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

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PIOPOD G
(Pioglitazone Hydrochloride and Glimepiride Tablets)

COMPOSITION
PIOPOD G 1
Each uncoated tablet contains:

Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone	15 mg
Glimepiride I.P.	1 mg
Excipients	q.s.
Colour : Red Oxide of Iron	

PIOPOD G 2
Each uncoated tablet contains:

Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone	15 mg
Glimepiride I.P.	2 mg
Excipients	q.s.

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.**

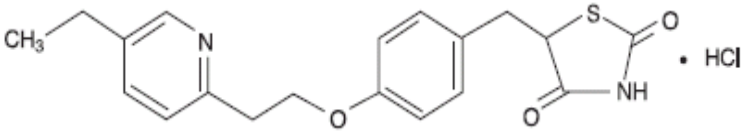
- **Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.**

DESCRIPTION

PIOPOD G (pioglitazone hydrochloride and glimepiride) tablets contain two oral antihyperglycemic agents used in the management of type 2 diabetes: pioglitazone hydrochloride and glimepiride.

Pioglitazone Hydrochloride

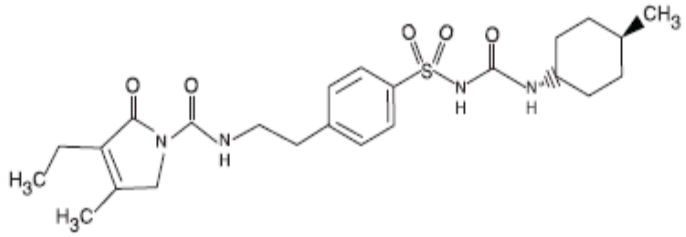
Pioglitazone hydrochloride is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that Pioglitazone hydrochloride improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone hydrochloride improves glycemic control while reducing circulating insulin levels. Pioglitazone is [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. It is used as racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90. It is soluble in N, N-dimethyl formamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Glimepiride

Glimepiride is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1- carboxamido)ethyl] phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea. It had a molecular formula of $C_{24}H_{34}N_4O_5S$ and a molecular weight of 490.62. The structural formula is:



CLINICAL PHARMACOLOGY

PIOPOD G contains two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral

glucose utilization, whereas sulfonylureas are insulin secretogogues that act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Pioglitazone Hydrochloride
Pioglitazone depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulindependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective 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, hyper insulinemia, and hypertriglyceridemia characteristic of insulinresistant 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. Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Glimepiride
The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacokinetic
Absorption
Pioglitazone
Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Glimepiride
After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and C_{max} at 2 to 3 hours.

Distribution

Pioglitazone

The mean apparent volume of distribution (V/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. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Glimepiride

After intravenous (IV) dosing in normal subjects, Vd/F 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, Elimination and Excretion

Pioglitazone

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

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 studies of Pioglitazone in combination with P450 inhibitors and substrates have been performed. Urinary 6β-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer. Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and total Pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Glimepiride

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). CYP2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that

recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations
Renal Insufficiency
Pioglitazone
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.

Glimepiride
Glimepiride serum levels decreased as renal function decreased. However, metabolite serum levels increased in case of renal failure condition. The apparent terminal half-life (T½) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased.

Hepatic Insufficiency
Pioglitazone
Patients with impaired hepatic functions (Child-Pugh Grade B/C), pioglitazone mean peak concentration decreased by half but no change in the mean AUC values. Therapy with combination should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceeds 2.5 times the upper limit of normal.

Glimepiride
No studies were performed in patients with hepatic insufficiency.

Elderly
Pioglitazone
In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Glimepiride
Comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤ 65 years and those >65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady-state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatrics

Pioglitazone

Pharmacokinetic data in the pediatric population are not available. Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of combination Piopod G, have not been determined in this population.

INDICATIONS

PIOPOD G is a thiazolidinedione and sulfonylurea combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone.

The drug should not be used as first line of therapy for diabetes.

