Pioglitazone HCl

Piozone®
15 mg & 30 mg Tablet
oral hypoglycemic

FORMULATION

Each tablet contains:
Pioglitazone (as hydrochloride) …… 15 mg or 30 mg

PRODUCT DESCRIPTION

15 mg Tablet: White to off-white, 3/16" round, biconvex tablet, plain on both sides
30 mg Tablet: White, 9/32" round, flat tablet, bisected on one side and plain on the other side

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pioglitazone, a potent and highly selective peroxisome proliferator-activated receptor gamma (PPARγ) agonist, is a thiazolidinedione oral antidiabetic agent that acts primarily by reducing insulin resistance. It improves glycemic control by increasing insulin sensitivity in target tissues, primarily skeletal muscle and adipose tissue, and by decreasing hepatic gluconeogenesis.

Activation of PPARγ nuclear receptors, which are found in key target tissues for insulin action (e.g., adipose tissue, skeletal muscle, liver), modulates the transcription of insulin-responsive genes involved in the control of glucose and lipid metabolism.

Like other thiazolidinediones, pioglitazone minimizes the risk of hypoglycemia associated with the treatment of type 2 diabetes by decreasing insulin resistance without stimulating insulin release from pancreatic beta-cells.

Pharmacokinetics

Pioglitazone is absorbed rapidly with peak plasma concentrations occurring within two hours after oral administration (fasting state). Repeated dosing does not result in accumulation of pioglitazone or metabolites. Pioglitazone is more than 80% bioavailable. While food slightly delays pioglitazone's absorption, the extent of absorption is not altered.

Pioglitazone is more than 99% plasma protein bound and its mean apparent volume of distribution after single-dose administration is about 0.63±0.41 L/kg body weight. Metabolites M-III and M-IV are also extensively bound to serum albumin (>98%).

Pioglitazone is extensively metabolized by hydroxylation and oxidation through the cytochrome P450 isoforms (mainly CYP2C8 and to a lesser degree CYP3A4, with additional contributions from other isoforms including the mainly extrahepatic CYP1A1); the metabolites are also partly converted to glucuronide or sulfate conjugates. M-II, M-III and M-IV are its pharmacologically active metabolites. Studies of pioglitazone in combination with P450 inhibitors and substrates have been performed and have shown that pioglitazone is not a strong CYP3A4 enzyme inducer.

Steady-state serum concentrations of both pioglitazone and total pioglitazone (pioglitazone plus active metabolites) are achieved within 7 days. At steady state, two of the pharmacologically active metabolites of pioglitazone, M-III and M-IV, reach serum concentrations equal to or greater than pioglitazone. At steady state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30-50% of the peak total pioglitazone concentrations and 20-25% of the total area under the serum concentration-time curve (AUC).

C_{max}, AUC and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg/day.

Pioglitazone is primarily excreted through the bile as unchanged drug or as metabolites and eliminated in the feces. About 15-30% of an oral pioglitazone dose is recovered in the urine (as metabolites and its conjugates); its renal elimination is negligible. Pioglitazone's plasma elimination half-life is up to 7 hours while its active metabolites have a half-life of up to 24 hours.

Special Populations

Renal Insufficiency: Compared with normal subjects, the serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30-60 mL/min) to severe (creatinine clearance <30 mL/min) renal impairment.

Hepatic Insufficiency: Compared with normal subjects, patients with hepatic dysfunction (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak plasma concentrations and no change in the mean AUC values. Do not initiate the drug in patients who exhibit clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal.

Elderly: Peak serum concentrations of pioglitazone and total pioglitazone are not significantly different in healthy elderly subjects. However, the AUC values in these patients are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes are considered to be clinically irrelevant.

INDICATIONS

Treatment of type 2 diabetes mellitus:

- As monotherapy in patients whose hyperglycemia cannot be controlled by diet and exercise alone, to decrease insulin-resistance and blood glucose levels.
- In combination with a sulfonylurea, metformin or insulin when adequate glycemic control is not achieved by diet, exercise and monotherapy.

DOSAGE AND ADMINISTRATION

- Include nutritional counseling, weight reduction (as needed), and exercise in the management of type 2 diabetes.
- Individualize antidiabetic therapy based on glycemic control and patient's response to treatment.
- Patients should be carefully monitored for adverse reactions related to fluid retention and signs of congestive heart failure after initiation of pioglitazone or with dose increase (see **WARNINGS AND PRECAUTIONS**).
- Liver enzymes should be checked prior to initiation of pioglitazone therapy (see **WARNINGS AND PRECAUTIONS**).
- As adverse events such as edema and weight gain appear to be dose-related, the smallest effective dose should be used.
- During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to pioglitazone hydrochloride and identify the minimum effective dose. Thereafter, glycosylated hemoglobin (HbA_{1c}) should be measured at intervals of approximately three months.

