For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Pioglitazone, Glimepiride & Extended Release Metformin HCl Tablets
(Brand Name: K-PIO™- GM 1 mg / K-PIO™- GM 2 mg Tablets)

BOX WARNING

1. The drug should not be used as first line therapy for diabetes.
2. Advice for healthcare professionals:

- **Pioglitazone should not be used as first line of therapy for diabetes. 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 to 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 (e.g., 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.**

2. Qualitative and Quantitative Composition

K-PIO-GM 1 mg Tablets

Each uncoated bilayered tablet contains:
Pioglitazone Hydrochloride IP equivalent to Pioglitazone ……..… 15 mg.
Glimepiride IP …….. 1 mg.
Metformin Hydrochloride IP ……... 500 mg.
(as extended release)
Excipients …….. q.s.
Colours: Lake of Erythrosine.

K-PIO-GM 2 mg Tablets
Each uncoated bilayered tablet contains:
Pioglitazone Hydrochloride IP equivalent to Pioglitazone ……..… 15 mg.
Glimepiride IP …….. 2 mg.
Metformin Hydrochloride IP ……... 500 mg.
(as extended release)
Excipients …….. q.s.
Colours: Lake of Brilliant Blue FCF.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Pioglitazone 15 mg/15 mg, glimepiride 1 mg/2 mg, and metformin (ER) 500 mg/500 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-PIO-GM Tablets are indicated as second line therapy in adults with type 2 diabetes mellitus inadequately controlled by diet, exercise, and with other antidiabetic drugs.
K-PIO-GM Tablets should not to be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

4.2Posology and Method of Administration

For oral administration in adults.
In adults, recommended dose is 1 tablet of K-PIO-GM 1 mg to be administered once daily. After a 2 to 4 week interval, dosage requirement should be assessed based on glycemic control. If good glycemic control is achieved with this therapy, continue the same dose as a maintenance therapy. If goal is not achieved, switch to higher dosage strength. In this case, 1 tablet of K-PIO-GM 2 mg to be administered once daily. If glycemic control is optimum, continue the dose as maintenance therapy. If glycemic control is not satisfactory, consider a change to more appropriate treatment i.e., higher doses of individual components may be given separately or addition of other anti-diabetic drugs should be considered. Dosage should be individualized on the basis of both efficacy and gastrointestinal tolerance.
Dosage of individual components should not exceed the maximum daily dose.

- Maximum recommended dose of pioglitazone: 45 mg/day.
- Maximum recommended dose of glimepiride: 8 mg/day.
- Maximum recommended dose of metformin: 2000 mg/day in divided doses.

K-PIO-GM Tablets should be strictly administered with first main meal of the day to avoid the risk of hypoglycemia in diabetic patients. Swallow the tablets whole with water and never crush, cut or chew.

Or, as prescribed by the physician.

4.3Contraindications

K-PIO-GM Tablets are contraindicated in the following:

- Hypersensitivity to pioglitazone or to glimepiride/other sulfonylureas or to metformin or to any component of the formulation.
- Patients with established NYHA Class III or IV heart failure.
- Type 1 diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Pregnancy.
- Lactation.
- Current bladder cancer or a history of bladder cancer.
- Uninvestigated macroscopic hematuria.
- Severe renal impairment.
- Severe hepatic impairment, acute alcohol intoxication, alcoholism.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, and shock.
- Acute conditions with the potential to alter renal function such as dehydration, trauma, surgery, severe infection, shock, intravascular administration of iodinated contrast agents.

4.4Special Warnings and Precautions for Use

Pioglitazone

Congestive Heart Failure (CHF): Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive and rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.

Edema: In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related. In post-marketing experience, reports of new onset or worsening edema have been received. Pioglitazone 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, pioglitazone should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone should be monitored for signs and symptoms of congestive heart failure.

Bladder Cancer: Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone than in control groups. Available epidemiological data

also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g., cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic hematuria should be investigated before starting pioglitazone therapy. Patients should be advised to promptly seek the attention of their physician if macroscopic hematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of Liver Function/ Hepatic Effects: There have been rare reports of hepatocellular dysfunction during post-marketing studies with pioglitazone. Therefore, it is recommended that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times of ULN) or with any other evidence of liver disease.

Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgment. If ALT levels are increased to 3 times of ULN during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times of ULN, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be evaluated. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgment and laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Weight Gain: In clinical trials with pioglitazone there was evidence of dose-related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure. Therefore, weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Hematology: There was a small reduction in mean hemoglobin (4% relative reduction) and hematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with hemodilution. Similar changes were seen in metformin (hemoglobin 3 to 4% and hematocrit 3.6 to 4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (hemoglobin 1 to 2% and hematocrit 1 to 3.2% relative reductions)-treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia: As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary. The use of pioglitazone in combination with insulin is not indicated.

Eye Disorders/Macular Edema: Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with thiazolidinediones, including

pioglitazone. Many of these patients reported concurrent peripheral edema. It is unclear whether or not there is a direct association between pioglitazone and macular edema but prescribers should be alert to the possibility of macular edema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Fractures: An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomized, controlled, double blind clinical trials with treatment for up to 3.5 years. Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women. The risk of fractures should be considered in the long term care of patients treated with pioglitazone.

Ovulation: As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Elderly: Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure. In light of age-related risks (especially bladder cancer, fractures, and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

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, and 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 post marketing 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 the therapy, 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. Use with caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also post-marketing 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 (tolbutamide 1.5 grams per day) 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 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.

Monitoring of Glycemic Control: Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated hemoglobin (HbA1c) is recommended.

Others: Regular hepatic and hematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride.

Glimepiride should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

In stress-situations (e.g., accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. 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.

Excessive Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Acute alcohol intoxication is associated with an increased risk of lactic acidosis. Warn patients against excessive alcohol intake while receiving metformin therapy.

Radiologic Studies with Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) of any kind, 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 therapy, the drug should be promptly discontinued.

Cardiac Function: Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Renal Function: As metformin is excreted by the kidney, creatinine clearance should be determined before initiating treatment and regularly thereafter at least annually in patients with normal renal function and at least 2 to 4 times a year in patients with creatinine clearance levels at the upper limit of normal and in elderly subjects.

Loss of Blood Glucose Control: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold oral antidiabetic agents and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

Surgery: Metformin should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or when normal renal function has been established.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency: Long-term use of metformin may decrease absorption of vitamin B12 with resultant decrease in plasma B12 levels. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. It is recommended to measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: The usual laboratory tests for diabetes monitoring should be performed regularly. Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic drugs.

4.5Drug Interactions

Pioglitazone

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 (t½) 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.

Oral Contraceptives: Administration of thiazolidinediones with oral contraceptives containing ethinyl oestradiol and norethindrone may reduce the plasma concentrations of both hormones by approximately 30%. This could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Topiramate: A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate. The clinical relevance of this decrease is unknown; however, when pioglitazone and topiramate are used concomitantly, monitor patients for adequate glycemic control.

Glimepiride

Cytochrome P450 2C9 Interactions: Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9) enzyme. Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole). If glimepiride is given simultaneously with those drugs metabolized by cytochrome P4502C9, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. Results from an *in-vivo* interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Drugs Affecting Glucose Metabolism: A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

I. **Drugs which increases glucose-lowering effect of glimepiride:** The following are examples of drugs that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia:
   Oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase (MAO) inhibitors. When these

medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia.

II. **Drugs which decreases glucose-lowering effect of glimepiride:** The following are examples of drugs that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control:
Danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening of glycemic control.

III. **Sympatholytic drugs:** Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glucose-lowering effects of glimepiride. The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

IV. **Alcohol:** Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

Anticoagulants: Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
Miconazole: A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported.
Colesevelam: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction has been observed when glimepiride administered at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

<u>Metformin</u>

Carbonic Anhydrase Inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide): Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce hyperchloremic non-anion gap metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients is recommended.

Drugs that Reduce Metformin Clearance (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine): Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Drugs Affecting Glycemic Control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid): These drugs tend to produce hyperglycemia and may lead to loss of glycemic control. When these drugs are administered to a

patient receiving metformin, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycemia.

