Piompride 30 mg /4 mg

Tablet

WARNING: CONGESTIVE HEART FAILURE

Thiazolidinediones, including pioglitazone, which is a component of Piompride, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions].*

After initiation of Piompride and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, 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 Piompride must be considered *[see Warnings and Precautions].*

Piompride is not recommended in patients with symptomatic heart failure *[see Warnings and Precautions].*

Initiation of Piompride in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Contraindications and Warnings and Precautions].*

INDICATIONS AND USAGE

Piompride is 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 sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone.

Important Limitations of Use

Pioglitazone exerts its antihyperglycemic effect only in the presence of endogenous insulin. Piompride should not be used to treat type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

Use caution in patients with liver disease *[see Warnings and Precautions]*.

DOSAGE AND ADMINISTRATION

1- Recommendations for All Patients

Piompride should be taken once daily with the first main meal.

Piompride tablets are available as a 30 mg pioglitazone plus 4 mg glimepiride tablet. If therapy with a combination tablet containing pioglitazone and glimepiride is considered appropriate the recommended starting dose is:

- 30mg/4 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,

- For patients inadequately controlled on glimepiride monotherapy: 30 mg/4 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- for patients who are changing from combination therapy of pioglitazone plus glimepiride as separate tablets: Piompride should be taken at doses that are as close as possible to the dose of pioglitazone and glimepiride already being taken,
- for patients currently on a different sulfonylurea monotherapy or switching from combination therapy of pioglitazone plus a different sulfonylurea (e.g., glyburide, glipizide, chlorpropamide, tolbutamide, acetohexamide): 30 mg/2 mg once daily and adjusted after assessing adequacy of therapeutic response. Observe for hypoglycemia for one to two weeks due to the potential overlapping drug effect.
- for patients with systolic dysfunction, the lowest approved dose of Piompride should be prescribed only after titration from 15 mg to 30 mg of pioglitazone has been safely tolerated.

After initiation of Piompride or with dose increase, monitor patients carefully for hypoglycemia and adverse reactions related to fluid retention such as weight gain, edema, and signs and symptoms of congestive heart failure *[see Boxed Warning* and *Warnings and Precautions]*.

Liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) should be obtained prior to initiating Piompride. Routine periodic monitoring of liver tests during treatment with Piompride is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of Piompride or who are found to have abnormal liver tests while taking Piompride should be managed as described under Warnings and Precautions *[see Warnings and Precautions* and *Clinical Pharmacology]*.

2- Concomitant Use with an Insulin Secretagogue or Insulin

If hypoglycemia occurs in a patient coadministered Piompride and an insulin secretagogue, the dose of the insulin secretagogue should be reduced.

If hypoglycemia occurs in a patient coadministered Piompride and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.

3- Concomitant Use with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors. If gemfibrozil or other CYP2C8 inhibitors need to co-administered, patients should switch to individual components of Piompride because the minimum dose of pioglitazone in Piompride exceeds 15 mg *[see Drug Interactions and Clinical Pharmacology]*.

4-Concomitant Use with Colesevelam

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, Piompride should be administered at least four hours prior to colesevelam

[see Drug Interactions and *Clinical Pharmacology]*.

CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure *[see Boxed Warning]*.
- Use in patients with known hypersensitivity to pioglitazone, glimepiride or any other component of Piompride *[see Warnings and Precautions]*.
- Use in patients with known history of an allergic reaction to sulfonamide derivatives.

Reported hypersensitivity reactions with glimepiride include cutaneous eruptions with or without pruritus as well as more serious reactions (e.g., anaphylaxis, angioedema, Stevens-Johnson Syndrome, dyspnea) *[see Warnings and Precautions and Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

1- Congestive Heart Failure

Pioglitazone

Pioglitazone, like other thiazolidinediones, can cause dose- related fluid retention when used alone or in combination with other antidiabetic medications and is most common when Piompride is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of Piompride must be considered *[see Boxed Warning, Contraindications and Adverse Reactions**]*.**

2- Hypoglycemia

Glimepiride

All sulfonylureas, including glimepiride, a component of PIOMPRIDE, can cause severe hypoglycemia *[see Adverse Reactions]*. 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 Piompride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other antidiabetic 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.

