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PIOMET® Tablets
(Pioglitazone / Metformin HCl)

پائیومیٹ®

COMPOSITION:
PIOMET 500 tablet
Each film coated tablet contains:
Pioglitazone HCl U.S.P equivalent to
Pioglitazone ..... 15 mg.
Metformin HCl B.P. ..... 500 mg.
(CCL Pharmaceuticals Specifications)

PIOMET 850 tablet
Each film coated tablet contains:
Pioglitazone HCl U.S.P equivalent to
Pioglitazone ..... 15 mg.
Metformin HCl B.P. ..... 850 mg.
(CCL Pharmaceuticals Specifications)

DESCRIPTION:
PIOMET 500 and **PIOMET** 850 constitute two oral antihyperglycemic agents in tablets containing Pioglitazone 15mg with Metformin HCl 500mg and Pioglitazone15mg with Metformin HCl 850mg, respectively for oral administration.

CLINICAL PHARMACOLOGY
Mechanism of action
PIOMET combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type II diabetes: Pioglitazone Hydrochloride, a member of the thiazolidinedione class, and Metformin Hydrochloride, a member of the biguanide class.
Pioglitazone Hydrochloride
Pioglitazone 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.
Metformin Hydrochloride
Metformin Hydrochloride improves glucose tolerance in patients with type II diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Rationality for Combination of Pioglitazone and Metformin
The concomitant use of Pioglitazone and Metformin has been previously approved in patients with type II diabetes inadequately controlled on Metformin.

INDICATIONS
PIOMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type II diabetes who are already treated with a combination of Pioglitazone and Metformin or whose diabetes is not adequately controlled with Metformin alone, or for those patients who have initially responded to Pioglitazone alone and require additional 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
The maximum recommended dose for Pioglitazone is 45 mg daily & the maximum recommended daily dose for Metformin is 2550 mg in adults. **PIOMET** should be given in divided daily doses with meals to reduce the gastrointestinal side effects associated with Metformin.
Starting dose for patients inadequately controlled on Metformin monotherapy
Based on the usual starting dose of Pioglitazone (15-30 mg daily), **PIOMET** may be initiated at either the 15 mg/500 mg or 15 mg/850 mg tablet strength once or twice daily, and gradually titrated after assessing adequacy of therapeutic response.
Starting dose for patients who initially responded to Pioglitazone monotherapy and require additional glycemic control
Based on the usual starting doses of Metformin (500 mg twice daily or 850 mg daily), **PIOMET** may be initiated at either the 15 mg/500 mg twice daily or 15 mg/850 mg tablet strength once daily, and gradually titrated after assessing adequacy of therapeutic response.
Starting dose for patients switching from combination therapy of Pioglitazone plus Metformin as separate tablets
PIOMET may be initiated with either the 15 mg/500 mg or 15 mg /850 mg tablet strengths based on the dose of Pioglitazone and Metformin already being taken.

PHARMACOKINETICS
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 - 4 hours, but does not alter the extent of absorption. The absolute bioavailability of a 500 mg Metformin tablet given under fasting conditions is approximately 50% - 60%. Food decreases the extent of and slightly delays the absorption of Metformin
Distribution:
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. Metformin is negligibly bound to plasma proteins.
Metabolism, Elimination and Excretion:
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of Pioglitazone) and M-III (keto derivative of Pioglitazone) are pharmacologically active. In addition to Pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. Following oral administration, approximately 15% to 30% of the Pioglitazone dose is recovered in the urine. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.
Intravenous single-dose in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

CONTRAINDICATIONS
PIOMET is contraindicated in patients with:
1. Known hypersensitivity to Pioglitazone, Metformin or any other component of drug.
2. Acute or chronic metabolic acidosis.
3. Renal disease or renal dysfunction.

WARNINGS AND PRECAUTIONS

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Warnings
Pioglitazone Hydrochloride
Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antihyperglycemic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure.
Metformin Hydrochloride
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to Metformin accumulation during treatment with **PIOMET**. **PIOMET** lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. In a patient with lactic acidosis who is taking Metformin, the drug should be discontinued immediately and general supportive measures should promptly be instituted.
Precautions
Pioglitazone Hydrochloride
Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin. Therefore, **PIOMET** should not be used in patients with type I diabetes or for the treatment of diabetic ketoacidosis. Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status. Dose related weight gain was observed with Pioglitazone alone and in combination with other hypoglycemic agents. **PIOMET** should be used with caution in patients with edema. 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. In patients receiving Pioglitazone, mean hemoglobin values declined by 2% to 4%. 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 and have rarely been associated with any significant hematologic clinical effects. Therapy with Pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women should be recommended while taking **PIOMET.**
Metformin Hydrochloride
Cardiovascular collapse, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving **PIOMET** therapy, the drug should be promptly discontinued. Metformin is known to be substantially excreted by the kidney, and the risk of Metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive **PIOMET**. Hypoglycemia does not occur in patients receiving Metformin alone under usual circumstances of use, but could occur when caloric intake is deficient. When a patient stabilized on any anti-diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold **PIOMET** and temporarily administer insulin. **PIOMET** may be reinstituted after the acute episode is resolved. **PIOMET** should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
Pregnancy
PIOMET should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.
Nursing Mothers
It is not known whether Pioglitazone and / or Metformin are excreted in human milk, because many drugs are excreted in human milk. **PIOMET** should not be administered to a breastfeeding woman.
Pediatric Use
Safety and effectiveness of **PIOMET** in pediatric patients have not been established.
Elderly Use
In case of Pioglitazone Hydrochloride there is no significant differences in effectiveness and safety between elder patients and younger patients. Metformin should only be used in patients with normal renal function.

DRUG INTERACTIONS
Pioglitazone Hydrochloride
In vivo drug-drug interaction studies have suggested that Pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.
Metformin Hydrochloride
Furosemide: Furosemide increased the Metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in Metformin renal clearance.
Nifedipine: Nifedipine appears to enhance the absorption of Metformin. Metformin had minimal effects on nifedipine.
Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems.
Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving **PIOMET**, the patient should be closely observed to maintain adequate glycemic control.

SIDE EFFECTS
The most common side effects of therapy include diarrhea, combined edema/peripheral edema, headache, myalgia, tooth disorder , diabetes mellitus aggravated and pharyngitis. Pioglitazone may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with Pioglitazone appears to be dose related. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. During testing with Pioglitazone, sporadic, transient elevations in creatinine phosphokinase levels (CPK) were observed. These elevations resolved without any apparent clinical sequelae. The relationship of these events to Pioglitazone therapy is unknown.

OVERDOSAGE AND MANAGEMENT
Pioglitazone Hydrochloride
Overdosage of Pioglitazone is rare. In the event of overdosage, appropriate supportive treatment should be initiated according to patients clinical signs and symptoms.
Metformin Hydrochloride
Overdosage of Metformin Hydrochloride occurs by ingestion of amounts greater than 50 grams. Symptoms of overdosage include hypoglycemia, lactic acidosis etc. Hemodialysis is useful for removal of accumulated Metformin from patients in whom Metformin overdosage is suspected.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

PRESENTATION
PIOMET 500 and **PIOMET** 850 are available in the packs of 14 tablets each.

For further informations please contact:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.