United Pharmaceuticals

UNIGLIT®

Pioglitazone HCl

Description:

UNIGLIT® (Pioglitazone HCl) is a thiazolidinedione oral antidiabetic agent that acts primarily by decreasing Insulin resistance. UNIGLIT® is used in the management of type II diabetes mellitus (non-Insulin dependent diabetes mellitus (NIDDM)). UNIGLIT® improves sensitivity to Insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. UNIGLIT® improves glycemic control while reducing circulating Insulin levels. UNIGLIT® depends on the presence of Insulin for its mechanism of action. It decreases Insulin resistance in the periphery and in the liver resulting in increased Insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, Pioglitazone is not an Insulin secretagogue, Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ receptors are found in tissues important for Insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPRγ nuclear receptors modulates the transcription of a number of Insulin responsive genes involved in the control of glucose and lipid. Pioglitazone reduces the hyperglycemia, hyper-insuilnemia, and hyper-triglyceridemia characteristic of Insulin-resistant states such as type II diabetes. The metabolic changes produced by Pioglitazone result in increased responsiveness of Insulin-dependent tissues.

Properties:

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

Distribution: The mean apparent volume of distribution of Pioglitazone following single-dose administration is 0.63 ± 0.41 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 metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and MIV (hydroxy derivatives of Pioglitazone) and M-III (keto derivative of Pioglitazone) are pharmacologically active. In addition to Pioglitazone, M-III and MIV are the principal drug-related species found in human serum following multiple dosing. Pioglitazone does not inhibit P450 activity. The major cytochrome P450 isoforms involved in the hepatic metabolism of Pioglitazone are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the mainly extra-hepatic CYP1 A1.

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. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of Pioglitazone and total Pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, calculated to be 5 to 7 L/hr. The mean Cmax and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, Metformin, or Insulin, UNIGLIT® improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A1C (HbA1C) decreases from baseline were generally greater for females than for males (average mean difference in HbA1C 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Indications:

UNIGLIT® is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type II diabetes (non-Insulin dependent diabetes mellitus, NIDDM). UNIGLIT® is indicated for monotherapy and also for use in combination with a sulfonylurea; Metformin or Insulin when diet and exercise plus the single agent do not result in adequate glycemic control.

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

Dosage and administration:

UNIGLIT® should be taken once daily without regard to meals. The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA1C which is a better indicator of long-term glycemic control than FBG alone. HbA1C reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with UNIGLIT® for a period of time adequate to evaluate change in HbA1C, (three months) unless glycemic control deteriorates.

Monotherapy

UNIGLIT® monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of UNIGLIT® the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination therapy

Sulfonylurea: UNIGLIT® in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of UNIGLIT® therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: UNIGLIT® in combination with Metformin may be initiated at 15 mg or 30 mg once daily. The current Metformin dose can be continued upon initiation of UNIGLIT® therapy. It is unlikely that the dose of Metformin will require adjustment due to hypoglycemia during combination therapy with UNIGLIT®.

Insulin: UNIGLIT® in combination with Insulin may be initiated at 15 mg or 30 mg once daily. The current Insulin dose can be continued upon initiation of UNIGLIT® therapy. In patients receiving UNIGLIT® and Insulin, the Insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dl. Further adjustments should be individualized based on glucose-lowering response.

Maximum recommended dose:

The dose of UNIGLIT® should not exceed 45 mg once daily since doses higher than 45 mg once daily have not been studied in placebo-controlled clinical studies. No placebo-controlled clinical studies of more than 30 mg once daily have been conducted in combination therapy.

Special populations:

- **Renal Insufficiency:** Dose adjustment in patients with renal insufficiency is not recommended.
- **Hepatic Insufficiency:** Therapy with Pioglitazone should not be initiated with patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy. Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with Pioglitazone and periodically thereafter.
- There are no data on the use of Pioglitazone in patients under 18 years of age; therefore, use of Pioglitazone in pediatric patients is not recommended.
- No data are available on the use of Pioglitazone in combination with another thiazolidinedione.

Contraindications:

Pioglitazone is contraindicated in patients with

- Known hypersensitivity to this product or any of its components.
- Established New York Heart Association (NYHA) Class III or IV heart failure.
- Active bladder cancer.

Precautions:

Cardiac Failure and Other Cardiac Effects: Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of Pioglitazone must be considered. Patients with NYHA Class III and IV cardiac statuses were not studied during pre-approval clinical trials, and Pioglitazone is not recommended in these patients. Pioglitazone should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment, with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

General: Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin; therefore, it should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

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

Ovulation: In premenopausal anovulatory patients with insulin resistance, treatment with thiazolidinediones, including Pioglitazone, may result in resumption of ovulation. As a consequence of their improved insulin sensitivity; these patients may be at risk for pregnancy if adequate contraception is not used.

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit. These changes may be related to increased plasma volume and have not been associated with any significant hematologic clinical effects.