3- Hypersensitivity Reactions

Glimepiride

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

4- Potential Increased Risk of Cardiovascular Mortality with Sulfonylureas Glimepiride

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.

5- Hepatic Effects

Pioglitazone

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone-controlled clinical trial database to date *[see Adverse Reactions]*.

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating Piompride therapy. In patients with abnormal liver tests, Piompride should be initiated with caution.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than 3 times the upper limit of the reference range), Piompride treatment

should be interrupted and investigation done to establish the probable cause. Piompride should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on Piompride. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with Piompride can be used with caution.

6- Urinary Bladder Tumors

Pioglitazone

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.

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

7-Edema

Pioglitazone

In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related *[see Adverse Reactions]*. In postmarketing experience, reports of new onset or worsening edema have been received.

Piompride 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, Piompride should be used with caution in patients at risk for congestive heart failure. Patients treated with Piompride should be monitored for signs and symptoms of congestive heart failure *[see Boxed Warning, Warnings and Precautions, and Patient Counseling Information]*.

8- Fractures

The risk of fracture should be considered in the care of patients, especially female patients, treated with Piompride and attention should be given to assessing and maintaining bone health according to current standards of care.

9- Hemolytic Anemia

Glimepiride

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because Piompride contains glimepiride, which belongs to the class of sulfonylurea agents, use

caution in patients with G6PD deficiency and consider the use of a nonsulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency *[see Adverse Reactions]*.

10- Macular Edema

Pioglitazone

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 others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of the thiazolidinedione.

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings *[see Adverse Reactions]*.

11- Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PIOGLITAZONE+Glimepiride.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Congestive Heart Failure *[see Boxed Warning and Warnings and Precautions]*
- Hypoglycemia *[see Warnings and Precautions]*
- Edema *[see Warnings and Precautions]*
- Fractures *[see Warnings and Precautions]*
- Hemolytic Anemia *[see Warnings and Precautions]*

The adverse events reported in at least 5% of patients in the controlled 16-week clinical studies between placebo plus a sulfonylurea and pioglitazone (15 mg and 30 mg combined) plus sulfonylurea treatment arms were upper respiratory tract infection, accidental injury, and combined edema/peripheral edema, respectively.

Adverse Events that Occurred in ≥5% of Patients

Hypoglycemia - Upper Respiratory Tract Infection - Weight Increased - Edema Lower Limb – Headache - Urinary Tract Infection – Diarrhea – Nausea - Pain in Limb.

Anemia was reported in ≤2% of patients treated with pioglitazone plus a sulfonylurea *[see Warnings and Precautions]*.

Pioglitazone

In the PROactive trial, the incidence of withdrawals due to adverse events was 9.0% for patients treated with pioglitazone and 7.7% for placebo-treated patients. Congestive heart failure was the most common serious adverse event leading to withdrawal occurring in 1.3% of patients treated with pioglitazone and 0.6% of patients treated with placebo.

Adverse Events Reported at an Incidence >5% and More Commonly in Patients Treated with Pioglitazone than in Patients Treated with Placebo:

Upper respiratory tract infection- headache- sinusitis-myalgia-pharyngitits.

Incidence and Types of Adverse Events Reported in >5% of Patients Treated with Pioglitazone and More Commonly than Placebo

Hypoglycemia – Edema - Cardiac Failure - Pain in Extremity - Back Pain -Chest Pain.

- **Congestive Heart Failure**
- **Cardiovascular Safety**
- **Weight Gain**
- **Edema**
- **Hepatic Effects**
- **Hypoglycemia**
- **Urinary Bladder Tumors**

Glimepiride

Adverse events that occurred in controlled clinical trials with placebo and glimepiride monotherapy, other than hypoglycemia, included: headache, accidental injury, flu syndrome, nausea and dizziness, respectively.

