients do not respond adequately to the maximum dose of glimepiride monotherapy, consider addition of metformin.
- Glycemic control may be obtained by adjusting the dose of each drug. Identify the minimum effective dose of each drug to achieve this goal.
- The risk of hypoglycemia associated with glimepiride may be increased with concomitant metformin therapy. Undertake necessary precautions.

Glimepiride-Insulin Combination Therapy
- Combination therapy with glimepiride and insulin may also be used in patients with secondary failure.
- The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum.

Recommended Glimepiride Adult Dose: 8 mg once daily with the first main meal
Start with low dose insulin and adjust weekly, guided by frequent FPG monitoring.
Once stable, patients on combination therapy should monitor their capillary blood glucose, preferably on a daily basis.
Periodic adjustments of insulin may be necessary during maintenance as guided by glucose and HbA_{1c} levels.

Or, as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to glimepiride, other sulfonylureas or any ingredient of the product.
- Type 1 diabetes mellitus
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- Pregnancy or breastfeeding
- Severe renal or hepatic insufficiency

WARNINGS AND PRECAUTIONS
Allergic reaction to glimepiride may be experienced by persons allergic to other sulfonamide derivatives.

Increased Risk of Cardiovascular Mortality
Based on a long-term prospective study conducted by the University Group Diabetes Program (UGDP), it has been reported that diabetic patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day), a sulfonylurea, had a risk of cardiovascular mortality approximately 2 ½ times that of patients treated with diet alone.

In the United Kingdom Prospective Diabetes Study (UKPDS), however, intensive glycemic control with either sulfonylurea or insulin did not have an adverse effect on cardiovascular outcomes. Despite questions regarding the design of these studies and interpretation of the results, these studies provide a basis for caution especially in high-risk patients with cardiovascular disease.

More patients receiving glimepiride and insulin reported an increase in peripheral edema in clinical trials compared with patients receiving insulin alone. Patients using this combination therapy should be asked to report any edema or weight gain.

Hypoglycemia
Sulfonylureas, including glimepiride, are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemic episodes.

Symptoms of hypoglycemia may be characterized by headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence, and loss of consciousness including coma, shallow respiration and bradycardia. Signs of adrenergic counter-regulation (i.e., sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias) may also be present. A severe hypoglycemic attack may resemble that of a stroke.

Hypoglycemia may occur when caloric intake is deficient and therefore, glimepiride should be taken shortly before or during a meal to prevent hypoglycemia. These symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect.

Other factors which contribute to the risk of hypoglycemia include: unwillingness of patients to cooperate with therapy, undernutrition, irregular mealtimes or missed meals or periods of fasting, alterations in diet, strenuous exercise not compensated by caloric supplementation, alcohol consumption, concomitant use with other glucose-lowering agents (such as other sulfonylureas and insulin) or overdosage with glimepiride.

Elderly, debilitated or malnourished patients, those with renal or hepatic dysfunction, and those with adrenal or pituitary insufficiency are particularly susceptible to hypoglycemia. It may be difficult to recognize hypoglycemic states in the elderly, in patients with autonomic neuropathy and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

Loss of Control of Blood Glucose
Loss of control of blood glucose may occur in patients stabilized on any antidiabetic regimen exposed to stress (e.g., fever, trauma, infection, or surgery). In such cases, insulin may be added to glimepiride therapy or monotherapy with insulin be used.

The efficacy of any oral hypoglycemic drug may be reduced in many patients over a period of time due to progression of severity of the diabetes or to diminished responsiveness to the drug (secondary failure). In patients who experience secondary failure with glimepiride or metformin monotherapy, combination therapy with glimepiride and metformin or glimepiride with insulin may be beneficial. Insulin therapy should be initiated in patients who experience secondary failure after combination therapy.

Hypersensitivity Reactions
Hypersensitivity reactions, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome (SJS) have been reported in postmarketing studies. Glimepiride should be immediately discontinued if hypersensitivity reaction is suspected. The patient should be assessed for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia
Sulfonylureas may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Use sulfonylureas with caution and consider a non-sulfonylurea alternative in these patients. Hemolytic anemia has also been observed in patients who did not have known G6PD deficiency in postmarketing reports.

Spontaneous reports of severe thrombocytopenia with platelet count less than 10,000/microL and thrombocytopenic purpura were reported.

