METFORMIN
GLICLAZIDE
PIOGLITAZONE

℞

TRIZERIC
500 mg / 80 mg / 15 mg
Film-Coated Tablet
ORAL HYPOGLYCEMIC

FORMULATION
Each film-coated tablet contains:
Metformin (as hydrochloride), BP 500mg
Gliclazide, BP 80mg
Pioglitazone (as hydrochloride), USP 15mg

DESCRIPTION
White to off-white, capsule shape, film coated tablets with breakline on one side and plain on other side.

PHARMACODYNAMICS
Trizeric (Gliclazide 80 mg, Metformin Hydrochloride 500 mg and Pioglitazone Hydrochloride 15 mg Tablets) combines three antidiabetic medications with different mechanisms of action to improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide and gliclazide a sulphonylurea. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, biguanides act primarily by decreasing endogenous hepatic glucose production, whereas sulphonylurea stimulates insulin secretion from functional pancreatic - β-cells and increases the sensitivity of the β-cells to a glucose stimulus.

Gliclazide
Gliclazide is a sulphonylurea hypoglycemic agent. Gliclazide stimulates insulin secretion from functional pancreatic - β-cells and increases the sensitivity of the β-cells to a glucose stimulus (some residual β-cell function is therefore necessary). Gliclazide restores the diminished first-phase of insulin secretion noted in non-insulin dependent diabetes mellitus.
Any long-term hypoglycemic activity of gliclazide can be attributed to an ability to maintain its effect on insulin secretion
Extrapancreatic effects may also be involved in the long-term efficacy of gliclazide.
Extrapancreatic effects demonstrated for gliclazide include improvement in insulin mediated glucose utilization and potentiation of post receptor insulin sensitive pathways.
At normal therapeutic doses in man, gliclazide reduces platelet adhesiveness and aggregation.

Pioglitazone
Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism of action.
Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output.
Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.
In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and
hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.
Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Metformin hydrochloride
Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects and does not
cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Gliclazide
Absorption
Gliclazide is absorbed in the gastrointestinal tract reaching peak serum concentrations within 4 to 6 hours. Single dose studies have demonstrated that maximal falls in blood glucose levels (23% of an 80 mg dose; 30% of a 160 mg dose) occur approximately five hours after drug administration; nine hours after a dose of 160 mg, a reduction of 20% was still in evidence.
The half-life of gliclazide is approximately 12 hours.
Distribution
Gliclazide is distributed to the extracellular fluid. In animals, high concentrations of the drug were found in the liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue.
Penetration of gliclazide into the CNS was negligible. It crosses the placental barrier and penetrates the fetus.
The apparent volume of distribution of gliclazide 20 to 40% expressed as a percentage of body weight is low and probably reflects the high degree of protein binding. At a plasma concentration of approximately 8 microgram/ml, 94.2% of the drug was protein bound and 5.8% was free.
Metabolism and Excretion
There is little information available in relation to the metabolism of the drug. Employing thin layer chromatography and gas-liquid chromatography, at least 8 metabolites (3 major) have been identified. Some of these were glucuronic acid conjugates. Only one of the metabolites has been identified (p-toluene sulphonamide). The liver is the probable site of metabolism.
Approximately 70% of the administered dose appears to be excreted in the urine and 11% in the feces. The urinary excretion of the drug is slow and the maximum rates do not occur until 7 to 10 hours after initial administration. The metabolic products are detectable in the urine 120 hours after oral administration. Elimination through the feces is usually completed within 144 hours of oral administration.

Pioglitazone
Absorption
Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.
Cmax, AUC, and trough serum concentrations (Cmin) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.
Following oral administration of pioglitazone, Tmax of pioglitazone was within two hours. Food delays the Tmax to three to four hours, but does not alter the extent of absorption (AUC).
Distribution
The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. M-III and M-IV are also extensively bound (>98%) to serum albumin.
Metabolism
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.
In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone which include CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. In vivo study of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate. Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.
Excretion and Elimination
Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life (t) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hr.