Hypoglycemia

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) [see Warnings and Precautions].

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 two times the upper limit of the reference range.

Laboratory Abnormalities

Pioglitazone

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. In placebo- controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Creatine Phosphokinase

During protocol- specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2150 to 11400 IU/L) and in no comparator -treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

Postmarketing Experience

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

Pioglitazone

- New onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions]*.
- Fatal and nonfatal hepatic failure *[see Warnings and Precautions]*.

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

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see Boxed Warning and Warnings and Precautions]*.

Glimepiride

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson Syndrome *[see Warnings and Precautions]*.
- Hemolytic anemia in patients with and without G6PD deficiency *[see Warnings and Precautions]*.
- 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/mcL) 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.

DRUG INTERACTIONS

1- Strong CYP2C8 Inhibitors

Pioglitazone

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration- time curve or AUC) and half-life ($t_{½}$) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors. Since the minimum dose of pioglitazone in PIOMPRIDE exceeds 15 mg, patients taking concomitant strong CYP2C8

inhibitors should switch to individual components of PIOMPRIDE, unless the prescribing health care provider determines that the benefit of PIOMPRIDE clearly outweighs the risk of increased pioglitazone exposure *[see Dosage and Administration and Clinical Pharmacology]*.

2- CYP2C8 Inducers

Pioglitazone

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 *[see Clinical Pharmacology]*.

3- Topiramate

Pioglitazone

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

4- Drugs Affecting Glucose Metabolism

Glimepiride

A number of medications affect glucose metabolism and may require Piompride 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, a component of Piompride, 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 Piompride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving Piompride, 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 Piompride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving Piompride, monitor the patient closely for hypoglycemia.

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

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of Piompride 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.

5- Miconazole

Glimepiride

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.

6- CYP2C9 Interactions

Glimepiride

There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of CYP2C9. 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.

7- Concomitant Administration of Colesevelam

Glimepiride

Colesevelam can reduce the maximum plasma concentrations and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered four hours prior to colesevelam. Therefore, Piompride should be administered at least four hours prior to colesevelam *[see Clinical Pharmacology]*.

USE IN SPECIFIC POPULATIONS

1-Pregnancy

Limited data with (PIOGLITAZONE+Glimepiride) or pioglitazone in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are clinical considerations related to fetal and neonatal adverse reactions and drug discontinuation if glimepiride is used during pregnancy. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Neonates of women with gestational diabetes, who are treated with sulfonylureas during pregnancy, may be at increased risk for neonatal intensive care unit admission, and may develop respiratory distress, hypoglycemia, birth injury, and be large for gestational age.

Piompride should be discontinued at least two weeks before expected delivery.

2- Lactation

There is no information regarding the presence of pioglitazone or glimepiride in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone and glimepiride are present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Piompride and any potential adverse effects on the breastfed infant from Piompride or from the underlying maternal condition.

3- Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some anovulatory women.

4- Pediatric Use

Safety and effectiveness of Piompride in pediatric patients have not been established.

Piompride is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors *[see Warnings and Precautions]*.

5- Geriatric Use

To minimize the risk of hypoglycemia, the initial dosing, dose increments, and maintenance dosage of Piompride should be conservative. During initiation of Piompride therapy and any subsequent dose adjustments, geriatric patients should be observed carefully for hypoglycemia.

6- Renal Impairment

To minimize the risk of hypoglycemia, the initial dosing, dose increments and maintenance dosage of Piompride should be conservative. During initiation of Piompride therapy and any subsequent dose adjustments, these patients should be observed carefully for hypoglycemia.

OVERDOSAGE

Pioglitazone

In the event of overdosage, appropriate supportive treatment should be initiated according to the 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 *[see Warnings and Precautions]*.