Cardiovascular: The incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with Pioglitazone as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with Pioglitazone in combination with insulin. Patients with NYHA Class III and IV cardiac status were not studied in these Pioglitazone clinical trials, Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status. In post marketing experience with Pioglitazone, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Maculat Edema: Macular edema has been reported in post-marketing experience in diabetic patients who were taking Pioglitazone or another thiazolidinedione; some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. It is unknown whether or not there is a causal relationship between Pioglitazone and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.

Fractures: In a randomized trial (PRO active) in patients with type 2 diabetes (mean duration of diabetes 9.5 years), an increased incidence of bone fracture was noted in female patients taking Pioglitazone. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with Pioglitazone. The risk of fracture should be considered in the care of patients, especially female patients, treated with Pioglitazone, and attention should be given to assessing and maintaining bone health according to current standards of care.

Edema: Pioglitazone should be used with caution in patients with edema. In double-blind clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with Pioglitazone.

Information for patients:

- Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure should immediately report these symptoms to their physician.
- There may be an increased chance of having bladder cancer when you take Pioglitazone.
- You should not take Pioglitazone if you are receiving treatment for bladder cancer.
- Tell your doctor right away if you have any of the following symptoms of bladder cancer: blood or red color in urine; urgent need to urinate or pain while urinating; pain in back or lower abdomen.

Hepatic: Serum transaminase level: During all clinical studies in the USA patients treated with Pioglitazone had ALT value >/= 3 limes the upper limit of normal during treatment. All patients with follow-up value had reversible elevation in ALT. In the population of patient treated with Pioglitazone, mean values far bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Less than 0.09 % of patient treated with Pioglitazone were withdrawn from clinical trials in the U.S. due to abnormal lever function test.

Although available clinical data show no evidence of Pioglitazone-induced hepatotoxicity or ALT elevations, it is recommended that patients treated with Pioglitazone undergo periodic monitoring of liver enzymes. Serum ALT (alanine transaminase) levels should be evaluated prior to the initiation of therapy with Pioglitazone in all patients, every two months for the first year of therapy, and periodically thereafter. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g.: nausea; vomiting, abdominal pain, fatigue, anorexia, dark urine. The decision whether to continue the patient on therapy with Pioglitazone should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy 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). Glycemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

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 risks for cancer recurrence.

Laboratory Tests: FBG and HbA1c measurements should be performed periodically to monitor glycemic control and the therapeutic response to Pioglitazone.

Use during pregnancy and lactation:

Pregnancy category **C**

Pregnancy: There are no adequate and well controlled studies in pregnant women. Pioglitazone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of canonical anomalies, as well as increased neonatal morbidly and mortality, most experts recommend that Insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Lactation: It is not known whether Pioglitazone secreted in human milk. Because many drugs are excreted in human milk Pioglitazone should not be administered to a breast-feeding woman.

Drug interactions:

- The pharmacokinetics of co administration of Pioglitazone and oral contraceptives have not been evaluated in patients receiving Pioglitazone and an oral contraceptive, Therefore, additional caution regarding contraception should be exercised in patients receiving Pioglitazone and an oral contraceptive.
- The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of Pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with Pioglitazone and other drugs metabolized by this enzyme. In vitro, Ketoconazol appears to significantly inhibit the metabolism of Pioglitazone.

Side effects:

The overall incidence and types of side effects reported in placebo controlled clinical trials of Pioglitazone monotherapy are shown in the following table:

Side Effects	% of Patients	
	Placebo N= 259	Pioglitazone N= 606
Upper respiratory tract infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth disorder	2.3	5.3
Diabetes mellitus aggravated	6.1	5,1
Pharyngitis	0.6	5.1

The types of clinical side effects reported when Pioglitazone was used in combination with sulfonylureas, Metformin or Insulin were generally similar to those reported during Pioglitazone monotherapy with the exception of an increase in the occurrence of edema in the Insulin combination study. Mild to moderate hypoglycemia was reported during combination therapy with sulfonylurea or Insulin, Pioglitazone may cause decreases in hemoglobin and hematocrit. These changes may be related to increased plasma volume associated with Pioglitazone therapy and have not been associated with any significant hematologic clinical effects. Less than 0.12% of Pioglitazone-treated patients were withdrawn from clinical trials due to abnormal liver function tests. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure.

Overdosage:

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

Storage conditions:

Store up to 30ºC, protected from moisture.

Presentation:

UNIGLIT® **15:** Each tablet contains Pioglitazone Hydrochloride equivalent to 15 mg Pioglitazone in packs of 30 tablets.

UNIGLIT® **30:** Each tablet contains Pioglitazone Hydrochloride equivalent to 30 mg Pioglitazone in packs of 30 tablets.

Excipients:-

Lactose, Hydroxy propyl cellulose, Carboxy Methyl Cellulose Calcium & Magnesium Stearate.

This is a medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

The United Pharmaceutical Manufacturing Co. Ltd.
P.O. Box 69 Amman 11591, Jordan

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