PIOGLITAZONE HYDROCHLORIDE

GLITAZ

30 mg Tablet

ORAL HYPOGLYCEMIC

FORMULATION
Each tablet contains:
Pioglitazone Hydrochloride
Equivalent to Pioglitazone . . . . . .30 mg

PRODUCT DESCRIPTION
White to off white colored round biconvex uncoated tablets.

PHARMACODYNAMICS
Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excluding, insulins.

Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with Pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of Pioglitazone vs. Gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of HbA1c $\geqslant$ 8.0% after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in patients treated with Gliclazide, compared with Pioglitazone. At two years, glycaemic control (defined as HbA1c < 8.0%) was sustained in 69% of patients treated with Pioglitazone, compared with 50% of patients on Gliclazide. In a two-year study of combination therapy comparing Pioglitazone with Gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA1c was similar between treatment groups after one year. The rate of deterioration of HbA1c during the second year was less with Pioglitazone than with Gliclazide.

PHARMACOKINETICS
Absorption
Following oral administration, Pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged Pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2–60 mg. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.

Distribution
The estimated volume of distribution in humans is 0.25 L/kg.
Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99%).

Biotransformation
Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations, and protein binding are taken into account, Pioglitazone and metabolite M-III contribute equally to efficacy. On this basis, M-IV contribution to efficacy is approximately three-fold that of pioglitazone, while the relative efficacy of M-II is minimal.

In vitro studies have shown no evidence that Pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man.
Interaction studies have shown that Pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of Pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of Pioglitazone.

Elimination
Following oral administration of radiolabelled Pioglitazone to man, recovered label was mainly in feces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged Pioglitazone can be detected in either urine or feces. The mean plasma elimination half-life of unchanged Pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Elderly
Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.

Patients with renal impairment
In patients with renal impairment, plasma concentrations of Pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus, free (unbound) Pioglitazone concentration is unchanged.

Patients with hepatic impairment
Total plasma concentration of Pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of Pioglitazone.

INDICATIONS
Pioglitazone is a thiazolidinedione oral antidiabetic. It is used in the management of type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION
Pioglitazone is given as Pioglitazone hydrochloride but doses are expressed in terms of the base; Pioglitazone hydrochloride 1.1 mg is equivalent to about 1 mg of Pioglitazone. The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary, when used as monotherapy or with Metformin or a sulfonylurea. The dose should not exceed 45 mg/day since doses higher than 45 mg/day have not been studied in clinical trials. Pioglitazone may be taken with or without food.

Pediatric Use:
Safety and effectiveness in pediatrics patients have not been established.

Elderly Use:
No significant differences in safety and efficacy were observed between these patients and younger patients.

Use in Pregnancy:
There are no adequate and well controlled studies in pregnant women. Pioglitazone should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Use in Lactation:
It is not known whether Pioglitazone is secreted in human milk. Pioglitazone should not be administered to lactating women.

CONTRAINDICATIONS
Pioglitazone is contraindicated in patients with known hypersensitivity or allergy to Pioglitazone or any of its excipients.

WARNINGS AND PRECAUTIONS
Fluid retention and cardiac failure
Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or edema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when Pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Since insulin and Pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of edema. Post marketing cases of peripheral edema and cardiac failure have also been reported in patients with concomitant use of Pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

A cardiovascular outcome study of Pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure; however, this did not lead to an increase in mortality in this study.

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

Bladder cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with Pioglitazone (19 cases from 12,506 patients, 0.15%) than in control groups (7 cases from 10,212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, p=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on Pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with Pioglitazone, although not all studies identified a statistically significant increased risk.

Risk factors for bladder cancer should be assessed before initiating Pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing. It is recommended, therefore, that patients treated with Pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Pioglitazone in all patients. Therapy with Pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 x upper limit of normal) or with any other evidence of liver disease.
Following initiation of therapy with Pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 x upper limit of normal during Pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain >3 x the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued.

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

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

Hypoglycaemia
As a consequence of increased insulin sensitivity, patients receiving Pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with thiazolidinediones, including Pioglitazone. Many of these patients reported concurrent peripheral edema. It is unclear whether or not there is a direct association between Pioglitazone and macular edema but prescribers should be alert to the possibility of macular edema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.
The risk of fractures should be considered in the long-term care of patients treated with Pioglitazone.
As a consequence of enhancing insulin action, Pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

Pioglitazone tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

WARNINGS AND PRECAUTIONS
- Do not use Pioglitazone in patients with active bladder cancer.
- Use Pioglitazone with caution in patients with a prior history of bladder cancer.
- The benefits of blood sugar control with Pioglitazone should be weighed against the unknown risk for cancer recurrence.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
There are no adequate human data to determine the safety of Pioglitazone during pregnancy. Fetal 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 fetal growth. The relevance of such a mechanism in humans is unclear and Pioglitazone should not be used in pregnancy.

Breast-feeding
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.

Fertility
In animal fertility studies, there was no effect on copulation, impregnation or fertility index.

ADVERSE DRUG REACTIONS
Adverse effects reported include upper respiratory-tract infections, haematuria, myalgia, and visual disturbances. Effects of lipids: Thiazolidinediones are reported to affect serum concentrations of lipids. Compared with placebo, Pioglitazone has been found to reduce triglycerides, increase high-density lipoprotein (HDL) - cholesterol, and have little or no effect on low-density lipoprotein (LDL) and total cholesterol.
Effects on the liver: There have been isolated reports of hepatocellular injury in patients receiving Pioglitazone. Liver enzymes should be checked before starting therapy with Pioglitazone; patients with alanine aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given Pioglitazone concentrations should then be monitored every 2 months during the first 12 months of treatment and periodically thereafter. If ALT concentrations rise to more than 3 times the upper limit of normal and remains so after retesting then treatment with Pioglitazone should be stopped; treatment should also be stopped if jaundice develops.

DRUG INTERACTIONS
Antibacterials: A report of hypoglycemia when gatifloxacin was given to patient already receiving oral hypoglycaemics.
Gemfibrozil: reported to result in a 3-fold increase in the AUC of Pioglitazone.
Rifampicin: reported to result in a 54% decrease in the AUC of Pioglitazone.
Oral contraceptives reduced the plasma concentrations of hormones by approximately 30%.
Glipizide: does not alter the steady-state pharmacokinetics of glipizide.
Digoxin: does not alter the steady-state pharmacokinetics of digoxin.
Warfarin: does not alter the steady-state pharmacokinetics of warfarin.
Metformin: does not alter the steady-state pharmacokinetics of metformin.

OVERDOSE AND TREATMENT
In clinical studies, patients have taken Pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.
Hypoglycaemia may occur in combination with sulphonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

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

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION
Store at temperatures not exceeding 30ºC.

Keep all medicines out of reach of children.

AVAILABILITY
Alu/Alu Blister Pack x 10's (Box of 100's)

DRP-2807-02
Date of First Authorization: August 3, 2017
Date of Renewal of Authorization: May 31, 2019
Date of Last Revision of Package Insert: August 23, 2019

STLGLIT02/IN00
2YER1112

Distributed by:
THE CATHAY YSS DISTRIBUTORS CO., INC.
2/F Vernida I Condo., 120 Amorsolo St.,
Legaspi Village, Makati City

Manufactured by:
STALLION LABORATORIES PVT. LTD.
C-1B, 305/2, 3, 4 & 5, G.I.D.C., Kerala, Bavla-
382 220, Dist. Ahmedabad, Gujarat, India

Imported by:
AMBICA INTERNATIONAL CORPORATION
#9 Amsterdam Extension, Merville Park Subd.,
Parañaque, Metro Manila