Renal and Hepatic Insufficiency
Treatment with glimepiride (i.e., starting dose, dose increments and maintenance dose) in patients with renal and hepatic insufficiency should be conservative to avoid hypoglycemic reactions.

Effects on Ability to Drive or Use Machines
Glimepiride may cause visual abnormalities due to changes in blood glucose (hypoglycemia/ hyperglycemia). Patients receiving glimepiride should be advised to take precautions while performing activities requiring mental alertness or physical coordination especially if diabetes is not satisfactorily controlled (usually at the beginning of treatment). It should be carefully considered whether it is advisable to drive or operate machinery under these circumstances.

INTERACTIONS WITH OTHER MEDICAMENTS
Aspirin: Co-administration of aspirin and glimepiride resulted in an increased mean AUC and decreased mean C_{max} of glimepiride. However, there is no evidence of clinically significant adverse interactions with concurrent administration of aspirin and other salicylates.

H_2 Receptor Antagonists: Co-administration of either cimetidine or ranitidine with a single oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.

Propranolol: Concomitant administration of propranolol and glimepiride may result in significant increases in the C_{max}, AUC and $t_{1/2}$ of glimepiride.

Miconazole: Potential interactions between oral miconazole and oral hypoglycemic agents including glimepiride leading to severe hypoglycemia have been reported. It is not known whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole.

Coumarin Anticoagulants: The pharmacodynamic response to warfarin may be potentiated or weakened by concomitant administration with glimepiride. This may cause very small reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment.

Cytochrome P450: Glimepiride is metabolized by cytochrome P450 2C9. 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). *In vivo*, concomitant administration with fluconazole (a potent CYP2C9) resulted in a 2-fold increase in glimepiride's AUC.

Sympatholytic Agents: Signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent when glimepiride and sympatholytics (e.g., beta-blockers, clonidine, guanethidine, and reserpine) are taken concomitantly.

Colesevelam: Absorption of glimepiride is reduced when concomitantly administered with colesevelam. However, absorption is not reduced when glimepiride is administered 4 hours before taking colesevelam.

Alcohol: Acute and chronic alcohol intake may unpredictably potentiate or reduce the activity of glimepiride.

Drugs that may potentiate the hypoglycemic action of glimepiride and other sulfonylureas:
Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen, phenylbutazone, oxyphenbutazone and azapropazone; clarithromycin, highly protein-bound drugs, coumarins, probenecid, beta blockers, salicylates, aminosalicylic acid, anabolic steroids and male sex hormones, chloramphenicol, certain long-acting sulfonamides, tetracyclines, quinolone antibiotics, fenfluramine, fibrates, ACE inhibitors, fluoxetine, monoamine oxidase inhibitors, disopyramide, allopurinol, sulfinpyrazone, sympatholytics, cyclophosphamide, trosphosphamide, ifosfamide, miconazole, fluconazole, pentoxifylline (high-dose parenteral), tritoqualine, insulin, and other oral antibiabetic drugs

Drugs that tend to produce hyperglycemia and may lead to loss of glycemic control when co-administered with glimepiride:
Thiazides and other diuretics, corticosteroids, phenothiazines, chlorpromazine, thyroid products, estrogens, progestogens, nicotinic acid (high doses) and nicotinic acid derivatives, laxatives (long-term use), oral contraceptives, phenytoin, diazoxide, glucagons, barbiturates, rifampicin, acetazolamide, adrenaline, sympathomimetics, and isoniazid

Although no specific interaction study was performed, data from pooled clinical studies showed no evidence of clinically significant adverse interactions were observed with uncontrolled concurrent calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG-CoA reductase inhibitors, sulfonamides, or thyroid hormone.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy: *Category C*
Glimepiride is not recommended during pregnancy. Current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Lactation
Glimepiride has been shown to be secreted in the milk of rats. It is not known whether breastfeeding will lead to exposure of the human infant to glimepiride. However, other sulfonylureas are excreted in human milk. Discontinue use in breastfeeding mothers because of the potential risk of hypoglycemia in breastfeeding infants.

Pediatrics
The pharmacokinetics, safety and efficacy of glimepiride in children have not been established in pediatric patients. Glimepiride use is not recommended in this age group.