CONTRAINDICATION

Initiation of Pioglitazone hydrochloride and Glimepiride combination in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. In addition, Pioglitazone hydrochloride and Glimepiride combination is contraindicated in patients with: Known hypersensitivity to pioglitazone, glimepiride or any other component of PIOPOD G. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

Glimepiride

Glimepiride is contraindicated in patients with a history of a hypersensitivity reaction to:

• Glimepiride or any of the product's ingredients.

Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to Glimepiride. Do not use Glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

Reported hypersensitivity reactions include cutaneous eruptions with or without pruritus as well as more serious reactions (e.g. anaphylaxis, angioedema, Stevens-Johnson syndrome, dyspnea)

WARNINGS AND PRECUATIONS

Increased Risk of Cardiovascular Mortality

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. 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 (Diabetes, 19 supp. 2: 747-830, 1970). 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 tablets 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.

Pioglitazone

Cardiac Failure and Other Cardiac Effects

Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antihyperglycemic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of congestive heart failure exacerbation.

Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin; hence combination should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia

Patients receiving pioglitazone in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular

Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status. Post-marketing experience with pioglitazone, cases of congestive heart failure been reported in both with and without previously known heart disease.

Edema

Edema is reported in placebo controlled trials and is known to be dose-related. Patients should be monitored for sign and symptoms of heart failure during the treatment with Pioglitazone hydrochloride.

Weight Gain

Dose related weight gain was observed with pioglitazone alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Ovulation
Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women should be recommended while taking pioglitazone hydrochloride and metformin hydrochloride combination.

Hematologic
From the clinical trial, pioglitazone decreases the mean haemoglobin level by 2% to 4%.Combination also decreases the haematocrit level.

Hepatic Effects
Therapy with pioglitazone and metformin extended release combination should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes [ALT levels at 1 to 2.5 UNL (Upper normal limit)] at baseline or any time during therapy with combination should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with pioglitazone and metformin extended release combination in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 UNL), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 UNL, the test should be repeated as soon as possible. If ALT levels remain > 3 UNL or if the patient is jaundiced, combination should be discontinued.

Macular Edema
Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.

Fractures
An increased incidence of bone fracture was noted in female patients taking pioglitazone. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone.

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 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.

DRUG INTERACTION
Glimepiride
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.

The following are examples of medications 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, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors. When these medications are administered to a patient receiving Glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications 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 glycemic control. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for hypoglycemia.

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of Glimepiride’s glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of Glimepiride in an unpredictable fashion. The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Miconazole
A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

Cytochrome P450 2C9 Interactions
There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

Concomitant Administration of Colesevelam
Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, Glimepiride should be administered at least 4 hours prior to colesevelam.

Pioglitazone
Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. In vitro studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMG-CoA reductase inhibitors are not to be expected. Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered. Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered.

ADVERSE REACTIONS
PIOGLITAZONE MONOTHERAPY
Eye disorders
Common: visual disturbance

Infection and infestations
Common: upper respiratory tract infection
Uncommon: sinusitis

Investigations
Common: weight increased

Nervous system disorders
Common: hypoaesthesia
Uncommon: insomnia

PIOGLITAZONE IN COMBINATION THERAPY WITH SULPHONYLUREA
Ear and labyrinth disorders
Uncommon: vertigo

Eye disorders
Uncommon: visual disturbance

Gastrointestinal disorders
Common: flatulence

General disorders and administration site conditions
Uncommon: fatigue

Investigations
Common: weight increased
Uncommon: increased lactic dehydrogenase

Metabolism and nutritional disorders
Uncommon: appetite increased, hypoglycaemia

Nervous system disorders
Common: dizziness
Uncommon: headache

Renal and urinary disorders
Uncommon: glycosuria, proteinuria

Skin and subcutaneous tissue disorders
Uncommon: sweating

POST-MARKETING DATA
Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination.Some patients had peripheral edema at the time macular edema was

diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. Oedema was reported in 6-9% of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2-5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2-3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic agents.

In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, Metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovaascular disease, the incidence of serious heart failure was 1.6 % higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. A pooled analysis was conducted of adverse event reports of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

Glimepiride

- Hypoglycemia
- Hemolytic anemia

Clinical Trials Experience
Approximately 2,800 patients with type 2 diabetes have been treated with Glimepiride in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with Glimepiride for at least 1 year.