DESCRIPTION

Piompride tablets are a thiazolidinedione and a sulfonylurea combination product that contains two oral antihyperglycemic agents: pioglitazone and glimepiride. The concomitant use of pioglitazone and a sulfonylurea, the class of drugs that includes glimepiride, has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on a sulfonylurea. Additional efficacy and safety information about pioglitazone and glimepiride monotherapies may be found in the prescribing information for each individual drug.

Pioglitazone is an oral antidiabetic medication.

CLINICAL PHARMACOLOGY

1- Mechanism of Action

PIOMPRIDE

Piompride combines 2 antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone, 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 secretagogues that act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Pioglitazone

Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Glimepiride

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

2- Pharmacodynamics

Pioglitazone

Pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin.

Patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone *[see Warnings and Precautions* and *Adverse Reactions]*.

Glimepiride

In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately by two to three hours after single oral doses of glimepiride.

3- Pharmacokinetics

Absorption and Bioavailability:

PIOMPRIDE

Bioequivalence studies were conducted following a single dose of the (PIOGLITAZONE+Glimepiride) 30 mg/4 mg tablets and concomitant administration of pioglitazone (30 mg) and glimepiride (4 mg) under fasting conditions in healthy subjects.

Based on the area under the curve (AUC) and maximum concentration (C_{max}) of both pioglitazone and glimepiride, (PIOGLITAZONE+Glimepiride)30 mg/4 mg were bioequivalent to pioglitazone 30 mg concomitantly administered with glimepiride (4 mg).

Food did not change the systemic exposures of glimepiride or pioglitazone following administration of Piompride. The presence of food did not significantly alter the time to peak serum concentration

(T_{max}) of glimepiride or pioglitazone and C_{max} of pioglitazone. However, for glimepiride, there was a 22% increase in C_{max} when (PIOGLITAZONE+Glimepiride) was administered with food.

Pioglitazone

Following once- daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

C_{max}, AUC, and trough serum concentrations (C_{min}) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.

Following oral administration of pioglitazone, T_{max} of pioglitazone was within two hours. Food delaysT_{max} to three to four hours but does not alter the extent of absorption (AUC).

Glimepiride

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C_{max}) two to three hours post-dose. When glimepiride was given with meals, the mean C_{max} and AUC were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance (CL/F) of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intra- and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15% to 23% and 24% to 29%, respectively.

Distribution

Pioglitazone

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. M-III and M-IV are also extensively bound (>98%) to serum albumin.

Glimepiride

After intravenous (IV) dosing in healthy 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

Pioglitazone

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone which include CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. *In vivo* study of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*. Urinary 6ß -hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

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 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several

cytosolic enzymes. In animals, M1 possesses about one -third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans. M2 is inactive.

Excretion and Elimination

Pioglitazone

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life ($t_{1/2}$) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hr.

Glimepiride

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

Renal Impairment

Pioglitazone

The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate [creatinine clearance (CLcr) 30 to 50 mL/min] and severe (CLcr <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required.

Glimepiride

In a single-dose, open-label study glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by CLcr: Group I consisted of five patients with mild renal impairment (CLcr >50 mL/min), Group II consisted of patients with moderate renal impairment (CLcr =20 to 50 mL/min) and Group III consisted of seven patients with severe renal impairment (CLcr <20 mL/min). Although, glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and

an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The t for glimepiride did not change, while the t for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

Hepatic Impairment

Pioglitazone

Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean C but no change in the mean AUC values. Therefore, no dose adjustment in patients with hepatic impairment is required.

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range. Use (pioglitazone+glimepride) with caution in patients with liver disease .

Glimepiride

It is unknown whether there is an effect of hepatic impairment on glimepiride pharmacokinetics because the pharmacokinetics of glimepiride has not been adequately evaluated in patients with hepatic impairment.

Geriatric Patients

Pioglitazone

In healthy elderly subjects, C of pioglitazone was not significantly different, but AUC values were approximately 21% higher than those achieved in younger subjects. The mean t of pioglitazone was also prolonged in elderly subjects (about 10 hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Glimepiride

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

Pediatric Patients

No pharmacokinetic studies(pioglitazone+glimepride) were performed in pediatric patients.