Insulin Secretagogues or Insulin: Co-administration of metformin with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Combinations Requiring Precautions for Use:

1. Some drugs may adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX)-2 inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
2. Glucocorticoids (systemic and local routes), beta 2-agonists, and diuretics have intrinsic hyperglycemic activity. More frequent blood glucose monitoring, especially at the beginning of treatment is required. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.
3. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

4.6Use in Special Populations

Pregnant Women

Pioglitazone: Pregnancy Category C; Glimepiride: Pregnancy Category C; Metformin: Pregnancy Category B. There are no adequate and well-controlled studies of this combination therapy in pregnant women. There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was likely to be related to the pharmacologic action (hypoglycaemia) of glimepiride. Thus, glimepiride should not be used during pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. There are no adequate human data to determine the safety of pioglitazone during pregnancy. Animal studies show increased rates of post-implantation loss, delayed development, reduced fetal weight, and delayed parturition at doses 10 to 40 times the maximum recommended human dose. The relevance of such a mechanism in humans is unclear. K-PIO-GM Tablets are contraindicated for use during pregnancy.

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. It also increases the fetal risk for major birth defects, still birth, and macrosomia-related morbidity. Thus, when the patient plans to become pregnant and during pregnancy, it is recommended that insulin be used to maintain blood glucose levels as close to normal as possible.

Lactating Women

It is not known whether pioglitazone and glimepiride are secreted in human milk. Both, pioglitazone and glimepiride are secreted in the milk of lactating rats. Other sulfonylurea drugs are excreted in human milk and there is a risk of hypoglycaemia in nursing infants. Thus, breastfeeding is not recommended during treatment with glimepiride-containing preparations. Metformin is excreted into human breast 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.
K-PIO-GM Tablets should not be administered to breast-feeding women. Accordingly, a decision should be made whether to discontinue nursing or discontinue therapy, taking into account the importance of these drugs to the mother.

Paediatric Patients
Safety and efficacy of this combination therapy in paediatric patient have not been established. Thus, K-PIO-GM Tablets are not recommended for use in children.

Geriatric Patients
With pioglitazone and glimepiride, no significant differences were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Both, glimepiride and metformin are known to be substantially excreted by the kidney. Thus, risk of serious adverse reactions to these drugs is greater in elderly patients as they are more likely to have renal impairment. Also, with metformin therapy, elderly patients are at higher risk of having lactic acidosis. In addition, hypoglycemia may be difficult to recognize in the elderly. No dose adjustment is usually required in elderly patients with normal renal and hepatic function. It is advised to initiate treatment with the lowest available dose and assess the renal function more frequently in this population.

Renal Impairment Patients
Pioglitazone can be administered in patients with impaired renal function. However, both, glimepiride and metformin are significantly excreted by renal route. Thus, caution should be exercised during administration of this combination product in patients with renal dysfunction. K-PIO-GM Tablets are contraindicated in severe renal impairment patients with an estimated glomerular filtration rate (eGFR) below 30 ml/minute/1.73 m^2.
Clinical studies have demonstrated that elimination of the two major metabolites of glimepiride is reduced in patients with renal impairment. To minimize the risk of hypoglycemia, the recommended starting dose of glimepiride is 1 mg daily for all type 2 diabetes patients with renal impairment. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. Before initiation of the metformin-containing preparation and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should

be assessed more frequently. Metformin-containing preparations should be discontinued immediately, if evidence of renal impairment is present (eGFR < 30 ml/minute/1.73 m^2).

Hepatic Impairment Patients

Hepatic impairment patients are particularly susceptible to the hypoglycemic action of glimepiride. Use of metformin in these patients has been associated with some cases of lactic acidosis. Pioglitazone should also be used with caution in patients with hepatic disease. Pioglitazone-containing preparations should not be initiated if a patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 times upper limit of normal - ULN) at baseline. K-PIO-GM Tablets are contraindicated in patients with severe hepatic impairment.
In patients with severe renal or hepatic impairment, insulin is indicated.