Table 1 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment duration ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of ≥5% among Glimepiride -treated patients and more commonly than in patients who received placebo.

Table 1. Eleven Pooled Placebo-Controlled Trials ranging from 13 weeks to 12 months: Adverse Events (Excluding Hypoglycemia) Occurring in ≥5% of Glimepiride -treated Patients and at a Greater Incidence than with Placebo*

	Glimepiride N=745 %	Placebo N=294 %
Headache	8.2	7.8
Accidental Injury†	5.8	3.4
Flu Syndrome	5.4	4.4
Nausea	5.0	3.4
Dizziness	5.0	2.4

* Glimepiride doses ranged from 1-16 mg administered daily †Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia

Hypoglycemia:
In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to Glimepiride 1 mg, 4 mg, 8 mg or placebo. Patients randomized to Glimepiride 4 mg or 8 mg underwent forced-titration from an initial dose of 1 mg to these final doses, as tolerated. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for Glimepiride 1 mg, 17% for Glimepiride 4 mg, 16% for Glimepiride 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg Glimepiride or placebo daily. The dose of Glimepiride was titrated to a target fasting plasma glucose of 90-150 mg/dL. Final daily doses of Glimepiride were 1, 2, 3, 4, 6 or 8 mg. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for Glimepiride vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: Glimepiride, like all sulfonylureas, can cause weight gain

Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of Glimepiride -treated

patients. These may resolve despite continued treatment with Glimepiride. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock).

Laboratory Tests: Elevated Serum Alanine Aminotransferase (ALT): In 11 pooled placebo-controlled trials of Glimepiride, 1.9% of Glimepiride -treated patients and 0.8% of placebo-treated patients developed serum ALT greater than 2 times the upper limit of the reference range.

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

OVERDOSAGE

Pioglitazone
Dose up to 180mg daily for seven days have been reported in literature but no any clinical symptoms seen in patient. In the event of overdosage, appropriate supportive treatment should be nitiated according to patient's clinical signs and symptoms.

Glimepiride
An overdosage of Glimepiride, as with other sulfonylureas, 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.

DOSAGES AND ADMINISTRATION

The use of Piopod G in the management of type 2 diabetes should be individualized on the basis of effectiveness, tolerability and starting dose as well as current regimen of combination. Selecting the starting dose of Piopod G should be based on the patient's current regimen of

pioglitazone and/or sulfonylurea. Those patients who may be more sensitive to antihyperglycemic drugs should be monitored carefully during dose adjustment. After initiation of Piopod G, patients should be carefully monitored for adverse events related to fluid retention. Starting dose for patients currently on pioglitazone monotherapy Based on the usual starting doses of glimepiride (1 mg or 2 mg once daily), and pioglitazone 15 mg or 30 mg, PIOPOD G may be initiated at once daily, and adjusted after assessing adequacy of therapeutic response. The total daily doses of Piopod G should not exceed the maximum recommended total daily doses of pioglitazone (45mg) or or glimepiride (8 mg). Any change in diabetic therapy should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. Patients should be observed carefully for hypoglycemia (1-2 weeks) when being transferred to PIOPOD G, especially from longer half-life sulfonylureas (e.g. chlorpropamide) due to potential overlapping of drug effect. Sufficient time should be given to assess adequacy of therapeutic response. Ideally, the response to therapy should be evaluated using A1C, which is a better indicator of long-term glycemic control than FPG alone. A1C reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with PIOPOD G for a period of time adequate to evaluate change in A1C (8-12 weeks) unless glycemic control as measured by FPG deteriorates Patients should be informed that Piopod G must be swallowed whole and not chewed, cut or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that resemble the original tablet.

