GLYSTOR®

Metformin hydrochloride tablets

QUALITATIVE AND QUANTITATIVE DESCRIPTION

GLYSTOR® tablets are available as 500 mg yellow, round quadrisect film coated tablets and 850 mg yellow, round film coated tablets.

Each GLYSTOR® tablet contains 500 mg or 850 mg of the active metformin HCl for oral administration.

The tablet core excipients are: microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, and magnesium stearate. The film coating contains: hypromellose, titanium dioxide, polyethylene glycol 6000, talc, and iron oxide yellow.

INDICATIONS AND USE

GLYSTOR® (metformin HCl tablets) is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride tablets as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin HCl is indicated in patients 10 years of age and older.

Metformin HCl may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS

Metformin HCl is 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.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin HCl 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

Lactic Acidosis: lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin hydrochloride 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. Metformin HCl 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 metformin HCl, gastrointestinal symptoms, which are common during initiation of therapy, 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 metformin HCl 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 metformin HCl, 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.

PRECAUTIONS

General: *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 metformin HCl. In patients with advanced age, metformin HCl 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, metformin HCl should not be titrated to the maximum dose.

Before initiation of 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 metformin HCl discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition: 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, metformin HCl 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 re-evaluated 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 metformin HCl therapy, the drug should be promptly discontinued.

Surgical procedures: 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 metformin HCl.

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

Vitamin B_{12} levels: in controlled clinical trials of metformin HCl of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, 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 HCl or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin HCl 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 HCl 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, metformin HCl must be stopped immediately and other appropriate corrective measures initiated.

Hypoglycemia: hypoglycemia does not occur in patients receiving metformin HCl 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 hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose: when a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin HCl and temporarily administer insulin. Metformin HCl may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either metformin HCl or sulfonylurea monotherapy, combined therapy with metformin HCl and sulfonylurea may result in a response. Should secondary failure occur with combined metformin HCl/sulfonylurea therapy it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Metformin HCl alone does not usually cause hypoglycemia, although it may occur when metformin HCl is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

Laboratory Tests: response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control.

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 HCl therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Drug Interactions: *Glyburide*: in a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not

result in any changes in either metformin pharmacokinetics or pharmacodynamics.

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 metformin HCl and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: certain drugs tend to produce hyperglycemia and may lead to loss of glycemic 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 metformin HCl, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin HCl, the patient should be observed closely for hypoglycemia.

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

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 the sulfonylureas, which are extensively bound to serum proteins.

Pregnancy: *Teratogenic Effects*: Pregnancy Category B.

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 levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin HCl should not be used during pregnancy unless clearly needed.

Nursing Mothers: studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If metformin HCl is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: the safety and effectiveness of metformin HCl for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years).

Geriatric Use: controlled clinical studies of metformin HCl did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin 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, metformin HCl should only be used in patients with normal renal function. Because aging is associated with reduced renal function, metformin HCl 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 of metformin HCl .

ADVERSE REACTIONS

Diarrhea, nausea and vomiting, flatulence, indigestion, abdominal discomfort, headache.

OVERDOSAGE

Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin HCl, 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

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with metformin HCl or any other pharmacologic agent. Dosage of metformin HCl must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of metformin HCl is 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age).

Metformin HCl should be given in divided doses with meals. Metformin HCl should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to metformin HCl and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin 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 HCl, either when used as monotherapy or in combination with sulfonylurea or insulin.

Short-term administration of metformin HCl may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Recommended Dosing Schedule: *Adults*: in general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of metformin HCl is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, metformin HCl may be given to a maximum daily dose of 2550 mg per day. Doses above 2000 mg may be better tolerated given three times a day with meals.

Pediatrics: the usual starting dose of metformin HCl is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses.

Transfer From Other Antidiabetic Therapy: when transferring patients from standard oral hypoglycemic agents other than chlorpropamide to metformin HCl, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant Metformin HCl and Oral Sulfonylurea Therapy in Adult Patients: if patients have not responded to four weeks of the maximum dose of metformin HCl monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing metformin HCl at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinctic drug-drug interaction data are currently available only for metformin plus glyburide.

With concomitant metformin HCl and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant metformin HCl and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (See Package Insert of the respective sulfonylurea). If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of metformin HCl and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without metformin HCl.

Concominant metformin HCl and Insulin Therapy in adult patients: the current Insulin dose should be continued upon initiation of metformin HCl therapy. Metformin HCl therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of metformin HCl should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2500 mg for metformin HCl. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and metformin HCl. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations: monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

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® Tablets 500 mg in blister pack of 30's.
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Manufactured in Zouk Mosbeh Lebanon by
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