Metformin HCl

Glumet® 500 mg Tablet
Glumet® 1 g Tablet
Glumet®-XR 500 mg Extended-Release Tablet

oral hypoglycemic

℞

FORMULATION
Each tablet contains:
Metformin hydrochloride ..... 500 mg or 1 g

Each extended-release tablet contains:
Metformin hydrochloride ..... 500 mg

PRODUCT DESCRIPTION
500 mg Tablet: White, round tablet, plain on one side and with "LRII" logo on the other side
1 g Tablet: White to off-white, elliptical tablet, bisected on one side and plain on the other side
500 mg Extended-Release Tablet: White, elliptical, plain, biconvex tablet

CLINICAL PHARMACOLOGY
Pharmacodynamics
Metformin is a biguanide antidiabetic agent that reduces both basal and postprandial plasma glucose concentrations in patients with type 2 diabetes mellitus by improving both peripheral and hepatic sensitivity to insulin. It does not stimulate insulin secretion and therefore does not produce hypoglycemia when used alone. Fasting insulin levels and day-long insulin response remain the same or may even decrease with metformin therapy.

Metformin may act via three mechanisms: It reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; increases insulin sensitivity in the skeletal muscles and adipocytes, improving peripheral glucose uptake and utilization; delays intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. It also increases the transport capacity of all types of membrane glucose transporters.

Metformin has demonstrated modest favorable effects on lipid metabolism in patients with type 2 diabetes. It lowers total cholesterol, mean fasting serum triglycerides and low density lipoprotein cholesterol levels; it has no adverse effects on other lipid levels.

Pharmacokinetics
Metformin HCl immediate-release (Glumet®) 1 g tablet and extended-release (Glumet®-XR) 500 mg tablet were shown to be bioequivalent to the reference product (innovator) in adults under fasting conditions. The following are important pharmacokinetic parameters of metformin in adult volunteers who received immediate-release metformin HCl (Glumet®) 1 g tablet (as a single oral dose) and extended-release metformin HCl (Glumet®-XR) 500 mg tablet (two 500-mg tablets given once a day for three days) under fasting conditions:

Pharmacokinetic Parameters	Immediate-release metformin HCl 1 g tablet	90% Confidence Interval
Tmax (hour)	1.69 ± 0.7	
Cmax ± S.D. (mcg/mL)	2.29 ± 0.6237	95.832 – 112.079
$AUC_{0\text{-}24h}$ ± S.D. (mcg-h/mL)	11.45 ± 3.94	99.685 – 112.259
$AUC_{0\text{-}inf}$ ± S.D. (mcg-h/mL)	12.12 ± 3.94	100.198 – 111.537
Kel (mcg/mL/hour)	0.24 ± 0.06	
$T_{1/2}$ (hour)	3.23 ± 1.62	

Tmax = time the drug reached its maximum concentration in the blood
Cmax = maximum plasma concentration of the drug at peak time
$AUC_{0\text{-}24h}$ = area under the curve from blood level profile (from zero to sampling time point)
$AUC_{0\text{-}inf}$ = area under the curve from blood level profile (extrapolated to infinity)
Kel = elimination rate constant
$T_{1/2}$ = elimination half-life

Pharmacokinetic Parameters	Extended-release metformin HCl 2 x 500 mg tablet given once a day for three days	90% Confidence Interval
$Tmax_{ss}$ (hour)	3	
$C_{ss,\ ave}$ ± S.D. (mcg/mL)	0.40 ± 0.13	
$C_{ss,\ max}$ ± S.D. (mcg/mL)	1.32 ± 0.47	93.09 – 111.38
$AUC_{0\rightarrow TSS}$ ± S.D. (mcg-h/mL)	9.56 ± 3.05	87.71 – 117.35

$Tmax_{ss}$ = time the drug reached its maximum concentration in blood at steady state
$C_{ss,\ ave}$ = average plasma concentration at steady state
$C_{ss,\ max}$ = maximum plasma concentration at steady state
$AUC_{0\rightarrow TSS}$ = area under the concentration-time curve at steady state for one dosing interval

Metformin HCl is slowly and incompletely absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of metformin HCl tablet under fasting conditions is approximately 50 to 60% with metformin HCl doses of 500 mg to 1,500 mg. Single doses of metformin HCl 500 mg to 1,500 mg show lack of dose proportionality with increasing doses which is due to decreased absorption rather than altered elimination.

