Gliclazide

Glubitor®-OD
30 mg Modified-Release Tablet
oral hypoglycemic

FORMULATION
Each modified-release tablet contains:
Gliclazide …….. 30 mg

PRODUCT DESCRIPTION
Gliclazide (Glubitor®-OD) 30 mg is a modified-release, white, plain, elliptical tablet intended for once-daily dosing to improve patient compliance and glycemic control in patients with type 2 diabetes.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Gliclazide is a sulfonylurea oral antidiabetic agent whose primary action is to increase the sensitivity of the β-cells from the pancreas. It potentiates glucose-stimulated insulin secretion from functioning pancreatic islet β-cells inhibiting ATP-sensitive potassium (K^+-ATP) channels resulting in depolarization which opens voltage-sensitive calcium channels and brings about influx of calcium that triggers insulin release.

As with other sulfonylureas, gliclazide has actions on peripheral tissues. Gliclazide enhances glycogen synthesis and inhibits glycogenolysis and gluconeogenesis in the liver. Gliclazide may also improve peripheral glucose uptake in muscles.

Pharmacokinetics
Gliclazide is readily absorbed from the gastrointestinal tract although systemic bioavailability of an oral dose may vary considerably depending more on first- pass metabolism than absorption.

After an 80 mg dose of the immediate release preparation in normal volunteers, the average time to reach peak plasma concentration is about 4-6 hours. Gliclazide is about 95% bound to plasma proteins, mostly to albumin. Its volume of distribution is low. It has a mean plasma half-life of about 10-12 hours.

Gliclazide modified-release (Gliclazide OD) is a once-daily gliclazide formulation. The progressive release of gliclazide in this formulation parallels the 24-hour glycemic profile in untreated patients with type 2 diabetes. Gliclazide OD is highly bioavailable and its absorption is unaffected by food intake.

The following are important pharmacokinetic parameters of Gliclazide OD in adult volunteers who received 60 mg (2 tablets) single oral dose:

Parameters	Gliclazide OD (Glubitor OD)
1. Tmax (hour)	8
2. Cmax ± S.D. (mcg/mL)	2.4 ± 0.89
3. $AUC_{0\text{-}24h}$ ± S.D. (mcg-h/mL)	65.22 ± 21.77
Tmax = time the drug reached its maximum concentration in the blood *Cmax = maximum concentration of the drug at peak time* *$AUC_{0\text{-}24}$ = area under the curve from blood level profile*	

Gliclazide OD's apparent clearance in type 2 diabetic patients is 0.9 L/h and its apparent volume of distribution is 19 L; the effective half-life is approximately 16 hours.

Gliclazide is distributed to the extracellular fluid, with high concentrations found in the liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue in animals. Gliclazide has been also shown to cross the placental barrier and penetrate the fetus.

Gliclazide is extensively metabolized with about <1% excreted in the urine unchanged. Approximately 60-70% of the administered dose appears to be excreted in the urine and 10-20% excreted in the feces.

The metabolism and excretion of sulfonylureas such as gliclazide may be slowed in patients with impaired renal and hepatic function.

INDICATION
Type 2 diabetes mellitus uncontrolled by diet and exercise.

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:

- There is usually no fixed dosage regimen with any hypoglycemic agent for the management of diabetes mellitus. Adjust dose according to patient's response.

- Monitor glycemic control through frequent measurements of fasting blood glucose and periodic testing of glycosylated hemoglobin (HbA_{1c}). These measurements are important in determining the minimum effective dose for the patient, detecting primary failure (i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication), and detecting secondary failure (i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness).

- Fever, trauma, infection, or surgical intervention may affect blood glucose control in patients receiving anti-diabetic treatment. These patients should be closely monitored and administration of insulin may be required.

- Hepatic function should be assessed prior to initiation and periodically thereafter in patients with impaired hepatic function.

- Periodic monitoring and special care is required in the elderly especially those who are malnourished, and those with impaired hepatic, renal, or adrenal function.