Pioglitazone

Safety and efficacy of pioglitazone in pediatric patients have not been established. (pioglitazone+glimepride) is not recommended for use in pediatric patients

Gender

Pioglitazone

The mean C and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, HbA1c decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). Because therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Glimepiride

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Ethnicity

Pioglitazone

Pharmacokinetic data among various ethnic groups are not available.

Glimepiride

No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the reduction in HbA1c was comparable in Caucasians (n=536), blacks (n=63), and Hispanics (n=63).

Obese Patients

The pharmacokinetics of glimepiride and its metabolites were measured in patients with type 2 diabetes who either had normal body weight or were morbidly obese.

While the Tmax , CL/F, and Vd/F of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower Cmax and AUC than those of normal body weight. The mean Cmax , AUC 0-24 , AUC 0-∞ values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours·ng/mL vs. 2820 ± 1110 hours·ng/mL and 4000 ± 1320 hours·ng/mL versus 3280 ± 1360 hours·ng/mL, respectively.

Drug-Drug Interactions

Coadministration of pioglitazone (45 mg) and a sulfonylurea (5 mg glipizide) administered orally once daily for seven days did not alter the steady-state pharmacokinetics of glipizide. Glimepiride and glipizide have similar

metabolic pathways and are mediated by CYP2C9; therefore, drug-drug interaction between pioglitazone and glimepiride is considered unlikely. Specific pharmacokinetic drug interaction studies with (pioglitazone+glimepride) have not been performed, although such studies have been conducted with the individual pioglitazone and glimepiride components.

Pioglitazone

Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs					
	Coadministered Drug				
Pioglitazone Dosage Regimen (mg)*	**Name and Dose Regimens**	**Change in AUC†**		**Change in C_{max}†**	
45 mg	Warfarin‡				
	Daily loading then maintenance Doses based PT and INR values Quick's Value = 35 ± 5%	R-Warfarin	↓3%	R-Warfarin	↓2%
		S-Warfarin	↓1%	S-Warfarin	↑1%
45 mg	**Digoxin**				
	0.250 mg twice daily (loading dose) Then 0.250 mg daily (maintenance dose, 7 days)	↑15%		↑17%	
45 mg daily for 21 days	**Oral Contraceptive**				
	[Ethinyl Estradiol (EE) 0.035 mg plus	EE	↓11%	EE	↓13%
	Norethindrone (NE) 1 mg] for 21 days	NE	↑3%	NE	↓7%
45 mg	**Fexofenadine**				
	60 mg twice daily for 7 days	↑30%		↑37%	
45 mg	**Glipizide**				
	5 mg daily for 7 days	↓3%		↓8%	
45 mg daily for 8 days	**Midazolam**				
	7.5 mg single dose on Day 15	↓26%		↓26%	
45 mg	**Ranitidine**				
	150 mg twice daily for 7 days	↑1%		↓1%	
45 mg daily for 4 days	**Nifedipine ER**				
	30 mg daily for 4 days	↓13%		↓17%	
45 mg	**Atorvastatin Ca**				
	80 mg daily for 7 days	↓14%		↓23%	
45 mg	**Theophylline**				
	400 mg twice daily for 7 days	↑2%		↑5%	

*Daily for 7 days unless otherwise noted

†% change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively

‡Pioglitazone had no clinically significant effect on prothrombin time

Table 14. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

Coadministered Drug and Dosage Regimen	Pioglitazone		
	Dose Regimen (mg)*	Change in AUC†	Change in C_{max}†
Gemfibrozil 600 mg twice daily for 2 days (N=12)	15 mg single dose	↑3.2-fold‡	↑6%
Ketoconazole 200 mg twice daily for 7 days (N=28)	45 mg	↑34%	↑14%
Rifampin 600 mg daily for 5 days (N=10)	30 mg single dose	↓54%	↓5%
Fexofenadine 60 mg twice daily for 7 days (N=23)	45 mg	↑ 1%	0%
Ranitidine 150 mg twice daily for 4 days (N=23)	45 mg	↓ 13%	↓16%
Nifedipine ER 30 mg daily for 7 days (N=23)	45 mg	↑5%	↑4%
Atorvastatin Ca 80 mg daily for 7 days (N = 24)	45 mg	↓24%	↓31%
Theophylline 400 mg twice daily for 7 days (N=22)	45 mg	↓4%	↓2%
Topiramate 96 mg twice daily for 7 days§ (N=26)	30 mg§	↓15%¶	0%