Metformin HCl extended-release tablet is intended for once-a-day dosing. Once-a-day dosing is possible through control of metformin release rate and prolonging absorption in the upper gastrointestinal tract.

Metformin distributes rapidly to peripheral body tissues and fluids. It also appears to distribute slowly into erythrocytes and into a deep tissue compartment. Metformin is negligibly bound to plasma proteins. Steady-state plasma concentrations of metformin are generally <1 mcg/mL and are reached within 24 to 48 hours at usual clinical doses and dosing schedules.

Renal elimination of metformin is via glomerular filtration and secretion by the proximal convoluted tubules as unchanged drug. The principal plasma elimination half-life of metformin is about 6.2 hours with 90% of the total dose being cleared within 24 hours in patients with normal renal function. In the blood, the elimination half-life is about 17.6 hours.

Special Population
Renal Insufficiency
The plasma and blood half-life of metformin is prolonged and the renal clearance decreased in proportion to the decrease in creatinine clearance in patients with decreased renal function (based on measured creatinine levels).

Geriatrics
The limited pharmacokinetic data of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. It appears that the change in metformin pharmacokinetics with aging is primarily related to a change in renal function.

Pediatrics
After oral administration of a single metformin HCl 500 mg tablet with food, C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years old) compared with healthy adults (20 to 45 years old), all with normal renal function.

The safety and efficacy of metformin HCl extended-release tablet has not been established in pediatric patients. Pharmacokinetic studies have not been conducted in these patients.

INDICATION
As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

Metformin may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:
- There is usually no fixed dosage regimen with any antidiabetic agent for the management of hyperglycemia in patients with diabetes mellitus. Dosage of metformin HCl tablets must be individualized based on both effectiveness and tolerance while not exceeding the maximum recommended daily doses.
- During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to metformin HCl tablet and identify the minimum effective dose. Thereafter, glycosylated hemoglobin (HbA_{1c}) should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of metformin when used as monotherapy or in combination with other oral antidiabetic agents or insulin.
- Monitoring of glycemic control through frequent measurements of fasting blood glucose and periodic testing of HbA_{1c} will detect primary failure (i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication), and secondary failure (i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness).
- It is recommended that metformin HCl be administered with meals to ensure optimum delivery of metformin to the systemic circulation and minimize gastric intolerance. Administration of metformin in the fed state has been shown to significantly increase the systemic delivery of metformin compared to the fasted state.

RECOMMENDED ADULT (17 years and older) ORAL DOSING SCHEDULE	
Metformin HCl 500 mg or 1 g Tablet	• ***Usual Starting Dose:*** 500 mg twice a day, with meals • Dosage may be increased in increments of 500 mg weekly, up to a **maximum of 2,500 mg per day** given in divided doses with meals. Doses of 1 g may be given as 1 g tablet or two 500-mg tablets. • Dosage above 2,000 mg may be better tolerated if given in three divided doses with meals.
Metformin HCl 500 mg Extended-Release Tablet	***Swallow the extended-release tablet whole.*** ***Do not chew or crush.*** • ***Usual Starting Dose:*** 500 mg once a day with the evening meal • Dosage may be increased in increments of 500 mg weekly up to a **maximum of 2,000 mg once daily** with the evening meal. • If glycemic control with metformin extended-release 2,000 mg once daily remains unsatisfactory, a dose of 1,000 mg twice daily may be considered.
	Advice to patients The matrix core of metformin HCl extended-release tablet usually is broken up in the gastrointestinal tract, but patients should be advised that occasionally the biologically inert compounds of the tablet may remain intact and be passed in the stool as a soft, hydrated mass that may resemble the original tablet.

Recommended Oral Dose of Immediate-Release Metformin Tablet in Children 10 to 16 years Old with Type 2 Diabetes Mellitus
Usual starting dose: 500 mg twice a day, given with meals
- Dosage may be increased by 500 mg weekly up to a maximum of 2,000 mg daily given in divided doses.
- The efficacy and safety of extended-release metformin in pediatric patients have not been established.