Dosage Format	**Recommended Oral Dose** *(To be taken orally, preferably at the same time each morning)*
Glubitor-OD 30 mg Modified-Release Tablet *(Swallow tablet whole. Do not chew or crush.)*	**Recommended Dose:** 30-120 mg (1 to 4 tablets) taken once daily. **Recommended Initial Dose:** 30 mg (1 tablet) taken once daily. • Titration of dosage may be done in increments of 30 mg at 2-4 week intervals. • Gliclazide 30 mg modified-release tablet can replace an antidiabetic treatment without any transitional period. However, if a patient is switched from a hypoglycemic sulfonylurea with a prolonged half-life such as chlorpropamide, careful monitoring is required for 1 to 2 weeks to avoid hypoglycemia. • Maturity onset diabetes with no ketoacidosis or history of metabolic decompensation and whose insulin requirements are less than 40 units per day may be considered for the delayed-release

	preparation after cessation of insulin. **Usual Oral Maintenance Dose:** 60 mg (2 tablets) taken once daily. **Maximum Daily Dose:** 120 mg (4 tablets)
	Or, as recommended by a physician.

CONTRAINDICATIONS

- Hypersensitivity to gliclazide, other sulfonylureas, sulfonamides, or to any ingredient in this product
- Type 1 diabetes mellitus
- Unstable or brittle diabetes
- Severe renal or hepatic insufficiency
- Diabetes complicated by ketosis and acidosis
- Diabetic pre-coma and coma
- Use in pregnant and breastfeeding women is contraindicated
- Treatment with miconazole via systemic route or oromucosal gel drugs (See **INTERACTIONS WITH OTHER MEDICAMENTS**)
- During stress conditions, e.g., serious infection, trauma or surgery

WARNINGS AND PRECAUTIONS

Development of complications peculiar to diabetes mellitus (e.g., heart disease, blindness, kidney disease, hypertension, nerve damage, etc.) will not be prevented by the use of gliclazide.

Gliclazide should not be used as a substitute for diet. It must be considered only as an additional treatment to proper dietary regimen.

Administration of gliclazide over a long period of time decreases its efficacy in many patients. This may be due to continuing depletion of β-cell reserve. Discontinue the use of gliclazide if a loss of adequate blood glucose-lowering response is detected. Insulin therapy may be required in these patients.

Hypoglycemia

All sulfonylureas, including gliclazide, may cause severe hypoglycemia. Debilitated or malnourished patients, those with adrenal, pituitary, renal or hepatic insufficiency and patients controlled with diet alone are particularly susceptible to the hypoglycemic action of gliclazide. Use of gliclazide in combination with other oral hypoglycemic agents may increase the potential for hypoglycemia.

Inadequate caloric intake, severe or prolonged exercise, and alcohol ingestion may also increase the risk of hypoglycemia.

Gliclazide overdose, certain endocrine disorders (i.e., thyroid disorders, hypopituitarism and adrenal insufficiency) as well as withdrawal of prolonged and/or high dose corticosteroid therapy, severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease) and concomitant administration of certain drugs (See **INTERACTIONS WITH OTHER MEDICAMENTS**) may also increase the risk of hypoglycemia.

The following measures are recommended to reduce the risk of hypoglycemia:

- initiate treatment of type 2 diabetes mellitus by diet alone, if possible,
- take into account the patient's age: blood sugar levels not strictly controlled by diet alone might be acceptable in the elderly
- adjust gliclazide dose according to the blood glucose response and to the 24-hour urinary glucose during the first days of treatment.

Patients with mild symptoms of hypoglycemia such as sweating, pallor, hunger pangs, tachycardia, sensation of malaise may require treatment with oral glucose and adjustments in gliclazide dose and/or meal patterns.

Loss of Control of Blood Glucose
Exposure to stress such as fever, trauma, infection, or surgery may lead to loss of glycemic control. Temporary discontinuation of oral hypoglycemic therapy and administration of insulin may be necessary in such cases.