Monotherapy

- ***Starting Dose in Patients without Congestive Heart Failure:*** 15 mg or 30 mg once a day, with or without meals
- ***Starting Dose in Patients with NYHA Class I or II Heart Failure:*** 15 mg once a day

Dosage may be titrated in increments of 15 mg ***up to a maximum of 45 mg once a day*** *based on glycemic response as determined by HbA_{1c}.*

Combination Therapy with Metformin
- Pioglitazone in combination with metformin may be initiated at 15 mg or 30 mg once a day.
- Continue current metformin dose when starting pioglitazone therapy.

Combination Therapy with Sulfonylurea
- Pioglitazone in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once a day.
- Continue current sulfonylurea dose when starting pioglitazone therapy.
- Decrease the sulfonylurea dose if patients report hypoglycemia during combination therapy.

Combination with Insulin
- Continue current insulin dose upon starting pioglitazone therapy.
- Decrease insulin dose by 10-25% if the patient reports hypoglycemia or if fasting plasma glucose (FPG) decreases to below 100 mg/dL.
- Individualize further adjustments based on the glucose-lowering response.

Coadministration with strong CYP2C8 Inhibitors (see **INTERACTIONS WITH OTHER MEDICAMENTS**)
- The maximum recommended dose is 15 mg once a day.

Missed Dose
- When a dose is missed, pioglitazone should be taken as soon as the patient remembers. In cases where the time is too close to the next dose, the missed dose should be skipped and treatment should be resumed with the next scheduled dose.

CONTRAINDICATIONS
- Hypersensitivity to pioglitazone hydrochloride or to any component of this product
- New York Heart Association (NYHA) Class III or IV heart failure
- Serious hepatic impairment
- Pregnancy
- Type 1 diabetes or diabetic ketoacidosis

WARNINGS AND PRECAUTIONS

CONGESTIVE HEART FAILURE

- Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients (see **WARNINGS AND PRECAUTIONS**).
- After initiation of pioglitazone, 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 pioglitazone must be considered.
- Pioglitazone is not recommended in patients with symptomatic heart failure.
- Initiation of pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**)

Fluid Retention and Congestive Heart Failure *(see BOXED WARNING)*
Like other thiazolidinediones, pioglitazone can cause fluid retention when used alone or in combination with other antidiabetic medicines and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure.

Pioglitazone should be used with caution in patients with existing edema or heart failure. The incidence of heart failure increases in patients with a history of cardiac disease such as coronary artery disease, previous coronary artery bypass graft procedures and myocardial infarction. Weight gain, usually dose-dependent and probably due to a combination of fluid retention and fat accumulation, has been reported with pioglitazone use. Patients who experience weight gain should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Initiate pioglitazone therapy at the lowest approved dose when treating patients who have at least one risk factor for development of congestive heart failure. Monitor patients for signs and symptoms of heart failure and fluid retention. In particular, patients who are at risk for heart failure including those receiving concurrent therapy which increases insulin levels (i.e., insulin, sulfonylureas) should be closely monitored (see Undesirable Effects).

Urinary Bladder Tumors

- ***Do <u>not</u> use pioglitazone in patients with active bladder cancer.***
- ***Use pioglitazone with caution in patients with prior history of bladder cancer. The benefits of blood sugar control with pioglitazone should be weighed against the unknown risk for cancer recurrence.***

Results from a 5-year interim analysis of a 10-year observational cohort study showed a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, in particular those who were treated for the longest durations and with the highest cumulative doses. The study suggest that the use of pioglitazone for more than one year increased the relative risk of developing bladder cancer in any given year by 40% (absolute risk of 3 cases in 10,000). Although there is insufficient evidence to determine whether pioglitazone promotes the development of urinary bladder tumors, pioglitazone should not be used in patients with active bladder cancer. In patients with a history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered.

Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, back or abdominal pain, as these may be due to bladder cancer.

Hepatic Effects

Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels, i.e., ALT >2.5 times the upper limit of normal (ULN), or active liver disease.

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking pioglitazone. These reports, however, contain insufficient information necessary to establish the probable cause.

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). These patients may also have other forms of liver disease many of which can be treated or managed. It is therefore recommended that prior to therapy with pioglitazone, a liver function test panel [i.e., aspartate aminotransferase (AST), alanine aminotransfease (ALT), alkaline phosphatase, and total bilirubin] be obtained and patient be assessed for liver disease. Pioglitazone should be initiated with caution in patients with abnormal liver tests.