Metformin hydrochloride

Absorption

The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% - 60%. Studies using single oral doses of metformin tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean Cmax , a 25% lower AUC, and a 35-minute prolongation of Tmax following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

The Vd/F of metformin following single oral doses of 850 mg immediate-release metformin averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion and Elimination

Renal clearance is approximately 3.5 times greater than creatinine clearance (CLcr), which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination t of approximately 6.2 hours. In blood, the elimination t is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

INDICATIONS

Trizeric (Gliclazide 80 mg, Metformin Hydrochloride 500 mg and Pioglitazone Hydrochloride 15 mg Tablets) is indicated as second line treatment of type 2 diabetes mellitus adult patients, particularly overweight patients, when diet, exercise, and the single agents or dual therapy do not result in adequate glycemic control.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

CONTRAINDICATIONS

- Initiation in patients with established NYHA Class I or IV heart failure
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
- Use in patients with known hypersensitivity to pioglitazone, metformin, and gliclazide or any other component of the formulation.
- Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- Should not be used in diabetes complicated by acidosis, ketosis or coma, or in patients with a history of repeated episodes of ketoacidosis or coma.
- As sulphonylurea hypoglycemic agents are not effective in juvenile onset, unstable or brittle diabetes, gliclazide should not be used in these conditions.
- Caution should be exercised and dosage reduction may be required when using gliclazide in patients with impaired hepatic function.

DOSAGE AND ADMINISTRATION

Trizeric (Gliclazide 80 mg, Metformin Hydrochloride 500 mg and Pioglitazone Hydrochloride 15 mg Tablets) is 1 tablet two or three times daily, at the same time every day, and immediately before or after a meal. Tablets should be swallowed with a glass of water. Taking the tablet with, or just after food, may reduce gastrointestinal symptoms associated with metformin. Or as prescribed by the physician.

Patients inadequately controlled on metformin monotherapy

In patients inadequately controlled on maximum tolerated doses of metformin and with an HbA1c ≥ 8.5%, start with 1 tablet twice daily immediately before or after a meal, and at the same time every day. Dosage may be increased to one tablet three times daily according to response after 4-8 weeks.

Patients inadequately controlled on pioglitazone monotherapy

In patients inadequately controlled on maximum tolerated doses of pioglitazone and with an HbA1c ≥ 8.5%, start with 1 tablet twice daily immediately before or after a meal, and at the same time every day. Dosage may be increased to one tablet three times daily according to response after 4-8 weeks.

Patients who are changing from combination therapy of pioglitazone plus metformin in separate tablet

In patients inadequately controlled on maximum tolerated doses of a combination of pioglitazone with metformin and with an HbA1c ≥ 8.0%, start with 1 tablet twice daily immediately before or after a meal, and at the same time every day. Dosage may be increased to one tablet three times daily according to response after 4-8 weeks

WARNINGS and PRECAUTIONS

Acute complications such as severe trauma, fever, infection or surgery

These acute complications provoke additional metabolic stress, which accentuates the predisposition to hypoglycemia and ketosis. Patients presenting with such conditions may require insulin to maintain control. It is not appropriate to increase the dosage of gliclazide.

Hypoglycemia

Close observation and careful initiation and adjustment of dosage are mandatory in patients who are elderly and debilitated, malnourished, semi-starved or simply neglecting dietary restrictions.

In such patients, severe hypoglycemia may occur and may require corrective therapy over a period of several days. Certain conditions such as alcoholism, insulinoma, adrenal thyroid and pituitary insufficiency increase the sensitivity to sulphonylureas and may dispose to hypoglycemia.

Congestive Heart Failure

Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with Gliclazide, Metformin and Pioglitazone combination should be observed for signs and symptoms of congestive heart failure.

If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of Gliclazide, Metformin and Pioglitazone combination must be considered.

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally greater than 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Gliclazide, Metformin and Pioglitazone combination. In Gliclazide, Metformin and Pioglitazone combination -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Gliclazide, Metformin and Pioglitazone combination and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment

The post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include

- Before initiating Gliclazide, Metformin and Pioglitazone combination obtain an eGFR.
- Gliclazide, Metformin and Pioglitazone combination is contraindicated in patients with an eGFR less than 30mL/min /1.73 m^2. Initiation of Gliclazide, Metformin and Pioglitazone combination is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking Gliclazide, Metformin and Pioglitazone combination. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking Gliclazide, Metformin and Pioglitazone combination whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.