Transfer from Metformin HCl Immediate-Release Tablet to Metformin HCl Extended-Release Tablet
In patients already treated with metformin HCl immediate-release tablet, the starting dose of metformin HCl extended-release tablet should be equivalent to the daily dose of metformin HCl immediate-release tablet. Switching to metformin HCl extended-release is not recommended in patients treated with metformin HCl immediate-release at doses above 2,000 mg daily. If glycemic control is still not achieved with metformin HCl extended-release tablets 2,000 mg daily, patients may be switched to metformin HCl immediate-release tablets up to a maximum dose of 3,000 mg daily.

Transfer from Other Antidiabetic Therapy
No transition period is generally necessary when transferring patients from standard oral hypoglycemic agents other than chlorpropamide. When transferring patients from chlorpropamide, exercise caution during the first two weeks because overlapping drug effects and hypoglycemia may occur due to prolonged retention of chlorpropamide in the body.

Concomitant Metformin and Oral Sulfonylurea Therapy
- Gradual addition of an oral sulfonylurea while continuing maximum dose metformin therapy may be considered in patients who have not responded to four weeks of maximum dose metformin therapy.
- Consider alternative therapies such as insulin (with or without metformin) if response to 1 to 3 months maximum dose of sulfonylurea and metformin combination therapy remains unsatisfactory.

Concomitant Metformin and Insulin Therapy
- The current insulin dose should be continued upon initiation of metformin therapy.
- ***Initial Oral Dose of Metformin HCl Tablet:*** 500 mg once a day
- Metformin dose may be increased by 500 mg after approximately one week and by 500 mg every week thereafter until adequate glycemic control is achieved.
- ***Maximum Recommended Daily Dose with Insulin:*** 2,500 mg
- It is recommended that the insulin dose be reduced by 10 to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL. Individualize further dose adjustments based on patient response in patients receiving metformin with insulin.

Or, as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to metformin HCl or to any ingredient in the product
- Unstable and/or type 1 (insulin-dependent) diabetes mellitus
- History of lactic acidosis irrespective of precipitating factors
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. ***Treat diabetic ketoacidosis with insulin.***
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- Acute conditions with the potential to alter renal function such as:
  - Dehydration due to persistent or severe diarrhea, recurrent vomiting
  - Severe infection
  - Diagnostic examinations (e.g., intravenous urography, angiography) that would involve the use of iodinated contrast agents/media
- Acute or chronic disease which may cause tissue hypoxia such as:
  - Cardiac or respiratory failure
  - Recent myocardial infarction
  - Shock
- Acute or chronic alcoholism
- Severe liver disease
- Pregnancy or breastfeeding

WARNINGS AND PRECAUTIONS

Warning on Lactic Acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia.

Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), reduced blood pH, electrolyte disturbance with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found.

Lactic acidosis is usually accompanied by nonspecific symptoms such as acidotic dyspnea, vomiting, abdominal pain with muscle cramps, and/or a general feeling of malaise with severe fatigue. Hypothermia followed by coma, hypotension, and resistant bradyarrhythmias may be seen with marked acidosis. Instruct patients to immediately alert their physicians if these symptoms occur. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful.

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Do not use metformin in patients with congestive heart failure receiving drugs such as digoxin and furosemide because of the risk of hypoperfusion and hypoxemia which may lead to lactic acidosis.

Monitoring of Renal Function
Impaired renal function would increase the risk of metformin accumulation and lactic acidosis. Renal function should be assessed and verified as normal before initiation of metformin therapy. Estimated glomerular filtration rate (eGFR) should be determined at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Initiating metformin therapy in patients with eGFR between 30 to 45 mL/min/1.73 m^2 is not recommended. In patients taking metformin whose eGFR later falls below 45 mL/min/1.73 m^2, the benefits and risks of continuing treatment should be assessed. Discontinue metformin if the patient's eGFR later falls below 30 mL/min/1.73 m^2.

Medications which may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin (i.e., cationic drugs) should be used with caution since these drugs are eliminated by renal tubular secretion.

Macrovascular Outcomes
Macrovascular risk reduction with the use of metformin or any antidiabetic drug has not been established in clinical studies.

Radiologic Studies
Administration of parenteral iodinated contrast agents has led to an acute decrease in renal function and the occurrence of lactic acidosis in patients receiving metformin. Discontinue metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2, history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart metformin if renal function is stable.

Hypoxic States
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. Promptly discontinue metformin when such events occur in patients on metformin therapy.

Surgical Procedures
Temporarily discontinue metformin use in patients undergoing surgery associated with restricted food or fluid intake. Metformin therapy may be reinstituted when the patient's oral intake has resumed and renal function has been found normal.