Geriatrics
There are no significant differences in glimepiride pharmacokinetics, safety and efficacy in patients with type 2 diabetes ≤65 years old and those >65 years. Although no dosage adjustment is necessary, elderly patients are more susceptible to the hypoglycemic action of glucose-lowering agents. To avoid hypoglycemia, carefully adjust the starting dose, dose increments and maintenance dose based on blood glucose levels.

Renal Insufficiency
Glimepiride is substantially excreted by the kidneys. The recommended starting dose of 1 mg daily for all patients with type 2 diabetes and renal impairment is recommended to minimize the risk of hypoglycemia in these patients.

UNDESIRABLE EFFECTS
Metabolic-Nutritional: Hypoglycemia, hyperglycemia, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, aggravation of diabetes mellitus, hyponatremia, increased appetite, anorexia, weight gain

Gastrointestinal (GI): Diarrhea, nausea, vomiting, heartburn, abdominal discomfort, abdominal distention, abdominal pain, gastrointestinal pain, dyspepsia, sensation of fullness, metallic taste

Cardiovascular: Bradycardia, palpitations, vasodilation

Hematologic: Anemia (aplastic and hemolytic), leukopenia, granulocytopenia, agranulocytosis, thrombocytopenia (including severe cases with platelet count less than 10,000 microL), thrombocytopenic purpura, erythrocytopenia, pancytopenia

Immune System Disorders: Leukocytoclastic vasculitis, hypersensitivity reactions worsening (e.g., dyspnea, fall in blood pressure, and shock); cross-sensitivity reaction to other sulfonylureas may also occur.

CNS: Disulfiram-like reactions, headache, dizziness, insomnia, tremor, parethesia, nervousness, dry mouth, hot flashes

Hepatobiliary: Cholestasis, jaundice, abnormal liver function, hepatitis which may lead to liver failure or hepatic dysfunction, hepatic porphyria reactions, increased liver enzyme levels

Skin and subcutaneous tissue disorders: Allergic or pseudo-allergic reactions (e.g., pruritus, rash, urticaria, erythema multiforme, erythema nodosum, morbilliform, maculopapular skin eruptions), Stevens-Johnson Syndrome (SJS), exfoliative dermatitis, porphyria cutanea tarda, photosensitivity reactions

Urogenital: Increased urinary frequency, nocturia

Miscellaneous: Asthenia, pain in extremity, allergic vasculitis, sweating, visual disturbance/ abnormal vision, flu syndrome, accidental injury, laboratory test abnormal, decrease in serum sodium concentration

OVERDOSAGE AND MANAGEMENT
Like other sulfonylureas, glimepiride overdosage may manifest as hypoglycemia which may last for 7-12 hours and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion.

Aggressively treat mild hypoglycemic symptoms with oral glucose and adjust drug dosage and/or meal patterns. Continue close monitoring until the patient is out of danger.

Prevent absorption of glimepiride by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium sulfate (laxative). Gastric lavage followed by activated charcoal and sodium sulfate is recommended in case of large ingestions of glimepiride.

In case of severe hypoglycemic reactions including coma, seizure or other neurological impairment, immediate hospitalization is required. In patients with diagnosed or suspected hypoglycemic coma, rapid intravenous injection of concentrated (50%) glucose solution followed by a continuous infusion of 10% glucose solution at a rate that will maintain blood glucose level at 100 mg/dL and above should be given. Monitor patients for 24 to 48 hours to prevent recurrence of hypoglycemia.

In case of accidental ingestion of glimepiride in infants and children, treat hypoglycemic symptoms by giving a carefully controlled dose of glucose (to avoid the possibility of producing hyperglycemia) and close monitoring of blood glucose until the patient is out of danger.

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

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Glimepiride (Norizec®) 1 mg Tablet, in blister pack x 10s (box of 60s)
Glimepiride (Norizec®) 2 mg Tablet, in blister pack x 10s (box of 60s)
Glimepiride (Norizec®) 3 mg Tablet, in blister pack x 10s (box of 60s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

Manufactured by **AMHERST LABORATORIES, INC.**
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare

Date of Revision: March 2018

Norizec 1 mg Tablet (DR-XY37555)
Date of First Authorization: March 2010

Norizec 2 mg Tablet (DR-XY37556)
Date of First Authorization: March 2010

Norizec 3 mg Tablet (DR-XY37554)
Date of First Authorization: March 2010

P300000021897

Reg. IPOPHIL