Drug Interactions

The concomitant use of Gliclazide, Metformin and Pioglitazone combination with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g. cationic drugs). Therefore, consider more frequent monitoring of patients.

Age 65 or Greater

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast
Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Gliclazide, Metformin and Pioglitazone combination 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; in patients with a history of hepatic impairment, 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 Gliclazide, Metformin and Pioglitazone combination if renal function is stable.
Surgery and Other Procedures
Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Gliclazide, Metformin and Pioglitazone combination should be temporarily discontinued while patients have restricted food and fluid intake.
Hypoxic States
Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Gliclazide, Metformin and Pioglitazone combination.
Excessive Alcohol Intake
Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Gliclazide, Metformin and Pioglitazone combination.
Hepatic Impairment
Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Gliclazide, Metformin and Pioglitazone combination in patients with clinical or laboratory evidence of hepatic disease.
Edema
In controlled clinical trials with pioglitazone, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose related. In postmarketing experience, reports of new onset or worsening of edema have been received.
Gliclazide, Metformin and Pioglitazone combination should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Gliclazide, Metformin and Pioglitazone combination should be used with caution in patients at risk for congestive heart failure. Patients treated with Gliclazide, Metformin and Pioglitazone combination should be monitored for signs and symptoms of congestive heart failure.
Hypoglycemia
Patients receiving Gliclazide, Metformin and Pioglitazone combination in combination with insulin or other antidiabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medication may be necessary to reduce the risk of hypoglycemia. Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement. 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.
Hepatic Effects
There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date.
Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating Gliclazide, Metformin and Pioglitazone combination therapy.
In patients with abnormal liver tests, Gliclazide, Metformin and Pioglitazone combination should be initiated with caution.
Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), Gliclazide, Metformin and Pioglitazone combination treatment should be interrupted and investigation done to establish the probable cause. Gliclazide, Metformin and Pioglitazone combination should not be restarted in these patients without another explanation for the liver test abnormalities.
Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury, and should not be restarted on Gliclazide, Metformin and Pioglitazone combination. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with Gliclazide, Metformin and Pioglitazone combination can be used with caution.
Urinary Bladder Tumors
Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.
Consequently, Gliclazide, Metformin and Pioglitazone combination should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with Gliclazide, Metformin and Pioglitazone combination should be considered in patients with a prior history of bladder cancer.
Fractures
The risk of fracture should be considered in the care of patients, especially female patients, treated with Gliclazide, Metformin and Pioglitazone combination and attention should be given to assessing and maintaining bone health according to current standards of care.
Macular Edema
Macular edema has been reported in post marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.
Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of the thiazolidinedione.
Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.
Vitamin B12 Levels
In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Gliclazide, Metformin and Pioglitazone combination and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at two- to three-year intervals may be useful.
Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Gliclazide, Metformin and Pioglitazone combination.

DRUG INTERACTIONS

Gliclazide

Disturbance of blood sugar control: As with all hypoglycemics, caution should be observed in administering thiazide diuretics to patients on gliclazide therapy, since thiazides have been reported to aggravate the diabetic state. Other drugs, which may adversely affect blood sugar control with hypoglycemic agents in some patients, include barbiturates, glucocorticoids and estrogens.
Potentiation of hypoglycemic effect: Certain drugs may potentiate the effect of gliclazide and thereby increase the risk of hypoglycemia. These include insulin, biguanides, sulphonamides,
oxyphenbutazone, phenylbutazone, clofibrate, salicylates, coumarin derivatives, chloramphenicol, MAOIs, P-blockers, cimetidine and ethanol.
Alcohol
Acute alcohol intoxication potentiates the hypoglycemic action of all sulphonylurea agents. Furthermore, ingestion of alcohol may cause a disulfiram-like reaction with characteristic flushing of the face, throbbing headache, giddiness, tachypnea, tachycardia or angina pectoris.
Chronic alcohol abuse may, as a result of liver enzyme induction, stimulate the metabolism of sulphonylurea drugs and shorten plasma half-life and duration of action.
Strong CYP2C8 Inhibitors
An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life (t1/2) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors.
CYP2C8 Inducers
An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone.
Therefore, if an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone
Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or
dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Gliclazide, Metformin and Pioglitazone combination may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance
Drugs that are eliminated by renal tubular secretion (e.g., cationic drugs such as cimetidine) have the potential for interaction with metformin by competing for common renal tubular transport systems, and may increase the accumulation of metformin and the risk for lactic acidosis. Consider more frequent monitoring of these patients.
Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Gliclazide, Metformin and Pioglitazone combination.