Impaired Hepatic Function
Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease since impaired hepatic function has been associated with lactic acidosis.

Alcohol
Combined use of alcohol and metformin may increase the risk of hypoglycemia and lactic acidosis since alcohol decreases lactate clearance and hepatic gluconeogenesis, and may increase insulin secretion. Excessive alcohol intake on an acute or chronic basis should be avoided in patients receiving metformin.

Vitamin B_{12} Levels
Evaluate hematologic parameters prior to initiation of metformin therapy and at least annually since decreases in serum vitamin B_{12} have been associated with metformin use.

Hypoglycemia
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemia. It may be difficult to recognize hypoglycemic states in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Maintaining Adequate Glycemic Control during Periods of Stress
Temporary discontinuation of metformin and administration of insulin may be necessary in periods of stress such as fever, trauma, infection, or surgery to maintain adequate glucose control. Metformin may be reinstituted after the acute episode is resolved.

Effects on Ability to Drive and Use Machines
Patients should be warned about driving a vehicle or operating machinery under conditions where risk of hypoglycemia is present.

INTERACTIONS WITH OTHER MEDICAMENTS
Cationic Drugs: Cationic drugs such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin that are eliminated by renal tubular secretion, theoretically may cause an increase in metformin peak plasma concentrations, whole blood concentrations and whole blood AUC by competing with metformin for common renal tubular transport systems. Concomitant administration of metformin and cimetidine has been observed to result in reduced urinary metformin excretion and increased plasma metformin concentrations.

Other Antidiabetic Agents: Hypoglycemia may occur when metformin is used concomitantly with other antidiabetic agents such as sulfonylureas, meglitinides, glitazones, or insulin.

Diuretics: Thiazide diuretics may exacerbate diabetes mellitus and may result in increased requirements of oral antidiabetic agents, metformin included. Temporary loss of diabetic control or secondary failure to the antidiabetic agent may also occur. Potassium-sparing diuretics, which are less diabetogenic, may be considered as a substitute. Furosemide may increase metformin plasma and blood concentrations and blood AUC without significantly affecting metformin renal clearance.

Nifedipine: Nifedipine increases the absorption, C_{max} and AUC of metformin, and increases metformin excretion in the urine. Metformin has minimal effects on nifedipine pharmacokinetics.

β-Adrenergic Blocking Agents: β-adrenergic blocking agents (e.g., propranolol, nadolol) may impair glucose tolerance and mask the true frequency or severity of hypoglycemia, block hypoglycemia-induced tachycardia but not hypoglycemic sweating, delay the rate of recovery of blood glucose concentration following drug-induced hypoglycemia, and impair peripheral circulation. Use these drugs with caution in patients with type 2 diabetes.

Protein-Bound Drugs: Interaction of metformin and highly protein-bound drugs (e.g., salicylates, sulfonamides, chloramphenicol, probenecid) is unlikely because metformin is negligibly bound to plasma proteins.

Angiotensin-Converting Enzyme (ACE) Inhibitors: ACE inhibitors (e.g., captopril, enalapril) may reduce fasting blood glucose concentrations. These drugs have also been associated with unexplained hypoglycemia in diabetic patients. Caution should be exercised when administering metformin together with ACE inhibitors to prevent severe hypoglycemia.

Alcohol: There is an increased risk of hypoglycemia and lactic acidosis when alcohol and metformin are used concomitantly since alcohol decreases lactate clearance and hepatic gluconeogenesis, and may increase insulin secretion. Acute or chronic intake of alcohol should be avoided in patients receiving metformin therapy.

Clomifene: Ovulatory response may be increased when clomifene and metformin are used concomitantly in premenopausal patients with polycystic ovary syndrome.

Anticoagulants: Metformin may affect the pharmacokinetic properties of coumarin anticoagulants when administered concomitantly. An increase in prothrombin time may occur upon cessation of metformin therapy, with an increased risk of hemorrhage. Patients receiving phenprocoumon or other vitamin K anticoagulants should be carefully monitored.

Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation with the risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the procedure, and withheld for 48 hours afterwards. Metformin may be reinstituted only after renal function has been re-evaluated and found to be normal.

Glyburide: Concomitant administration of metformin and glyburide produced no changes in metformin pharmacokinetics and pharmacodynamics. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. The clinical significance of this finding was unclear.

