BIOMET™-PG TABLETS

Each Tablet Contains

Pioglitazone - 15 mg

Metformin HCl – 500 mg (Sustain Release)

For Pioglitazone:

1. THE DRUG SHOULD BE USED AT FIRST LINE OF THERAPY FOR DIABETES.
2. **ADVICE FOR HEALTHCARE PROFESSIONALS**
   - Patients with active bladder cancer or with a history of bladder cancer and those with uninvestigated haematuria should not receive pioglitazone.
   - Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 month of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (e.g. reduction in Glycosylated hemoglobin HbA1C).
   - Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age, current or past history of smoking, exposure to some occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region.
   - Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.

PHARMACEUTICAL DESCRIPTION

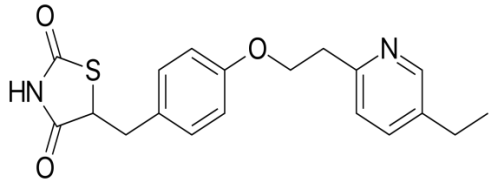
PIOGLITAZONE:

Generic name: Pioglitazone

Chemical name: 5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione

Molecular mass: 356.44 g/mol

Structural formula:

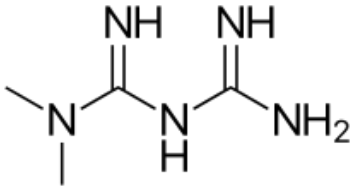


Empirical formula – $C_{19}H_{20}N_2O_3S$

METFORMIN:

Generic name: Metformin HCl

Chemical name: N, N-Dimethyl imidodi carbonimidic diamide
Molecular mass: 129.16364 g/mol
Structural formula:



Empirical formula - $C_4H_{11}N_5$

PHARMACOKINETIC PROPERTIES
Pioglitazone
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).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

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 (V_d/F) of pioglitazone following single-dose administration is 0.63 $\pm$ 0.41 (mean $\pm$ 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 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 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.

Pioglitazone incubated with expressed human P450 or human liver microsomes results in the formation of M-IV and to a much lesser degree, M-II. 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 CYP1A1. Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism in vitro at a concentration equal molar to pioglitazone. Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes. In vivo human studies have not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion
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, CL/F, calculated to be 5 to 7 L/hr.

Metformin Sustain-Release

The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of metformin sustain-release, C_{max} is achieved within 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. Both high and low fat meals had the same effect on the pharmacokinetics of sustain release. Protein binding of Metformin is Minimal and Metabolism is not done by liver Moreover Biological Half-life is 4-8.7 hours and Excretion us done by Urine (90%).

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION

Pioglitazone

Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. Additionally, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-γ. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone

reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated hemoglobin in the bloodstream.

Metformin

Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), 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.

INDICATION

Type 2 diabetes mellitus

- As an adjunct to diet and exercise in Non-insulin-dependent (type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise and weight reduction alone.
- The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.
  (a) Diet and/or exercise therapy alone
  (b) Use of sulfonylureas in addition to diet and/or exercise therapy
  (c) Use of thiazolidinediones in addition to diet and/or exercise therapy

CONTRAINDICATIONS

Pioglitazone

Initiation of Pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of Brand.

Metformin

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (arbitrarily defined as creatinine levels over 150 µmol/l (1.7 mg/dl), lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin.

DOSAGE AND ADMINISTRATION

Pioglitazone

The usual adult dosage is 15-30 mg of Pioglitazone administered orally once daily with meal. Initially may increase dose by 15 mg with careful monitoring to 45 mg once daily maximum.

Type 2 Diabetes Mellitus

- Indicated as monotherapy or with insulin or insulin secretagogues

- 15-30 mg orally with meal every daily initially; may increase dose by 15 mg with careful monitoring to 45 mg each day
- Monitor ALT at start of treatment, each month for 12 months, then every 3 months thereafter.

Dosage Modification:

- Co-administration with insulin secretagogue (sulfonylurea): Decrease insulin secretagogue dose
- Co-administration with insulin: Decrease insulin dose by 10-25%
- Co-administration with strong CYP2C8 inhibitors (gemfibrozil): Limit maximum pioglitazone dose to 15 mg daily.

Not recommended for pediatric use

Metformin

The usual adult dosage is 500mg of metformin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 2550 mg once daily.

ADVERSE EFFECTS

Pioglitazone

The most Common adverse effects include headaches, muscle pains, inflammation of the throat, and swelling. Serious side effects may include bladder cancer, low blood sugar, heart failure, and osteoporosis. Use in not recommended in pregnancy or breastfeeding. It is in the thiazolidinedione (TZD) class and works by improving sensitivity of tissues to insulin.

Metformin

The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramps, nausea, vomiting, and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetic drugs.[The most serious potential side effect of metformin use is lactic acidosis; this complication is very rare, and the vast majority of these cases seem to be related to co-morbid conditions, such as impaired liver or kidney function, rather than to the metformin itself. Metformin has also been reported to decrease the blood levels of thyroid-stimulating hormone in people with hypothyroidism, the clinical significance of this is still unknown.

OVERDOSAGE

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and

then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

WARNINGS AND PRECAUTIONS

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect. It is known that, despite initially successful countermeasures, hypoglycaemia may recur.

Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalization. Factors favoring hypoglycaemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- under nutrition, irregular mealtimes or missed meals or periods of fasting, alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency),
- concurrent administration of certain other medicinal products

Special warning on increased risk of cardiovascular mortality

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It

should be considered whether it is advisable to drive or operate machinery in these circumstances.

DRUG INTERACTIONS

Pioglitazone

Combination of Pioglitazone with sulfonylureas or insulin reciprocally exponentiate risk of hypoglycemia. Therapy with pioglitazone will increases the chance of pregnancy in individuals taking oral contraception.

Metformin

The H_2-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys; both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cation (positively charged) form of cimetidine, may compete for the same transport mechanism. A small double-blind, randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism; theoretically, other cationic medications may produce the same effect.

SPECIAL POPULATIONS:

Pioglitazone

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. Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values. It should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceeds 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.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. Monotherapy and in combination with sulfonylurea, metformin, or insulin and improved glycemic control in both males and females. 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.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Metformin

Patients with Type 2 Diabetes

- In the presence of normal renal function, there are no differences between single- or multiple- dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.
- The pharmacokinetics of metformin hydrochloride extended-release tablets in patients with type 2 diabetes is comparable to those in healthy normal adults.

Renal Insufficiency

- In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency

- No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

- Limited data from controlled pharmacokinetic studies of metformin hydrochloride tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin hydrochloride extended release tablets treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

STORAGE CONDITION- Store below 30°C in dry place. Keep out of reach of children.

PRESENTATION- Pioglitazone 15mg + Metformin HCl 500mg Sustain Release Tablets

PACKING- 1*10 TAB

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