GLYSTOR plus®

Glyburide and Metformin hydrochloride tablets

QUALITATIVE AND QUANTITATIVE DESCRIPTION

GLYSTOR plus® tablets are available for oral administration in two strengths as:

- pink, round, quadrisect film-coated tablets containing 2.5 mg Glyburide and 500 mg metformin hydrochloride / tab as active ingredients.
- yellow, round, quadrisect film-coated tablets containing 5 mg Glyburide and 500 mg metformin hydrochloride / tab as active ingredients.

The tablet core excipients are: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The film coating of GLYSTOR plus® (2.5 mg/500 mg) contains: lactose monohydrate, hypromellose, titanium dioxide, polyethylene glycol 4000, iron oxide yellow, iron oxide red and iron oxide black. The film coating of GLYSTOR plus® (5 mg/500 mg) contains: lactose monohydrate, hypromellose, titanium dioxide, polyethylene glycol 4000, quinoline yellow aluminum lake, iron oxide yellow and iron oxide red.

INDICATIONS AND USAGE

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class.

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of type 2 diabetes.

Glyburide / Metformin HCl tablets are indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Glyburide / Metformin HCl tablets are indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes.

CONTRAINDICATIONS

Glyburide / Metformin HCl tablets are contraindicated in patients with:

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to metformin hydrochloride or glyburide.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Glyburide / Metformin HCl tablets should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

WARNINGS

Metformin Hydrochloride

Lactic Acidosis: lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Glyburide / Metformin HCl tablets; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances 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 µg/mL are generally found.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Glyburide / Metformin HCl tablets should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Glyburide / Metformin HCl tablets, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Glyburide / Metformin HCl tablets do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Glyburide / Metformin HCl tablets, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. The patient should be informed of the potential risks and benefits of glyburide and of alternative modes of therapy.

PRECAUTIONS

General:

Glyburide / Metformin HCl tablets: *Hypoglycemia*: Glyburide / Metformin HCl tablets are capable of producing hypoglycemia or hypoglycemic symptoms; therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both glyburide and metformin hydrochloride and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Metformin Hydrochloride: *Monitoring of renal function*: metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Glyburide / Metformin HCl tablets. In patients with advanced age, Glyburide / Metformin HCl tablets should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, Glyburide / Metformin HCl tablets should not be titrated to the maximum dose. Before initiation of Glyburide / Metformin HCl therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Glyburide / Metformin HCl tablets discontinued if evidence of renal impairment is present.

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, Glyburide / Metformin HCl tablets should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

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. When such events occur in patients on Glyburide / Metformin HCl therapy, the drug should be promptly discontinued.

Surgical procedures: Glyburide / Metformin HCl therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake: alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Glyburide / Metformin HCl tablets. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired hepatic function: since impaired hepatic function has been associated with some cases of lactic acidosis, Glyburide / Metformin HCl tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels: in controlled clinical trials with metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} , without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12} -intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed.

Change in clinical status of patients with previously controlled type 2 diabetes: a patient with type 2 diabetes previously well controlled on metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Glyburide / Metformin HCl tablets must be stopped immediately and other appropriate corrective measures initiated .

Laboratory Tests: periodic fasting blood glucose and glycosylated hemoglobin (HbA 1c) measurements should be performed to monitor therapeutic response. Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

***Drug Interactions*:**

Glyburide / Metformin HCl tablets: certain drugs tend to produce hyper-

glycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Glyburide / Metformin HCl tablets, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Glyburide / Metformin HCl tablets, the patient should be observed closely for hypoglycemia. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

Glyburide: the hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving Glyburide / Metformin HCl tablets, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving Glyburide / Metformin HCl tablets, the patient should be observed closely for loss of blood glucose control.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Metformin Hydrochloride: *Furosemide*: furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance.

Nifedipine: nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs: cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Glyburide / Metformin HCl tablets and/or the interfering drug are recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: in healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Pregnancy: *Teratogenic Effects*: recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Glyburide / Metformin HCl tablets should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with Glyburide / Metformin HCl tablets or its individual components.

Non-teratogenic Effects: prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that Glyburide / Metformin HCl tablets be used during pregnancy. However, if it is used, Glyburide / Metformin HCl tablets should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers: although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue Glyburide / Metformin HCl tablets, taking into account the importance of the drug to the mother. If Glyburide / Metformin HCl tablets are discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: safety and effectiveness of Glyburide / Metformin HCl tablets in pediatric patients have not been established.

Geriatric Use: no overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Glyburide / Metformin HCl tablets should only be used in patients with normal renal function. Because aging is associated with reduced renal function, Glyburide / Metformin HCl tablets should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose.

ADVERSE REACTIONS

Upper respiratory infection; diarrhea; nausea; vomiting; abdominal pain; headache; dizziness; disulfiram-like reactions have very rarely been reported in patients treated with glyburide tablets.

OVERDOSAGE

Glyburide: overdosage of sulfonylureas, including glyburide tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Metformin Hydrochloride: hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin hydrochloride, although lactic acidosis has occurred in such circumstances. 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.

DOSAGE AND ADMINISTRATION

General Considerations: dosage of Glyburide / Metformin HCl tablets must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glyburide/2000 mg metformin. Glyburide / Metformin HCl tablets should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glyburide), to reduce GI side effects (largely due to metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to Glyburide / Metformin HCl tablets and to identify the minimum effective dose for the patient. Thereafter, HbA 1c should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA 1c to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA 1c (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

Glyburide / Metformin HCl Tablets As Initial Therapy: for patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of Glyburide / Metformin HCl tablet is 1.25 mg/250 mg once a day with a meal. As initial therapy in patients with baseline HbA 1c > 9% or an FPG > 200 mg/dL, a starting dose of Glyburide / Metformin HCl tablet 1.25 mg/250 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 1.25 mg/250 mg per day every two weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. In clinical trials of Glyburide / Metformin HCl tablets as initial therapy, there was no experience with total daily doses greater than 10 mg/2000 mg per day. Glyburide / Metformin HCl tablet 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia.

Glyburide / Metformin HCl Tablets Use in Previously Treated Patients (Second-Line Therapy): for patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the recommended starting dose of Glyburide / Metformin HCl tablets is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of Glyburide / Metformin HCl tablets should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

For patients previously treated with combination therapy of glyburide (or another sulfonylurea) plus metformin, if switched to Glyburide / Metformin HCl tablets, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken.

STORAGE CONDITIONS

Store in a dry place below 30°C, protected from light.
Do not refrigerate.
Do not use after expiry date.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep Medicament out of reach of children.

PRESENTATION

GLYSTOR plus® Tablets 2.5 mg/500 mg, in blister pack of 30's.
GLYSTOR plus® Tablets 5 mg/500 mg in blister pack of 30's.

Manufactured in Zouk Mosbeh Lebanon by
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