4.7Effect on Ability to Drive and Use Machines

All sulfonylurea class of drugs, including glimepiride, can cause hypoglycemia as an adverse drug reaction. Severe hypoglycemia can lead to unconsciousness or convulsions and impairment of brain function. 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. Patients should be advised to take precautions to avoid hypoglycaemia. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. Further, if patients feel any symptoms of hypoglycemia, driving or operating machinery should be strictly avoided.

4.8Undesirable Effects

Pioglitazone

Commonly reported adverse events with pioglitazone include edema, cardiac failure, pain in extremity, back pain, chest pain, upper respiratory tract infection, headache, sinusitis, myalgia, pharyngitis, and rarely hypoglycemia.

- Adverse events when pioglitazone is co-administered with metformin: Upper respiratory tract infection (URTI), headache, edema, and weight gain.
- Adverse events when pioglitazone is co-administered with sulphonylureas: Edema, headache, flatulence, weight gain, urinary tract infections (UTIs,) URTIs, and hypoglycemia.
- Adverse events when pioglitazone is co-administered with insulin: Hypoglycemia, edema, weight gain, UTIs, diarrhea, back pain, blood creatinine phosphokinase increased, sinusitis, and hypertension.

Clinical Trials Experience

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies are listed below:

Infections and Infestations: Upper respiratory tract infection, bronchitis, sinusitis.
Neoplasms (benign, malignant, and unspecified): Bladder cancer.
Blood and Lymphatic System Disorders: Anemia.
Immune System Disorders: Hypersensitivity and allergic reactions.
Metabolism and Nutrition Disorders: Hypoglycaemia, increase in appetite.
Nervous System Disorders: Hypo-aesthesia, headache, dizziness, insomnia.
Eye Disorders: Visual disturbance, macular edema.
Ear and Labyrinth Disorders: Vertigo.
Cardiac Disorders: Heart failure.
Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea.
Gastrointestinal Disorders: Flatulence.
Skin and Subcutaneous Tissue Disorders: Sweating.
Musculoskeletal and Connective Tissue Disorders: Bone fractures, arthralgia, back pain.
Renal and Urinary Disorders: Haematuria, glycosuria, proteinuria.
Reproductive System and Breast Disorders: Erectile dysfunction.
General Disorders: Edema, fatigue,
Investigations: Weight gain, increased blood creatine phosphokinase, increased lactic dehydrogenase, increased alanine aminotransferase.

Post-Marketing Experience
The following adverse reactions have been reported during post-marketing use of pioglitazone.

- New onset or worsening diabetic macular edema with decreased visual acuity.
- Fatal and nonfatal hepatic failure.
- Congestive heart failure.
- Unusually rapid increase in weight - Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

<u>Glimepiride</u>
Clinical Trials Experience
The most commonly reported adverse reactions of glimepiride include hypoglycemia, dizziness, asthenia, headache, nausea, accidental injury, and flu-like syndrome.
Hypoglycemia: In a randomized, double-blind, placebo-controlled, 14 week clinical trial, the overall incidence of possible hypoglycemia is 4% for glimepiride 1 mg and 17% for glimepiride 4 mg. The overall incidence of possible hypoglycemia for glimepiride vs. placebo is 19.7% vs. 3.2%.
Weight Gain: Glimepiride, like all sulfonylureas, can cause weight gain.
Allergic Reactions: Allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions have been reported rarely with glimepiride.
Laboratory Tests: Elevated levels of serum Alanine Aminotransferase (ALT) has been reported with glimepiride.

Post-Marketing Experience

The following adverse reactions have been reported 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, thrombocytopenia, aplastic anemia, and pancytopenia.
- Hepatic porphyria reactions and disulfiram-like reactions.
- Hyponatremia and syndrome of inappropriate antidiuretic hormone (ADH) secretion, most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of ADH.
- Dysgeusia.
- Alopecia.

