DESCRIPTION

Pioglitazone is an orally administered insulin sensitizing thiazolidinedione agent that has been developed for the treatment of type 2 diabetes mellitus. Pioglitazone activates the nuclear peroxisome proliferator activated receptor-gamma (PPAR-gamma), which leads to the increased transcription of various proteins regulating glucose and lipid metabolites. These proteins amplify the post-receptor actions of insulin in the liver and peripheral tissues, which leads to improved glycaemic control with no increase in the endogenous secretion of insulin.\(^1\)

Oglo brand name of Pioglitazone Hydrochloride Tablet is described chemically as \([(+)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2-4-]thiazolidinedione monohydrochloride.

Oglo is available as a tablet for oral administration containing 15mg or 30mg of pioglitazone and is white to off white, round, flat, bevel edged, scored, uncoated tablet, imprinted with "Oglo" on one side and "15" or "30" on the other side.

COMPOSITION

**OGLO - 15**
Each uncoated tablet contains:
Pioglitazone Hydrochloride equivalent to Pioglitazone.........................15mg

**OGLO - 30**
Each uncoated tablet contains:
Pioglitazone Hydrochloride equivalent to Pioglitazone.........................30mg

CLINICAL PHARMACOLOGY

**Mechanism of action**
Pioglitazone is a thiazolidinedione (glitazone) antidiabetic agent that is structurally and pharmacologically related to troglitazone and rosiglitazone but unrelated to other antidiabetic agents, including sulfonylureas, biguanides, and alpha-glucosidase inhibitors. Pioglitazone acts principally by increasing insulin sensitivity in target tissues, as well as decreasing hepatic gluconeogenesis. Pioglitazone is a peroxisome proliferator-activated receptor agonist that increases transcription of insulin-responsive genes and increases insulin sensitivity. Pioglitazone, like other thiazolidinediones, ameliorates insulin resistance.
associated with type 2 diabetes mellitus, without stimulating insulin release from pancreatic beta cells, thus avoiding the risk of hypoglycemia.  

PHARMACOKINETICS AND DRUG METABOLISM
Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

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

Distribution
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. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the major cytochrome P450 isoforms involved in the hepatic metabolism of pioglitazone are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms. Metabolites M-II and M-IV and M-III are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Excretion and Elimination
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.
The mean serum half life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively.

SPECIAL POPULATIONS
Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended.
Hepatic Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with impaired hepatic function.
Pioglitazone therapy should not be initiated if the patients exhibit clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal.
Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.
Gender: The mean $C_{\text{max}}$ and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, pioglitazone improved glycemic control in both males and females. In controlled clinical trials, hemoglobin $A_1c$ (HbA$_1c$) decreases from baseline were generally greater for females than for males (average mean difference in HbA$_1c$ 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

PHARMACODYNAMICS AND CLINICAL EFFECTS
Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower blood glucose concentrations, lower plasma insulin levels, and lower HbA$_1c$ values. Based on results from an open-label extension study, the glucose lowering effects of pioglitazone appear to persist for at least one year. In controlled clinical trials. Pioglitazone in combination with sulfonylureas, metformin or insulin has an additive effect on glycemia control. Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean change in LDL and total cholesterol.

In the two monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (16 weeks) and metformin (16 weeks), the results were generally consistent with the data above. For pioglitazone treated patients, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL cholesterol.$^{3,4}$

In the combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for pioglitazone-treated patients was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed.$^{5}$

DRUG INTERACTIONS
Glibenclamide and gliclazide: Administration of pioglitazone 30 mg/day for 7 days had no significant effect (relative to baseline) on the pharmacokinetic characteristics of glibenclamide 5 to 10 mg/day or gliclazide 160 mg/day in a study in 9 patients with type 2 diabetes mellitus.
Warfarin, Phenprocoumon, Glipizide, Metformin Or Digoxin:- Administration of pioglitazone 45 mg/day (single and multiple doses) had no significant effect on the pharmacokinetic or pharmacodynamic characteristics of warfarin, phenprocoumon, glipizide, metformin or digoxin in healthy volunteers.$^{8}$
Ethinylestradiol/Norethindrone / estrone. No clinically significant effect of pioglitazone 45 mg/day on the pharmacokinetic of combinations of ethinylestradiol/norethindrone /estrone.$^{9}$

Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral dose up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m$^2$). Drug-induced tumours were not observed in any organ except for the urinary bladder. Benign and / or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m$^2$). The relationship of these findings in male rats to humans is
unclear. A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m²). No drug induced tumours were observed in any organ.

**INDICATIONS AND USAGE**
Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM). Pioglitazone is indicated for monotherapy. It is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counselling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

**CONTRAINDICATIONS**
Pioglitazone is contraindicated in patients with known hypersensitivity to this product or any of its components.

**PRECAUTIONS**

**General**

Ovulatory Effects: Risk for pregnancy unless contraceptive measures initiated. Anovulatory premenopausal women with insulin resistance may resume ovulation during therapy. If menstrual dysfunction occurs, weigh risks versus benefits of continued pioglitazone.

Effect on Fluid Balance: Possible plasma volume expansion and preload-induced cardiac hypertrophy based on animal data. Caution in patients with edema or heart failure; use not recommended for those with NYHA class III or IV heart failure except when expected benefit is thought to outweigh potential risk.

