PATIENT INFORMATION LEAFLET

For the use of a Registered Medical Practitioner, or a hospital, or a Laboratory only.

GLIMEPIRIDE 1 MG / 2MG, PIOGLITAZONE HYDROCHLORIDE 15 MG / 15 MG & METFORMIN HYDROCHLORIDE (ER) 500 MG / 500 MG TABLETS

GLIPLEXIDE™ MP1

COMPOSITION:

Each uncoated bilayered tablet contains:	
Glimepiride IP	1 mg
Pioglitazone Hydrochloride IP Eq. to Pioglitazone	15 mg
Metformin Hydrochloride IP (in extended release form)	500 mg
Excipients	q.s.
Colour: Erythrosine	

GLIPLEXIDE™ MP2

Composition:

Each uncoated bilayered tablet contains:	
Glimepiride IP	2 mg
Pioglitazone Hydrochloride IP Eq. to Pioglitazone	15 mg
Metformin Hydrochloride IP (In extended release form)	500 mg
Excipients	q.s.
Colour: Tartrazine Lake	

DOSAGE FORM:
Tablets for oral use

INDICATIONS:
This combination tablets, used as a once per day, are indicated as an adjunct to diet and exercise, to lower blood glucose. It is indicated as second-line therapy when diet, exercise, single agents and dual combination therapy do not result in adequate glycaemic control in patients with type 2 diabetes.
Further, this FDC should not be used as first line of therapy for diabetes.

DOSE & ADMINISTRATION:
The combination should be given once daily with the first meal of the day. The maximum recommended daily dose in adults should not exceed 3 tablets. Tablet should not be crushed or chewed and should be taken as a whole with water.

Pediatrics: Safety and effectiveness has not been established.

Females of reproductive potential: Discuss the potential of unintended pregnancy with premenopausal females.

Renal Impairment: GFR should be assessed before initiation of treatment and at least annually thereafter. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses.

USE IN SPECIFIC POPULATIONS:

Pregnancy
Metformin
Risk Summary:
Limited data with Metformin hydrochloride tablets 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 mellitus in pregnancy.
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- and 5-times, respectively, a 2550 mg clinical dose, based on body surface area.
The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes mellitus with an HbA1C >7 and has been reported to be as high as 20 to 25% in women with a HbA1C > 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Glimepiride
Teratogenic Effects :
In animal studies there was no increase in congenital anomalies, but an increase in fetal deaths occurred in rats and rabbits at glimepiride doses 50 times (rats) and 0.1 times (rabbits) the maximum recommended human dose (based on body surface area). This fetotoxicity, observed only at doses inducing maternal hypoglycemia, is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride and has been similarly noted with other sulfonylureas. Glimepiride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because data suggest that abnormal blood glucose during pregnancy is associated with a higher incidence of congenital abnormalities, diabetes treatment during pregnancy should maintain blood glucose as close to normal as possible.
Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers receiving a sulfonylurea at the time of delivery.

Pioglitazone
Pregnancy Category C:
There are no adequate and well-controlled studies of Pioglitazone hydrochloride in pregnant women. Animal studies show increased rates of postimplantation loss, delayed development, reduced fetal weights, and delayed parturition at doses 10 to 40 times the maximum recommended human dose.

Nursing Mothers
Metformin:
Risk Summary
Limited published studies report that Metformin is present in human milk. However, there is insufficient information to determine the effects of Metformin on the breastfed infant and no available information on the effects of Metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Metformin hydrochloride tablets and any potential adverse effects on the breastfed child from Metformin hydrochloride tablets or from the underlying maternal condition.

Glimepiride or Pioglitazone:
No studies have been conducted with the combined components of Glimepiride and Pioglitazone. In studies performed with the individual components, pioglitazone was secreted in the milk of lactating rats and significant concentrations of glimepiride were present in the serum and breast milk of the dams and serum of the pups. It is not known whether pioglitazone or glimepiride are secreted in human milk. However, other sulfonylureas are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for Glimepiride and Pioglitazone to cause serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue Glimepiride and Pioglitazone, taking into account the importance of Glimepiride and Pioglitazone to the mother.

Pediatric Use(< 12 years of age)
Safety and effectiveness of Metformin, Glimepride and pioglitazone combine drug in pediatric patients have not been established.
Metformin, Glimepride and pioglitazone is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors.