Progression of the severity of diabetes may lead to secondary failure or decreased effectiveness of any hypoglycemic drug (including gliclazide). Adequate assessment of dosage adjustment and diet adherence is necessary before classifying secondary failure in a patient. Insulin therapy should be initiated in patients who experience secondary failure after therapy with gliclazide.

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 sulfonyurea, 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 sulfonylureas 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.

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.

Transferring to Gliclazide
Patients who have been previously treated with sulfonylureas or biguanides alone or in combination may be transferred to gliclazide alone or in combination with other oral antidiabetics. Careful observation is essential during the transitional phase.

Generally, it is not recommended that insulin treated patients be transferred to gliclazide.

Renal and Hepatic Insufficiency
Treatment with gliclazide (i.e., initial dosing, dose increments, and maintenance dose) in patients with renal and hepatic insufficiency should start in small doses to avoid hypoglycemic reactions. Careful patient monitoring is also recommended since the metabolism and excretion of sulfonylureas such as gliclazide may be slowed in patients with impaired renal and hepatic function.

Effects on Ability to Drive or Use Machines
Patients who need to perform activities requiring mental alertness or physical coordination should avoid gliclazide since it may affect concentration if diabetes is not satisfactorily controlled (usually at the beginning of treatment).

INTERACTIONS WITH OTHER MEDICAMENTS
Hepatic enzyme inhibitors such as sulfonamides, tuberculostatics, clarithromycin, phenylbutazone, clofibrate, coumarin derivatives, salicyclates, nonsteroidal anti-inflammatory agents (NSAIDs), probenecid, beta-blockers (e.g., propranolol), tetracycline compounds, chloramphenicol, azole antifungal agents (e.g., miconazole, ketoconazole, itraconazole), H2-receptor antagonists (e.g., cimetidine), disopyramide and angiotensin-converting enzymes (ACE)

inhibitors (e.g., captopril and enalapril), and monoamine oxidase (MAO) inhibitors may increase gliclazide's hypoglycemic effect.

Inducers of hepatic enzymes such as rifampicin, barbiturates, thyroid hormones and phenytoin may lower gliclazide's plasma concentration.

Concomitant administration with anticoagulants (*warfarin* and other anticoagulants) may lead to potentiation of anticoagulation. Adjustment of anticoagulant dosage may be necessary.

Drugs that induce hyperglycemia leading to a loss of control of blood sugar: diuretics (thiazides, furosemide), corticosteroids and tetracosactrin, danazol, chlorpromazine, ritodrine/salbutamol/terbutaline (IV), oral contraceptives (estrogens plus progestogens, and nicotinic acid in pharmacologic doses.

Acute or chronic alcohol intake may unpredictably potentiate or reduce the activity of gliclazide.

STATEMENT OF USAGE IN HIGH-RISK GROUPS

Pregnancy Category C

Oral hypoglycemic agents (including gliclazide) are not recommended during pregnancy. Maintaining blood glucose levels as close to normal as possible is necesssary during pregnancy since abnormal blood glucose levels are associated with a higher incidence of congenital abnormalities. Insulin is recommended during pregnancy.

Lactation

It is not known whether breastfeeding will lead to exposure of the human infant to gliclazide. However, gliclazide should not be used by breastfeeding mothers since other sulfonylureas have been found in human milk. Discontinue use in breastfeeding mothers because of potential hypoglycemia in breastfeeding infants. Consider insulin therapy for adequate glycemic control if gliclazide is discontinued.

Geriatrics

Elderly patients are particularly susceptible to hypoglycemia. Moreover, hypoglycemia may be difficult to recognize in the elderly. Carefully determine the appropriate initial dose, dose increments and maintenance dose to avoid hypoglycemic episodes.

Infants and Children

The safety and efficacy of gliclazide in children have not been established. Gliclazide is not recommended for use in infants and children.

UNDESIRABLE EFFECTS

Metabolic-Nutritional: Hypoglycemia characterized by weakness, nervousness, shakiness, paresthesia, and coma. Severe hypoglycemia which mimics acute CNS disorders may also occur. Predisposing factors may include hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism, adrenal or pituitary insufficiency.