Hepatic Effects: No evidence of hepatotoxicity in clinical studies to date. However, there is structural and pharmacological similarity with troglitazone, which has been associated with potentially fatal hepatotoxicity. Therefore, periodic liver function tests are recommended (prior to therapy, every 2 months for 1 years, then periodically). More frequent monitoring if used in patients with mild hepatic impairment (ALT 1-2.5 times the upper limit of normal). Development of manifestations suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine) should prompt rechecking liver function. If ALT increases to 3 times the upper limit of normal during therapy and remains elevated, or if jaundice develops, discontinue pioglitazone.

Hematologic Effects: Dose-related decreases in hemoglobin and hematocrit, usually becoming evident 4 - 12 weeks after initiation and remaining stable thereafter. These effects may be related to plasma volume expansion and have not been associated with clinically important hematologic manifestations.

Type I Diabetes Mellitus or Diabetic Ketoacidosis: Because pioglitazone requires insulin for activity, it is not indicated for type I diabetes mellitus or ketoacidosis.

Specific Populations

Pregnancy: Category C, however, because of strong suggestion that blood glucose abnormalities during pregnancy are associated with an increased incidence of congenital anomalies and neonatal morbidity and mortality, most clinicians recommended use of insulin for blood glucose control during pregnancy.

Nursing Women: Pioglitazone is distributed in to the milk of lactating rats. Since many drugs are excreted in human milk, “OGLO” should not be administered to breast-feeding women.

Pediatric Use: Safety and efficacy not established in children or adolescents: use in this age group currently is not recommended by the manufacturer.

Geriatric Use: Pharmacokinetics, efficacy, and adverse effect profiles similar to those in younger adults.

Hepatic Impairment: Use with caution in mild hepatic impairment: use is not recommended in moderate to severe hepatic impairment (ALT exceeding 2.5 times upper limit of normal, or
active liver disease), or in patients with troglitazone associated jaundice.

ADVERSE EVENTS
Upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorders, aggravation of diabetes mellitus and pharyngitis were reported in at least 5% of pioglitazone recipients (606 patients). Mild to moderate hypoglycaemia has been reported in patients undergoing therapy with pioglitazone in combination with a sulphonylurea or insulin in clinical studies. Adverse effects generally were similar with pioglitazone monotherapy versus combined therapy with sulphonylureas, metformin, or insulin; however, edema was more common during pioglitazone monotherapy or combined therapy with insulin than with placebo. Anemia and edema generally were mild to moderate and usually did not require drug discontinuance. Pioglitazone-induced reductions in hyperglycemia are associated with mild weight gain. Sporadic, transient elevations in creatinine kinase have been observed without any apparent clinical sequelae; relationship to pioglitazone therapy is unclear.

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

DOSAGE AND ADMINISTRATION
OGLO should be taken once daily without regards to meal.
Individualize the management of antidiabetic therapy. Evaluate the response to therapy using HbA1C, which is a better indicator of long-term glycaemic control than fasting blood glucose (FBG) alone. HbA1C reflects glycaemia over the past 2 to 3 months. In clinical use, it is recommended that patients be treated with pioglitazone for a period of time adequate to evaluate change in HbA1C (3 months) unless glycaemic control deteriorates.

Monotherapy: Initiate monotherapy with Oglo in patients not adequately controlled with diet and exercise at 15 or 30 mg once daily. For patients who respond inadequately to the initial dose of Oglo, the dose can be increased in increments up to 45 mg once daily. Consider combination therapy for patients not responding adequately to monotherapy.
COMBINATION THERAPY

**Sulfonylureas** - Initiate Oglo in combination with a sulfonylurea at 15 to 30 mg once daily. Continue the current sulfonylurea upon initiation of Oglo therapy. Decrease the dose of the sulfonylurea if patients report hypoglycemia.

**Metformin** - Initiate Oglo in combination with metformin at 15 to 30 mg once daily. Continue the current metformin dose upon initiation of Oglo therapy. It is unlikely that the dose of metformin will require adjustment because of hypoglycemia during combination therapy with Oglo.

**Insulin** - Initiate Oglo in combination with insulin at 15 or 30 mg once daily. Continue the current insulin dose upon initiation of Oglo therapy. Decrease the insulin dose by 10% to 25% in patients receiving Oglo and insulin if the patient reports hypoglycemia or if plasma glucose concentrations decrease to < 100 mg/dl. Individualize further adjustments based on glucose-lowering response.

MAXIMUM RECOMMENDED DOSE
Do not exceed > 45 mg once daily of pioglitazone because doses > 45 mg once daily have not been studied in placebo-controlled clinical studies.

STORAGE INSTRUCTIONS
Store at a temperature below 25°C, protect from light and moisture.

REFERENCES

3. Egan J, Rubin C, Mathisen A. Adding pioglitazone to metformin therapy improves the lipid profile in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A106
5. Rubin C, Egan J, Schneider C. Combination therapy with pioglitazone and insulin in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A110
9. Carey RA, Liu Y. Pioglitazone does not markedly alter oral contraceptive or hormone replacement therapy pharmacokinetics [abstract 405-P]. Diabetes 2000 May; 49(100) Suppl. 1.