Geriatrics
Metformin
Controlled clinical studies of Metformin hydrochloride tablets did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.
Glimepiride
In clinical trials of glimepiride, 1053 of 3491 patients (30%) were ≥65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
There were no significant differences in glimepiride pharmacokinetics between patients with type 2 diabetes ≤65 years (n=49) and those >65 years (n=42).
Pioglitazone
A total of 92 patients (15.2%) treated with pioglitazone in the three pooled 16-to 26week double-blind, placebo-controlled, monotherapy trials were ≥65 years old and two patients (0.3%) were ≥75 years old. In the two pooled 16-to 24-week add-on to sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were ≥65 years old and 19 (1.8%) were ≥75 years old. In the two pooled 16-to 24-week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥65 years old and 19 (1.9%) were ≥75 years old. In the two pooled 16-to 24-week add-on to insulin trials, 272 patients (25.4%) treated with pioglitazone were ≥65 years old and 22 (2.1%) were ≥75 years old.
Although clinical experiences have not identified differences in effectiveness and safety between the elderly (≥65 years) and younger patients, these conclusions are limited by small sample sizes for patients ≥75 years old.

Renal Insufficiency:
Metformin
Metformin is substantially excreted by the kidney, and the risk of Metformin accumulation and lactic acidosis increases with the degree of renal impairment. Metformin hydrochloride tablets are contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2.
Glimepiride
A single-dose, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (Clcr); (Group I, CLcr = 77.7 mL/min, n = 5), (Group II, CLcr = 27.7 mL/min, n = 3), and (Group III, CLcr = 9.4 mL/min, n = 7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal halflife (T1/2) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).
Pioglitazone hydrochloride
The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended.

Hepatic Insufficiency:
Metformin
Use of Metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin hydrochloride tablets.
Glimepiride
No studies were performed in patients with hepatic insufficiency.
Pioglitazone hydrochloride
Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

CONTRAINDICATIONS:

1. Initiation in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.
2. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ³1.5 mg/dL [males], ³1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
4. Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.
5. Known hypersensitivity to this product or any of its components.
6. Patients with active bladder cancer or with history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.

WARNINGS AND PRECAUTIONS:
Metformin
Lactic Acidosis
Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin hydrochloride and 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 concentrations (>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 reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin hydrochloride. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. metformin hydrochloride treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin hydrochloride should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.Because impaired hepatic function may significantly limit the ability to clear lactate, Metformin hydrochloride should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin hydrochloride, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin hydrochloride should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (In controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patents, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patents, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis.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.

Monitoring of Renal Function
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore Metformin is contraindicated in patients with renal impairment. Before initiation of metformin hydrochloride and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and metformin hydrochloride discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

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 hydrochloride therapy, the drug should be promptly discontinued.

Alcohol
Intake Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving metformin hydrochloride.

Impaired Hepatic Function
Because impaired hepatic function has been associated with some cases of lactic acidosis metformin hydrochloride should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Levels
In controlled, 29-week clinical trials of immediate release metformin, 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 hydrochloride or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin hydrochloride 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.

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 hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking betaadrenergic blocking drugs.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin hydrochloride or any other oral anti-diabetic drug.

Glimepiride
Hypoglycemia
All sulfonylureas, including glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions
There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia
Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency.

Increased Risk of Cardiovascular Mortality with Sulfonylureas
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. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug.

Pioglitazone
Congestive Heart Failure
Pioglitazone Hydrochloride, 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 Hydrochloride is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients 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 Pioglitazone Hydrochloride must be considered.

Edema
In controlled clinical trials, edema was reported more frequently in patients treated with Pioglitazone Hydrochloride than in placebo-treated patients and is dose-related. In postmarketing experience, reports of new onset or worsening edema have been received. Pioglitazone Hydrochloride should be used with caution in patients with edema. Because thiazolidinediones, including Pioglitazone Hydrochloride, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Pioglitazone Hydrochloride should be used with caution in patients at risk for congestive heart failure. Patients treated with Pioglitazone Hydrochloride should be monitored for signs and symptoms of congestive heart failure.

Hepatic Effects
There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking Pioglitazone Hydrochloride, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the Pioglitazone Hydrochloride 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 Pioglitazone Hydrochloride therapy. In patients with abnormal liver tests, pioglitazone hydrochloride 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 3 times the upper limit of the reference range), pioglitazone hydrochloride treatment should be interrupted and investigation done to establish the probable cause. pioglitazone hydrochloride 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 pioglitazone hydrochloride. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with pioglitazone hydrochloride can be used with caution.
Fractures
In PRO active (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone hydrochloride (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone hydrochloride versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with pioglitazone hydrochloride (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone hydrochloride and attention should be given to assessing and maintaining bone health according to current standards of care.

Urinary Bladder Tumors
Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see Nonclinical Toxicology (13.1)]. In two 3-year trials in which pioglitazone hydrochloride was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone hydrochloride compared to 5/3679 (0.14%) in patients not taking pioglitazone hydrochloride. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone hydrochloride and two (0.05%) cases on placebo. A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to pioglitazone hydrochloride, compared to subjects never exposed to pioglitazone hydrochloride (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of pioglitazone hydrochloride therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of pioglitazone hydrochloride use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking pioglitazone hydrochloride longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without pioglitazone hydrochloride] to approximately 10 in 10,000 [with pioglitazone hydrochloride]). There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, pioglitazone

hydrochloride should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone hydrochloride should be considered in patients with a prior history of bladder cancer.