USE IN SPECIFIC POPULATION

Pregnancy

Risk related to diabetes

When uncontrolled, diabetes (gestational or permanent) gives rise to an increase in congenital abnormalities and perinatal mortality. Diabetes must be controlled as far as possible during the period of conception in order to reduce the risk of congenital abnormalities. When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with this product, but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus. In case of treatment by this product, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Glimepiride

Pregnancy Category C

There are no adequate and well-controlled studies of Glimepiride in pregnant women. 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.

Renal Impairment
To minimize the risk of hypoglycemia, the recommended starting dose of Glimepiride is 1 mg daily for all patients with type II diabetes and renal impairment.

A multiple-dose titration study was conducted in 16 patients with type 2 diabetes and renal impairment using doses ranging from 1 mg to 8 mg daily for 3 months. Baseline creatinine clearance ranged from 10-60 mL/min. The pharmacokinetics of Glimepiride were evaluated in the multiple-dose titration study and the results were consistent with those observed in patients enrolled in a single-dose study. In both studies, the relative total clearance of Glimepiride increased when kidney function was impaired. Both studies also demonstrated that the elimination of the two major metabolites was reduced in patients with renal impairment.

Pioglitazone
There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy. In animal fertility studies there was no effect on copulation, impregnation or fertility index.

Lactation
Glimepiride
It is not known whether Glimepiride is excreted in human milk. During pre- and post-natal studies in rats, significant concentrations of glimepiride were present in breast milk and the serum of the pups. Offspring of rats exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Based on these animal data and the potential for hypoglycemia in a nursing infant, a decision should be made whether to discontinue nursing or discontinue Glimepiride, taking into account the importance of Glimepiride to the mother.

Pioglitazone
Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

Geriatric Use
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).

Glimepiride is substantially excreted by the kidney. Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly. Use caution when initiating Glimepiride and increasing the dose of Glimepiride in this patient population.

Pioglitazone
In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients. These clinical experiences have not identified differences in effectiveness and safety between the elderly (_ 65 years) and younger patients although small sample sizes for patients 75 years old limit conclusions.

Pediatric Use
Safety and effectiveness of Tri-Azulix tablets in pediatric patients have not been established. Use in pediatric patients is not recommended for the treatment of diabetes due potential adverse effects on body weight and hypoglycemia by pioglitazone and lack of long-term safety data of Pioglitazone component.

The pharmacokinetics, efficacy and safety of Glimepiride have been evaluated in pediatric patients with type 2 diabetes as described below. Glimepiride is not recommended in pediatric patients because of its adverse effects on body weight and hypoglycemia.

The pharmacokinetics of a 1 mg single dose of Glimepiride was evaluated in 30 patients with type 2 diabetes (male = 7; female = 23) between ages 10 and 17 years. The mean (± SD) AUC(0-last) (339±203 ng•hr/mL), Cmax (102±48 ng/mL) and t1/2 (3.1±1.7 hours) for glimepiride were comparable to historical data from adults (AUC(0-last) 315±96 ng•hr/mL, Cmax 103±34 ng/mL and t1/2 5.3±4.1 hours).

The safety and efficacy of Glimepiride in pediatric patients was evaluated in a single-blind, 24-week trial that randomized 272 patients (8-17 years of age) with type 2 diabetes to Glimepiride (n=135) or metformin (n=137). Both treatment-naïve patients (those treated with only diet and exercise for at least 2 weeks prior to randomization) and previously treated patients (those previously treated or currently treated with other oral antidiabetic medications for at least 3 months) were eligible to participate. Patients who were receiving oral antidiabetic agents at the time of study entry discontinued these medications before randomization without a washout period. Glimepiride was initiated at 1 mg, and then titrated up to 2, 4 or 8 mg (mean last dose 4 mg) through Week 12, targeting a self-monitored fasting fingerstick blood glucose < 126 mg/dL. Metformin was initiated at 500 mg twice daily and titrated at Week 12 up to 1000 mg twice daily (mean last dose 1365 mg).

EXPIRY DATE
Do not use later than date of expiry.

STORAGE
Store below 25^{o} C in a dry place. Protect from light. Keep out of reach of children.

PRESENTATION
PIOPOD G1 and PIOPOD G2 are available in strip of 10 tablets.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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