* Daily for 7 days unless otherwise noted

†Mean ratio (with/without coadministered drug and no change = 1-fold) % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively

‡The half-life of pioglitazone increased from 8.3 hours to 22.7 hours in the presence of gemfibrozil

§Indicates duration of concomitant administration with highest twice-daily dose of topiramate from Day 14 onwards over the 22 days of study

¶ Additional decrease in active metabolites; 60% for M-III and 16% for M-IV.

Glimepiride

Aspirin

Coadministration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride C_{max}.

Cimetidine and Ranitidine

Coadministration of cimetidine or ranitidine with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

Propranolol

Concomitant administration of propranolol and glimepiride significantly increased glimepiride C_{max}, AUC, and $t_{1/2}$ by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/F by 18%. The recovery of M1 and M2 from urine was not changed.

Warfarin

The concomitant administration of glimepiride did not alter the pharmacokinetics of *R*- and *S* -warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

Colesevelam

Concomitant administration of colesevelam and glimepiride resulted in reductions in glimepiride $AUC_{0-\infty}$ and C_{max} of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colesevelam, there was not significant change in glimepiride $AUC_{0-\infty}$ and C_{max}, -6% and 3%, respectively *[see Dosage and Administration (2.4) and Drug Interactions]*.

PATIENT COUNSELING INFORMATION

- Inform patients that Piompride is not recommended for patients with symptoms of heart failure.
- Inform patients that patients with severe heart failure (NYHA Class III or IV) cannot start Piompride as the risks exceed the benefits in such patients.
- It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly. Patients should also be informed of the potential risks and advantages of Piompride and of alternative modes of therapy.
- Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment as these may be due to bladder cancer.
- Prior to initiation of Piompride therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members *[see Warnings and Precautions]*. Combination therapy of Piompride with other antihyperglycemic agents may also cause hypoglycemia.

- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on Piompride should immediately report these symptoms to a physician.
- Tell patients to promptly stop taking Piompride and seek immediate medical advice if there is unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine as these symptoms may be due to hepatotoxicity.
- Inform female patients that treatment with pioglitazone, like other thiazolidinediones may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations]*.
- Patients should be told to take a single dose of Piompride once daily with the first main meal and instructed that any change in dosing should be made only if directed by their physician *[see Dosage and Administration]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is Important. It allows continued monitoring of the benefit/risk balance of the medicinal Product. Healthcare professionals are asked to report any suspected adverse reactions via:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

Or on the following address:

Block No 6048, 6th industrial zone Sadat city, Egypt. Tel: 0482630201/2, Fax: 0482630203

55 Hafez badawy street Nasr city, Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No. 1303

PHARMACEUTICAL PARTICULARS

1-Active Ingredients:

Each Tablet Contain: Glimepiride 4mg + Pioglitazone Hydrochloride 33.068mg (Eq. To Pioglitazone 30mg)

2-List of excipients

Starch 1500- Mannitol DC - Sodium lauryl sulfate - Magnesium stearate - Colloidal silicon dioxide.

3-Shelf life

3 years

4-Special precautions for storage

Store in temperature not exceeding 30°C in dry place.

5-Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

6-Pack

Carton box contains 1 or 3(AL/Opaque PVC) Strips, each of 10 tablets & an inner leaflet.

Produced by Averroes Pharma for pharmaceutical industries

Block No. 6048 6th industrial zone, Sadat city, Egypt.