Hypoglycemia
Patients receiving pioglitazone hydrochloride in combination with insulin or other anti-diabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant anti-diabetic medication may be necessary to reduce the risk of hypoglycemia.

Macular Edema
Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone hydrochloride 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.

Ovulation
Therapy with pioglitazone hydrochloride, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone hydrochloride. This effect has not been investigated in clinical trials, so the frequency of this occurrence is not known. Adequate contraception in all premenopausal women treated with pioglitazone hydrochloride is recommended.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone hydrochloride or any other anti-diabetic drug.

DRUG INTERACTIONS:
Cationic drugs: Cationic drugs (e.g: amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, ranitidine, or vancomycin) used concomitantly with metformin may increase the risk of lactic acidosis.
Miconazole (systemic route, oromucosal gel) and Phenylbutazone (systemic route): Increases hypoglycaemic effect of glimepiride.
Furosemide: Furosemide increased the metformin plasma and blood concentration without any significant change in metformin renal clearance.
Vitamin B12: Metformin may result in suboptimal oral vitamin B12 absorption by competitively blocking the calcium dependent binding of the intrinsic factor vitamin B12 complex to its receptor.
Nifedipine: Nifedipine appears to enhance the absorption of metformin; it increases plasma concentration of metformin.
Danazol: If the use of this active substance cannot be avoided, warn the patients and emphasize the importance of urine and blood glucose monitoring.
Salicylates: If salicylates are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycaemia.
Thiazide: Interactions between thiazide diuretics and oral antidiabetic agents decreases insulin sensitivity thereby leading to glucose intolerance and hyperglycaemia.
CYP2C8 inhibitors/ inducers: An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone.
Oral Contraceptives: Administration of pioglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception.
Other: Concomitant administration of angiotensin enzyme inhibitors, other antidiabetic drugs, beta-blockers, fluconozole, histamine (H2) receptor antagonist, monoamine oxidase inhibitors (MAOIs), sulphonamides and non-steroidal anti-inflammatory agents increases sensitivity to insulin and potentiation of blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur. Patients receiving corticosteroids, phenothiazines, thyroid products, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid should be closely monitored for loss of diabetic control when therapy is instituted or discontinued.

ADVERSE EFFECTS:

Metformin
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with Metformin 1500–2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

The incidence and type of adverse reactions reported by >5% of patients for the combined Metformingroup versus placebo group are hypoglycemia, diarrhea, and nausea.

Glimepiride
The following serious adverse reactions are:
- Hypoglycemia
- Hemolytic anemia

In clinical trials, the most common adverse reactions with Glimepiride were hypoglycemia, dizziness, asthenia, headache, and nausea.

Postmarketing Experience The following adverse reactions have been identified during post-approval use of Glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson Syndrome.
- Hemolytic anemia in patients with and without G6PD deficiency.
- Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis.
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia.
- Thrombocytopenia (including severe cases with platelet count less than 10,000/µL) and thrombocytopenic purpura.
- Hepatic porphyria reactions and disulfiram-like reactions.
- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone.

Pioglitazone
The following serious adverse reactions are discussed elsewhere in the labeling:
- Congestive heart failure
- Edema

The drug should not be used as first line therapy for diabetes.
Advice for Healthcare professionals:
- **Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.**
- **Prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg, reduction in glycosylated haemoglobin, HbA1c)**
- **Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age; current or past history of smoking; exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous irradiation of the pelvic region**
- **Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.**

Laboratory Abnormalities
Hematologic Effects: Pioglitazone hydrchloride may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with Pioglitazone hydrchloride compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with Pioglitazone hydrchloride therapy and are not likely to be associated with any clinically significant hematologic effects.
Creatine Phosphokinase: During protocol-specified measurement of serum creatine phosphokinase (CPK) in Pioglitazone hydrchloride clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in 9 (0.2%) patients treated with Pioglitazone hydrchloride (values of 2150 to 11400 IU/L) and in no comparator-treated patients. Six of these nine patients continued to receive Pioglitazone hydrchloride, two patients were noted to have the CPK elevation on the last day of dosing and one patient discontinued Pioglitazone hydrchloride due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to Pioglitazone hydrchloride therapy is unknown.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Pioglitazone hydrchloride. 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.
- New onset or worsening diabetic macular edema with decreased visual acuity.
- Fatal and non-fatal hepatic failure.

Postmarketing reports of congestive heart failure have been reported in patients treated with Pioglitazone hydrchloride, both with and without previously known heart disease and both with and without concomitant insulin administration.
In postmarketing 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.