Insulin Secretagogues or Insulin
If hypoglycemia occurs in a patient coadministered Gliclazide, Metformin and Pioglitazone combination and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced.
If hypoglycemia occurs in a patient coadministered Gliclazide, Metformin and Pioglitazone combination and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.
Drugs Affecting Glycemic Control
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 blockers, and isoniazid. When such drugs are administered to a patient receiving Gliclazide, Metformin and Pioglitazone combination, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient-receiving Gliclazide, Metformin and Pioglitazone combination, the patient should be observed closely for hypoglycemia.

PREGNANCY AND LACTATION

Pregnancy
Limited data with Gliclazide, Metformin and Pioglitazone combination or pioglitazone in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.
In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5- and 35-times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- to 6-times, respectively, a 2000 mg clinical dose, based on body surface area.
It is important to achieve strict normoglycemia during pregnancy. Oral hypoglycemic agents should be replaced by insulin.
The sulphonylureas may enter the fetal circulation and cause neonatal hypoglycemia. In animal studies, embryotoxicity and/or birth defects have been demonstrated

Lactation
There is no information regarding the presence of Gliclazide, Metformin and Pioglitazone or pioglitazone in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone is present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Limited published studies report that metformin is present in human milk. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gliclazide, Metformin and Pioglitazone combination and any potential adverse effects on the breastfed infant from Gliclazide, Metformin and Pioglitazone combination or from the underlying maternal condition.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients who experience visual disturbance should be cautious when driving or using machines.

ADVERSE EFFECTS
The following serious adverse reactions are discussed under section 4.4 (Special Warning and Precautions for use): Congestive heart failure, Lactic acidosis, Edema and Fractures.

Gliclazide
Adverse reactions have occurred in some 12% of cases in clinical studies. However, approximately 2% of patients were 1769/1 withdrawn from therapy because of adverse reactions, notably hypoglycemia, gastrointestinal disturbances (constipation, nausea, epigastric discomfort and heartburn), dermatological reactions (rash and transient itching), and biochemical abnormalities (elevated serum creatinine, increased serum alkaline phosphatase, raised serum AST, elevated BUN and raised serum bilirubin). Headache, slight disulfiram like reactions and lassitude have also been reported.
As is the case with all forms of antidiabetic therapy, hypoglycemic reactions may occur following gliclazide administration.
Severe hypoglycemia, though uncommon, may occur in patients receiving gliclazide.
Serious reactions, which have been reported with other sulphonylureas, are leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, hemolytic anemia, cholestatic jaundice and gastrointestinal hemorrhage. These reactions have not been reported with gliclazide.

Pioglitazone
Most common adverse reactions (>5%) are upper respiratory tract infection, edema, diarrhea, headache and weight gain.

Metformin
Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin than placebo-treated patients are Diarrhea, Nausea/Vomiting Flatulence, Asthenia Indigestion, Abdominal Discomfort, Headache.

Post marketing Experience
The following adverse reactions have been identified during post-approval use of pioglitazone. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pioglitazone
- New onset or worsening diabetic macular edema with decreased visual acuity
- Fatal and nonfatal hepatic failure

Post marketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.
In post marketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Metformin
Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

OVERDOSE AND TREATMENT

Gliclazide
Symptoms: Manifestations of severe hypoglycemia result from overdosage. Hypoglycemia caused by sulphonylurea agents differs in several aspects from insulin coma. Warning symptoms are often absent, neurological syndromes are frequent and coma is often prolonged.
Treatment: Consciousness should be restored by the administration of intravenous glucose or glucagon injection, care being taken to ensure against return of hypoglycemia by constant monitoring of the blood sugar level.

Pioglitazone
During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.
In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride 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 metformin from patients in whom metformin overdosage is suspected.

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

STORE AT TEMPERATURES NOT EXCEEDING 30°C

AVAILABILITY: 500 mg / 80 mg/ 15 mg Alu/Alu blister pack of 10's, box of 30 film-coated tablets

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

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