Metformin

The most common adverse reactions reported with metformin are nausea, vomiting, diarrhoea, indigestion, abdominal pain, abdominal discomfort, constipation, dyspepsia/heartburn, flatulence, dizziness, taste disturbance, headache, upper respiratory infection, asthenia, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Very rarely metformin may cause skin reactions such as erythema, pruritus, urticaria; abnormal liver function test or hepatitis; and lactic acidosis which generally resolve upon metformin discontinuation.

Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with post-marketing use of metformin.

4.9Overdose

Pioglitazone

In clinical studies, patients have taken pioglitazone at higher than the recommended maximum dose of 45 mg daily. The maximum reported dose of 120 mg/day for 4 days, then 180 mg/day for 7 days have not associated with any symptoms. Hypoglycaemia may occur in combination with sulphonylureas or insulin.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Glimepiride

An overdose of glimepiride can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

Metformin

Overdose of metformin hydrochloride has been reported with ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Lactic acidosis is a medical emergency and must be treated in hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom metformin overdose is suspected.

5. Pharmacological Properties

5.1 Mechanism of Action

Pioglitazone

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its unique 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 a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR-γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Glimepiride

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Glimepiride regulates insulin secretion by binding to the sulfonylurea receptor in the pancreatic beta cell plasma membrane, leading to closure of the ATP-sensitive potassium channel. Closing the potassium channel induces depolarisation of the beta cell and results in an increased influx of calcium (by opening of calcium channels) into the cell. This leads to insulin release through exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel, but which is different from the usual sulfonylurea binding site.

Metformin

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effects via following 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of intestinal glucose absorption.

5.2Pharmacodynamic Properties

Pioglitazone

Pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels. Fasting and post-prandial glycemic control is improved in patients with type 2 diabetes mellitus. The decreased insulin resistance produced by pioglitazone results in lower blood glucose concentrations, lower plasma insulin levels and lower HbA1c values. Pioglitazone reduces the hyperglycemia, hyperinsulinaemia, and hypertriglyceridaemia which are characteristics of insulin-resistant diabetes mellitus. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues. Pioglitazone enhances the effects of circulating insulin by decreasing insulin resistance. Therefore, it does not cause hypoglycemia.

Glimepiride

Glimepiride is an orally active hypoglycemic agent which belongs to the sulphonylurea class. Glimepiride is used in the management of non-insulin dependent (type 2) diabetes mellitus. The effect of glimepiride is dose-dependent and reproducible. In diabetic patients, optimum glycemic control over 24 hours can be achieved with a single daily dose of glimepiride.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. This effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects.

Extrapancreatic Activity: The extrapancreatic effects are an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver. The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins (called GLUT) located in the cell membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride rapidly increases the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Metformin

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non-glycemic effect of metformin is either weight neutral or modest weight loss.

5.3Pharmacokinetic Properties

Pioglitazone

Absorption: Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations (T_{max}) of unchanged pioglitazone are usually achieved within 2 hours after administration. Food delays the T_{max} to 3 to 4 hours, but does not alter the extent of absorption (AUC). The absolute bioavailability following oral administration is approximately 83%.
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 7 days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. Repeated dosing does not result in accumulation of the compound or metabolites.
Distribution: The estimated volume of distribution in humans is 0.25 l/kg. Pioglitazone is extensively bound to plasma protein (> 99 %), principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Major metabolite M-III and M-IV are also extensively bound (>98%) to serum albumin.
Metabolism: Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 and 3A4. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly converted to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.
Excretion: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Elimination of unchanged pioglitazone is negligible in either urine or feces. Pioglitazone is excreted primarily as metabolites and their conjugates. Most of the oral dose (55%) is excreted into the bile as metabolites and eliminated in the feces. The mean serum half-life ($t^{1/2}$) of pioglitazone and its metabolites (M-III and M-IV) range from 3 to 7 hours and 16 to 24 hours, respectively.