Hyperglycemia, lipid metabolism disorder, gout, glycosuria, hypercholesterolemia, hypertriglyceridemia, hyperlipemia, and thirst have also been reported.

Gastrointestinal: Nausea, vomiting, heartburn, gastroesophageal reflux, anorexia, diarrhea, constipation, abdominal pain, dyspepsia, gastric irritation, gastritis, gastroenteritis, anal fissure, colitis, duodenal ulcer, epigastric fullness, fecal incontinence, flatulence and metallic taste; other adverse effects include GI neoplasm benign, hemorrhoids, melena, dry mouth, saliva increased, toothache, and tooth disorder.

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

enzyme levels (AST, ALT, alkaline phosphatase). Discontinue treatment if cholestatic jaundice appears.

Dermatological: Allergic reactions (e.g., pruritus, rash, erythema, urticaria, morbilliform or maculopapular rash, bullous reactions), porphyria cutanea tarda, photosensitivity reactions, fungal dermatitis, dermatitis, skin disorder, eczema, hyperkeratosis, nail disorder, onychomycosis, dry skin, and skin ulceration have been reported.

Hematologic: Hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia, pancytopenia, erythrocytopenia, and allergic vasculitis.

Cardiovascular: Arteritis, cardiac failure, cerebrovascular disorder, coronary artery disorder, epistaxis, hypotension, hypertension, angina pectoris, myocardial infarction, edema legs, palpitations, tachycardia, thrombophlebitis, and vein disorder.

Endocrine Reactions: Hypothyhroidism - a report of decreased uptake of radioactive iodine by the thyroid gland has been reported with sulfonylurea drugs. This has not been shown with the use of gliclazide 80 mg in a small study involving 15 patients.

Respiratory: Rhinitis, bronchitis, pharyngitis, upper respiratory infection, coughing, pneumonia, dyspnea, asthma, tracheitis, and sinusitis.

CNS: Disulfiram-like reactions, anxiety, confusion, nervousness, dizziness, depression, insomnia, and neuralgia.

Urinary: Urinary tract infections, increased urinary frequency, albuminuria, cystitis, nocturia, polyuria, renal calculus, and renal cyst.

Musculoskeletal: Back pain, arthralgia, arthrosis, arthropathy, bursitis, hernia congenital, skeletal pain, spine malformation, arthritis, tendinitis, and myalgia.

Reproductive: Balanoposthitis, benign female breast neoplasm, impotence, mastitis, menstrual disorder, prostatic disorder, and vaginitis.

EENT: Conjunctivitis, visual disturbance/abnormal vision, cataract, conjunctival hemorrhage, diplopia, glaucoma, abnormal lacrimation, retinal disorder, vitreous disorder, xerophthalmia, otitis media, hearing decreased, tinnitus, and impaired speech disorder.

Body as a Whole: Headache, asthenia, allergy, carpal tunnel syndrome, chest pain, sweating, viral infection, infection, fungal infection, leg pain, malaise, pain.
Miscellaneous: Inflicted injury.

OVERDOSAGE AND TREATMENT
Overdosage with gliclazide and other sulfonylureas will likely result in hypoglycemia which may need to be treated with intravenous infusion of 5% glucose for 12 to 14 hours with frequent monitoring of blood glucose level. Potassium levels should also be monitored. Cerebral edema may also need to be treated in unusually severe cases.

In comatose patients, glucagon injection may be administered before intravenous glucose therapy although this may induce vomiting. Efficacy of this treatment will also be dependent on hepatic glycogen status.

In severe sulfonylurea overdose, diazoxide and octreotide may reduce insulin secretion and hypoglycemia.

Continue frequent oral feeding and blood glucose and potassium monitoring until recovery.

AVAILABILITY
Glilclazide (Glubitor®-OD) 30 mg Modified-Release Tablet, in blister pack x 10s (box of 60s)

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.

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