Measure liver tests promptly if manifestations suggestive of liver injury (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or jaundice) develop in patients receiving pioglitazone. Discontinue pioglitazone therapy if ALT increases to >3 times the ULN during therapy and remains elevated, or if jaundice develops. Patients should be investigated and should not be restarted on pioglitazone without establishing the probable cause of the liver injury.

Do not restart pioglitazone in patients with serum ALT elevations >3 times the ULN and serum total bilirubin >2 times the reference range without alternative etiologies since they are at risk for severe drug-induced liver injury. Initiation of, or continuation of therapy with pioglitazone in patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, should proceed with caution.

Increased Risk of Fracture in Women
In clinical trials, there were more reports of fractures in female patients taking thiazolidinediones, including pioglitazone, than those taking a comparator (either placebo or active). The incidence of bone fracture in females was 5.1% for pioglitazone versus 2.5% for placebo. The difference was noted after the first year of treatment and remained during the course of the study. Majority of fractures observed in female patients were nonvertebral fractures including fractures in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula, and tibia).

Consider the risk of fracture in the care of patients, especially female patients, being treated with pioglitazone or when starting pioglitazone treatment; attention should be given to assessing and monitoring bone health according to current standards of care.

Hypoglycemia
The use of pioglitazone in combination with insulin and other antidiabetic medicines particularly insulin secretagogues (such as sulfonylureas) may increase the risk for hypoglycemia. Reduction in the dose of the concomitant antidiabetic medicine may be necessary.

Macular Edema
Macular edema, some with blurred vision or decreased visual acuity, has been reported in patients receiving pioglitazone or other thiazolidinediones. Most patients reported concurrent peripheral edema. In some patients, macular edema improved after discontinuation of thiazolidinedione treatment.

Although it is not known whether there is causal relationship between pioglitazone and macular edema, regular eye examination by an ophthalmologist is recommended for all diabetic patients. Promptly report and refer any visual symptom to an ophthalmologist.

Ovulation
Pioglitazone, like other thiazolidinediones, may cause ovulation in anovulatory premenopausal women with insulin resistance. These women have an increased possibility of pregnancy unless contraceptive methods are initiated.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone or any other antidiabetic medicine. Pioglitazone should not be prescribed to lower the risk of cardiovascular diseases (i.e., myocardial infarction and stroke) or to lower cardiovascular mortality.

Type 1 Diabetes Mellitus or Diabetic Ketoacidosis
Pioglitazone is active only in the presence of endogenous insulin and should therefore not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hematologic
Pioglitazone may cause dose-related decreases in hemoglobin and hematocrit which usually become evident within the first three months of starting treatment. These hematologic effects may be related to plasma volume expansion.

INTERACTIONS WITH OTHER MEDICAMENTS
Oral Contraceptives: Coadministration of pioglitazone (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) resulted in 11%

and 11-14% decrease in ethinyl estradiol AUC and C_{max}, respectively. Clinical significance of a high variability on ethinyl estradiol pharmacokinetics is unknown.

Insulin or Insulin Secretagogues: The dose of insulin and insulin secretagogues (e.g., sulfonylurea) should be reduced since concomitant administration may result in hypoglycemia.

Midazolam: Administration of pioglitazone for 15 days followed by a 7.5 mg single dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Strong CYP2C8 Inhibitors: Gemfibrozil (an inhibitor of CYP450 2C8) resulted in a 3-fold increase in the plasma concentration of parent pioglitazone and also inhibited the further metabolism of M-III and M-IV. Careful blood glucose monitoring and dosage adjustments are suggested during coadministration of pioglitazone and gemfibrozil. If used in combination with gemfibrozil or other strong CYP2C8 inhibitors, a maximum dose of 15 mg pioglitazone should be used.

CYP2C8 Inducers: Coadministration of pioglitazone with rifampicin (an inducer of CYP450 2C8) resulted in a 54% reduction in pioglitazone's AUC. The dose of pioglitazone may need to be increased when rifampicin is coadministered and glycemic control closely monitored.

If an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, the maximum recommended dose of 45 mg should not be exceeded and changes in diabetes treatment may be needed based on the patient's clinical response.

Drugs Metabolized via Cytochrome P450: The cytochrome P450 isoform, CYP3A4, is partially responsible for the metabolism of pioglitazone. Potential pharmacokinetic interaction (reduction in peak plasma concentration and AUC) with CYP3A4 substrates (e.g., atorvastatin, nifedipine). Clinical significance of this finding is unknown.

