CoDiaglit®

Pioglitazone and Metformin Hydrochloride
Tablet

Description

CoDiaglit® (Pioglitazone and Metformin Hydrochloride) combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 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. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 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. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia.

Indication and Usage

CoDiaglit® is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of Pioglitazone and Metformin as separate tablets 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.

Dosage and Administration

General: The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of Pioglitazone 45 mg and Metformin 2550 mg.

Dosage Recommendations: Selecting the starting dose of CoDiaglit® should be based on the patient's current regimen of Pioglitazone and/or Metformin. CoDiaglit® 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), CoDiaglit® 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), CoDiaglit® 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

CoDiaglit® 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.

Maximum Recommended Dose: CoDiaglit® tablets are available as a 15 mg Pioglitazone plus 500 mg Metformin or a 15 mg Pioglitazone plus 850 mg Metformin formulation for oral administration. The maximum recommended dose for Pioglitazone is 45 mg daily. The maximum recommended daily dose for Metformin is 2550 mg in adults.

Special Patient Populations: The initial and maintenance dosing of combination of Pioglitazone and Metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of combination of Pioglitazone and Metformin. Monitoring of renal function is necessary to aid in prevention of Metformin associated lactic acidosis, particularly in the elderly. Therapy with combination of Pioglitazone and Metformin should not be initiated if the 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 combination of Pioglitazone and Metformin and periodically thereafter.

Precautions

General: Pioglitazone Hydrochloride: Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin. Therefore, combination of Pioglitazone and Metformin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Metformin Hydrochloride: 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 combination of Pioglitazone and Metformin. *Hypoglycemia:* Pioglitazone Hydrochloride: 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. Metformin Hydrochloride: Hypoglycemia does not occur in patients receiving Metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol.

Cardiovascular: Therapy with Pioglitazone, cases of congestive heart failure has been reported in patients both with and without previously known heart disease. Edema: Combination of Pioglitazone and Metformin should be used with caution in patients with edema. Since thiazolidinediones, including Pioglitazone can cause fluid retention, which can exacerbate or lead to congestive heart failure, combination of Pioglitazone and Metformin should be used with caution in patients at risk for heart failure.

Hepatic Effects: Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with combination of Pioglitazone and Metformin in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. If jaundice is observed, drug therapy should be discontinued. Loss of control of blood glucose: When a patient stabilized on any 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 combination of Pioglitazone and Metformin and temporarily administer insulin. Combination of Pioglitazone and Metformin may be reinstituted after the acute episode is resolved.

Contraindications

Combination of Pioglitazone and Metformin is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels >1.5 mg/dL [males], > 1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Known hypersensitivity to Pioglitazone, Metformin or any other component of combination of Pioglitazone and Metformin.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Combination of Pioglitazone and Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Adverse Effects

The most common adverse events were upper respiratory tract infection, diarrhea, combined edema/peripheral edema and headache, respectively. Most clinical adverse events were similar between groups treated with Pioglitazone in combination with metformin and those treated with pioglitazone monotherapy.

Use in Pregnancy and Lactation

Pregnancy category C. Combination of Pioglitazone and Metformin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women with combination of Pioglitazone and Metformin or its individual components. It is not known whether Pioglitazone and/or Metformin are secreted in human milk. Because many drugs are excreted in human milk, combination of Pioglitazone and Metformin should not be administered to a breastfeeding woman.

Use in Pediatric Patients

Safety and effectiveness of combination of Pioglitazone and Metformin in pediatric patients have not been established.

Use in Geriatric Patients

Pioglitazone: No significant differences in effectiveness and safety were observed between these patients and younger patients. Metformin: Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. Because aging is associated with reduced renal function, combination of Pioglitazone and Metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Drug Interaction

Pioglitazone Hydrochloride: In vivo drug-drug interaction studies have suggested that Pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate. Metformin Hydrochloride: i) Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. ii) Nifedipine: Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine. iii) 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. Metformin had no effect on cimetidine pharmacokinetics. iv) 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 combination of Pioglitazone and Metformin, the patient should be closely observed to maintain adequate glycemic control.

Pharmaceutical Precaution

Store in a cool and dry place. Protect from light and moisture.

Commercial Pack

CoDiaglit® 500 Tablet: Box containing 30 tablets in 3X10's blister strips. Each tablet contains Pioglitazone Hydrochloride INN equivalent to Pioglitazone 15 mg and Metformin Hydrochloride BP 500 mg.

CoDiaglit® 850 Tablet: Box containing 30 tablets in 3X10's blister strips. Each tablet contains Pioglitazone Hydrochloride INN equivalent to Pioglitazone 15 mg and Metformin Hydrochloride BP 850 mg.

BEXIMCO PHARMA

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