Glimepiride

Absorption: The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum plasma concentration (C_{max}) is reached approximately 2.5 hours after oral intake and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approximately 8.8 litres), high protein binding (>99%), and a low clearance (approximately 48 ml/min).
Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (CHMD) and the carboxyl derivative. Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to CHMD. CHMD is further metabolized to carboxyl derivative (inactive) by one or several cytosolic enzymes.
Excretion: Mean serum half-life of glimepiride is about 5 to 8 hours. After high doses, half-lives are slightly longer. After oral administration of glimepiride, about 58% is excreted in the urine and 35% in the faeces. No parent/unchanged drug has been detected in the urine or feces. Two metabolites are identified both in urine and faeces (i.e., CHMD and carboxyl derivative). The elimination half-lives of these metabolites are 3 to 6 and 5 to 6 hours, respectively.

Metformin Extended Release

Absorption: After an oral dose of the extended release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours). The AUC after a single oral administration of 2000 mg of metformin extended release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily. The extent of absorption (as measured by AUC) of metformin (in extended release form) increases when given with food. There was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin in extended release form.
Distribution: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ranged between 63 to 276 liters.
Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been detected in humans.
Excretion: Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus, the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

6. Nonclinical Properties

6.1 Animal Toxicology

Pioglitazone

Toxicity: Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone hydrochloride (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on

mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately four times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Carcinogenesis: A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder of male rats. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). Urinary calculi with subsequent irritation and hyperplasia were postulated as the mechanism for bladder tumors observed in male rats.

A two-year mechanistic study was conducted in male rats utilizing dietary acidification to reduce calculi formation. Dietary acidification decreased but did not abolish the hyperplastic changes in the bladder. The presence of calculi exacerbated the hyperplastic response to pioglitazone but was not considered the primary cause of the hyperplastic changes. The relevance to humans of the bladder findings in the male rat cannot be excluded.

A two-year carcinogenicity study was also conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

Mutagenesis: Pioglitazone hydrochloride was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

Impairment of Fertility: No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone hydrochloride daily prior to and throughout mating and gestation (approximately nine times the maximum recommended human oral dose based on mg/m^2).

Glimepiride

Carcinogenesis: Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation. No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Mutagenesis: Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).
Impairment of Fertility: There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (> 1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Metformin

Carcinogenesis: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.
Mutagenesis: There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.
Impairment of Fertility: Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.
Teratogenicity: Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively.

7. Description

K-PIO-GM 1 mg Tablets are pink/white colour, oblong shaped, biconvex, bilayered, uncoated tablets and scored in the middle of pink colour side and plain on the other side.
K-PIO-GM 2 mg Tablets are blue/white colour, oblong shaped, biconvex, bilayered, uncoated tablets and scored in the middle of blue colour side and plain on other side.

Each tablet of K-PIO-GM 1 mg contains 15 mg of pioglitazone, 1 mg of glimepiride, and 500 mg of metformin hydrochloride for oral administration in adults.
Each tablet of K-PIO-GM 2 mg contains 15 mg of pioglitazone, 2 mg of glimepiride, and 500 mg of metformin hydrochloride for oral administration in adults.

Pioglitazone

Pioglitazone is a thiazolidinedione class of oral antidiabetic drugs. Pioglitazone is an insulin sensitizing agent.

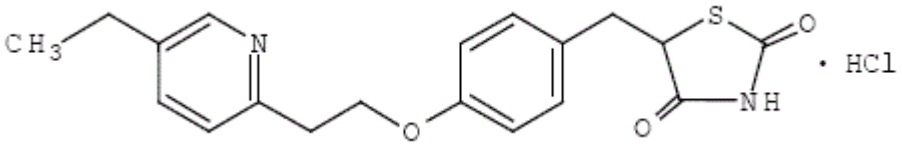
Pioglitazone hydrochloride is an odorless white crystalline powder.

Molecular Weight: 392.9 g/mol.

Molecular Formula: C19H20N2O3S•HCl.

Chemical Name: 5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione;hydrochloride.

Structural Formula:



Glimepiride

Glimepiride is a long-acting sulfonylurea class of oral antidiabetic agent.