Others: Drugs that may cause hyperglycemia and may exacerbate loss of glycemic control in patients with diabetes include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn in patients.
The pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies in healthy volunteers.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy: Pregnancy Category B. Oral hypoglycemic agents (including metformin) are not recommended during pregnancy. Maintaining blood glucose levels as close to normal as possible is necessary during pregnancy since abnormal blood glucose levels are associated with a higher incidence of congenital abnormalities. Insulin is recommended during pregnancy.

Lactation: Metformin is excreted into human milk and should therefore not be used by breastfeeding mothers. The importance of metformin to the mother should be considered when deciding whether to discontinue breastfeeding or discontinue metformin because the potential for hypoglycemia in breastfeeding infants may exist. Consider insulin therapy for adequate glycemic control if metformin is discontinued.

Elderly: Aging is associated with reduced renal function and metformin is known to be substantially excreted in the kidney. The risk of serious adverse reactions to metformin is greater in patients with reduced/impaired renal function especially in the elderly. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, dose of elderly patients should not be titrated to the maximum dose. Metformin treatment should not be initiated in patients ≥80 years old unless creatinine clearance demonstrates that renal function is not reduced.

Children: The use of metformin HCl immediate-release tablet has been established in pediatric patients 10 to 16 years old with type 2 diabetes.

The safety and efficacy of metformin HCl extended-release tablet have not been established in these patients.

UNDESIRABLE EFFECTS
Metformin may provoke or augment lactic acidosis particularly if it is present in high concentrations in the blood. Some of the symptoms of lactic acidosis may mimic certain adverse effects of metformin. Physicians should instruct their patients to recognize the onset of symptoms of lactic acidosis to avoid this adverse reaction.

The most frequent adverse effects reported with metformin include nausea, vomiting, diarrhea, abdominal pain and loss of appetite. These adverse effects occur during initiation of treatment and resolve spontaneously in most cases.

Blood and lymphatic system disorders: Decrease in serum vitamin B_{12}, megaloblastic anemia (rare); serum folic acid concentrations do not appear to decrease substantially in patients receiving metformin

Metabolism and nutrition disorders: Hyperglycemia, hypoglycemia (may occur when metformin is given concomitantly with sulfonylureas and/or alcohol), lactic acidosis, weight decreased

Nervous system disorders: Agitation, dizziness, headache, lightheadedness

Cardiac disorders: Chest discomfort, palpitations

Vascular disorders: Flushing, hypertension

Respiratory, thoracic and mediastinal disorders: Dyspnea, flu syndrome, pneumonitis with vasculitis, rhinitis, upper respiratory infection

Gastrointestinal disorders: Abdominal discomfort (e.g., bloating, abdominal cramps), abdominal distention, abnormal stools/loose stools, anorexia, constipation, dry mouth, dyspepsia/heartburn, epigastric discomfort, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, indigestion, taste disturbance specifically metallic taste in the mouth

Hepatobiliary disorders: Abnormal liver function tests, autoimmune hepatitis, cholestasis, hepatic injury, hepatitis

Skin and subcutaneous tissue disorders: Erythema, nail disorder, pruritus, rash, skin lesion, urticaria

Musculoskeletal and connective tissue disorders: Asthenia, chills, musculoskeletal pain, myalgia

Renal and urinary disorders: Urinary tract infection

General disorders and administration site conditions: Fatigue, increased sweating

OVERDOSE AND TREATMENT
There were no cases of overdose reported in clinical studies. Symptoms of metformin overdose include extensions of the common adverse effects (e.g., epigastric discomfort, nausea, vomiting, diarrhea, drowsiness, weakness, dizziness, malaise, and headache). Should these symptoms occur, lactic acidosis should be excluded. Metformin therapy should be discontinued and proper supportive therapy should be instituted.

Metformin ingestion of up to 50 g has been reported. Hypoglycemia was reported in 10% of cases, but no causal relationship with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

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
Metformin hydrochloride (Glumet®) 500 mg Tablet, in flex foil x 4s (box of 100s)
Metformin hydrochloride (Glumet®) 1 g Tablet, in flex foil x 4s (box of 100s)
Metformin hydrochloride (Glumet®-XR) 500 mg Extended-Release Tablet, in flex foil x 4s (box of 100s)

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

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Glumet 1 g Tablet (DR-XY33796)
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Reg. IPOPHIL