Peak plasma concentration and area under the concentration-time curve (AUC) of pioglitazone may increase when taken concomitantly with CYP3A4 inhibitors such as ***ketoconazole***. However, pharmacokinetic interaction is unlikely with ***ranitidine*** which is a relatively weak CYP3A4 inhibitor.

In vitro studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolized by these enzymes are unlikely: Ciclosporin, calcium channel blockers, and HMG-CoA reductase inhibitors.

Coadministration of pioglitazone with the following drugs did not show pharmacokinetic interactions: Metformin, glipizide, digoxin, phenprocoumon, fexofenadine, CYP2C9 substrates (e.g., warfarin), CYP1A2 substrates (e.g., theophylline)

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy: *Pregnancy Category C.*

Oral hypoglycemic agents (including pioglitazone) are not recommended during pregnancy. Although there are no adequate and well-controlled studies of pioglitazone in pregnant women, animal studies show increased rates of post-implantation loss, delayed development, reduced fetal weights, and delayed parturition at doses 10 to 40 times the maximum recommended human dose. Maintaining blood glucose levels as close to normal as possible is necessary during pregnancy since abnormal blood glucose levels are associated with a higher incidence of congenital abnormalities. Insulin is recommended during pregnancy.

Lactation
It is not known whether pioglitazone is excreted in human milk although pioglitazone is secreted in the milk of lactating rats. Pioglitazone should not be administered to breastfeeding women.

Infants and Children
The safety and efficacy of pioglitazone in children have not been established. Use in patients <18 years old is not recommended.

Geriatric Use (≥65 years old)
There are no significant differences in the pharmacokinetics, efficacy and safety of pioglitazone between geriatric and younger patients.

Renal Impairment
There is no information available on the use of pioglitazone in dialyzed patients. The use of pioglitazone is not recommended in these patients.

UNDESIRABLE EFFECTS
Respiratory Effects: Upper respiratory tract infection, dyspnea, sinusitis, bronchitis, pulmonary edema, and pharyngitis

Endocrine Effects: Aggravated diabetes mellitus, erectile dysfunction.
Dose-related mild to moderate hypoglycemia has been reported when pioglitazone was used in combination with either a sulfonylurea or insulin.

Cardiovascular Effects: Congestive heart failure and edema/peripheral edema have been reported especially when pioglitazone is used in combination with insulin.

Cardiac failure, heart failure, chest pain, abnormal ECG, hypertension, ischemia, angina pectoris, myocardial infarction, myocardial ischemia and transient ischemic attacks. Heart rate and rhythm disorders have also been reported.

CNS Effects: Headache, hypoesthesia, vertigo, dizziness, and insomnia

Musculoskeletal Effects: Arthralgia, myalgia, back pain, and cramps (legs). Increased risk of fractures in female patients taking pioglitazone has been reported (see **WARNINGS AND PRECAUTIONS**).

Hepatic Effects: Fatal and non-fatal hepatic failure and hepatitis have been reported. During all clinical trials in the U.S., 11 of 2561 (0.43%) patients treated with pioglitazone had ALT values ≥3 ULN. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with pioglitazone, mean values for bilirubin, AST, ALT, alkaline phosphatase, and Gamma-glutamyl transferase (GGT) were decreased at the final visit compared with baseline. Sporadic, transient elevations in creatine phosphokinase (CPK) levels have also occurred.

Hematologic Effects: Anemia has been reported in patients taking pioglitazone in combination with sulfonylureas, metformin or insulin.

Dose-related decreases in hemoglobin and hematocrit have been associated with pioglitazone use.

Renal Effects: Urinary tract infection, hematuria, glycosuria, and proteinuria

Gastrointestinal Effects: Flatulence, increased appetite and diarrhea

Eye Disorders: New onset or worsening diabetic macular edema with decreased visual acuity has been reported.

Tumors: Urinary bladder tumors (rare)

Others: Tooth disorder, accidental injury, fatigue, sweating, pain in extremity, weight gain, increased lactic dehydrogenase levels

OVERDOSAGE AND MANAGEMENT
There is limited data on pioglitazone overdosage in humans. Pioglitazone doses of up to 180 mg per day for seven days have been taken without any clinical symptom.

Hypoglycemia may occur in combination with sulfonylureas or insulin.

Initiate appropriate supportive treatment dictated by the patient's clinical signs and symptoms if overdose occurs.

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

AVAILABILITY
Pioglitazone hydrochloride (Piozone®) 15 mg Tablet, in flex foil x 10s (box of 30s)
Pioglitazone hydrochloride (Piozone®) 30 mg Tablet, in flex foil x 10s (box of 30s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.