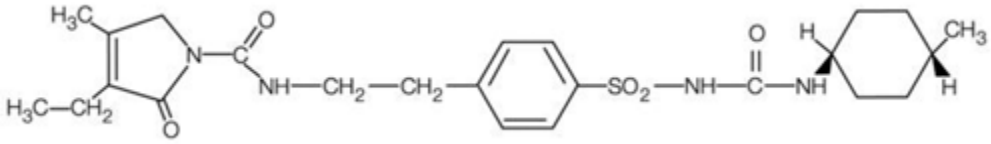
Glimepiride is a white to yellowish-white, crystalline, odorless powder.

Molecular Weight: 490.6 g/mol.

Molecular Formula: C24H34N4O5S.

Chemical Name: 4-ethyl-3-methyl-N-[2-[4-[(4-methylcyclohexyl) carbamoylsulfamoyl] phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide.

Structural Formula:



Metformin Hydrochloride

Metformin hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic effect.

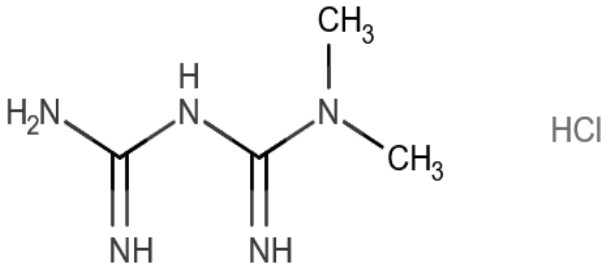
Metformin hydrochloride is white powder which is freely soluble in water and slightly soluble in alcohol.

Molecular Weight: 165.62 g/mol.

Molecular Formula: C4H12ClN5.

Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride.

Structural Formula:



Inactive ingredients (excipients) of K-PIO-GM 1 mg Tablet contain Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrollidone K-90, Purified Water, Talc, Magnesium Stearate, Lactose, Sodium Starch Glycollate, Colour Erythrosine lake IHS, Polyvinyl Pyrollidone K-30, Isopropyl Alcohol, Methylene Chloride, and Crospovidone.

Inactive ingredients (excipients) of K-PIO-GM 2 mg Tablet contain Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrollidone K-90, Purified Water, Talc, Magnesium Stearate, Lactose, Sodium Starch Glycollate, Colour Brilliant Blue Lake, Polyvinyl Pyrollidone K-30, Isopropyl Alcohol, Methylene Chloride, and Crospovidone.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Pregnant women and breastfeeding mothers should strictly avoid use of this medicine.
- Instruct patients not to take this medicine if they have liver and/or kidney dysfunction.

- Advise patients not to take this medicine if they have a severe infection or if they are seriously dehydrated.
- Patients are advised not to take this medicine for type 1 diabetes or for the treatment of diabetic ketoacidosis.
- This medicine is not advisable for use in children.
- Instruct patients not to take this medicine if they are going to have a contrast x-ray.
- Advise patients not to drink alcohol excessively while on this drug therapy.
- This medicine (as it contain pioglitazone) can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure.
- Do not take this medicine if you have severe heart failure or heart failure with symptoms such as shortness of breath or swelling.
- Do not take this medicine if you have or have had cancer of the bladder.
- Inform patients about the potential side effects of this medicine (as it contains glimepiride) including hypoglycemia (low blood sugar level) and weight gain. Explain the symptoms of hypoglycemia (dizziness, sweating, hunger, fast heartbeat, inability to concentrate, confusion, anxiety or nervousness, headache) and treatment (sugar, glucose biscuits, corn syrup, honey, fruit juice, candies/chocolates) as well as conditions that predispose to hypoglycemia.
- Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. Thus, patients are advised not to drive or operate machinery if they feel any hypoglycemic symptoms.

10. Details of Manufacturer

The Madras Pharmaceuticals
137-B, Old Mahabalipuram Road, Karapakkam,
Chennai – 600 096. Tamilnadu, India.

11. Details of Permission or License Number with Date

K-PIO-GM 1 mg: Mfg. Lic. No. : 247; Date of FDA Product Permission: 28/06/2017.
K-PIO-GM 2 mg: Mfg. Lic. No. : 247; Date of FDA Product Permission: 27/06/2017.

12. Date of Revision

April 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.