OVERDOSE:

Metformin
No cases of overdose were reported during Metformin clinical trials. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded.
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 drug from patients in whom metformin overdosage is suspected.

Glimepiride
Overdosage of sulfonylureas, including glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic 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, because hypoglycemia may recur after apparent clinical recovery..

Pioglitazone hydrochloride
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 patient's clinical signs and symptoms.

PHARMACODYNAMICS AND PHARMACOKINETIC PROPERTIES:

Machanism of action:

Metformin
Metformin is a biguanide that 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 patients with type 2 diabetes or in healthy subjects except in special circumstances, and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

Glimepiride
Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

Pioglitazone Hydrochloride
Pioglitazone Hydrochloride is a thiazolidinedione that depends on the presence of insulin for its mechanism of action. Pioglitazone hydrochloride 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.

Pharmacodynamics:
Metformin
Insulin is an important hormone that regulates blood glucose levels.Type II diabetes is characterized by a decrease in sensitivity to insulin, resulting in eventual elevations in blood glucose when the pancreas can no longer compensate. In patients diagnosed with type 2 diabetes, insulin no longer exerts adequate effects on tissues and cells (called insulin resistance) and insulin deficiency may also be present .
Metformin reduces liver (hepatic) production of glucose, decreases the intestinal absorption of glucose, and enhances insulin sensitivity by increasing both peripheral glucose uptake and utilization. In contrast with drugs of the sulfonylurea class, which lead to hyperinsulinemia, the secretion of insulin is unchanged with metformin use.
Effect on fasting plasma glucose (FPG) and Glycosylated hemoglobin (HbA1c)
HbA1c is an important periodic measure of glycemic control that is used to monitor diabetic patients. Fasting plasma glucose is also a useful and important measure of glycemic control. In a 29-week clinical trial of subjects diagnosed with type II diabetes, metformin decreased the fasting plasma glucose levels by an average of 59 mg/dL from baseline, compared to an average increase of 6.3 mg/dL from baseline in subjects taking a placebo. Glycosylated hemoglobin (HbA1c) was decreased by about 1.4% in subjects receiving metformin, and increased by 0.4% in subjects receiving placebo only.

Glimepiride
In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2-3 hours after single oral doses of glimepiride. The effects of Glimepiride on HbA1c, fasting plasma glucose, and post-prandial glucose have been assessed in clinical trials.

Pioglitazone
Clinical studies demonstrate that Pioglitazone Hydrochloride improves insulin sensitivity in insulin-resistant patients. Pioglitazone Hydrochloride enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by Pioglitazone Hydrochloride results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, Pioglitazone Hydrochloride had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin.
Patients with lipid abnormalities were included in clinical trials with Pioglitazone Hydrochloride. Overall, patients treated with Pioglitazone Hydrochloride had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with Pioglitazone hydrochloride or any other antidiabetic medication.

Pharmacokinetics:

Metformin

Absorption and Bioavailability:
Following a single oral dose of 1000 mg (2x500 mg tablets) Metformin after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7-8 hours. In both single and multiple-dose studies in healthy subjects, once daily 1000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), and up to 35% higher Cmax, of metformin relative to the immediate release given as 500 mg twice daily. Metformin tablets must be administered immediately after a meal to maximize therapeutic benef it. Single oral doses of Metformin from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and Cmax. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from Metformin tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax was not affected. In a two-way, single-dose crossover study in healthy volunteers, the 1000 mg tablet was found to be bioequivalent to two 500 mg tablets under fed conditions based on equivalent Cmax and AUCs for the two formulations.
Distribution :
The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg immediate release metformin hydrochloride averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 µg/mL. During controlled clinical trials, which served as the basis of approval for metformin, maximum metformin plasma levels did not exceed 5µg/mL, even at maximum doses.
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. Metabolism studies with extended-release metformin tablets have not been conducted.
Excretion :
Renal clearance is approximately 3.5 times greater than creatinine clearance, 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 half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Glimepiride

Absorption:
Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (Cmax) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean Cmax and AUC (area under the curve) were decreased by 8% and 9%, respectively. Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.
In healthy subjects, the intra- and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15-23% and 24-29%, respectively.
Distribution:
After intravenous dosing in healthy subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism:
Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Excretion:
When 14C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80-90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Pioglitazone

Absorption:
Following oral administration of pioglitazone hydrochloride, peak concentrations of pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum concentration (Tmax) to 3 to 4 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. The cytochrome P450 isoforms involved are 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 hydrochloride 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.

PACKAGING INFORMATION:
Blister pack of 15 Tablets.

STORAGE CONDITION:
Store protected from light and moisture, at a temperature not exceeding 25°C.

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Windlas Biotech Limited (Plant-3)
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