PIOGLITAZONE

GLITAZ

15mg Tablet

ORAL HYPOGLYCEMIC AGENT

FORMULATION
Each tablet contains:
Pioglitazone (as hydrochloride) ……15 mg

PRODUCT DESCRIPTION
Pioglitazone (Glitaz) 15 mg Tablet: White, oval, biconvex, uncoated tablet, plain both sides.

PHARMACODYNAMICS
Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations. A clinical trial of pioglitazone vs. gliclazide as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of HbA1c ≥ 8.0% after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in patients treated with gliclazide, compared with pioglitazone. At two years, glycaemic control (defined as HbA1c < 8.0%) was sustained in 69% of patients treated with pioglitazone, compared with 50% of patients on gliclazide.

PHARMACOKINETICS
Absorption
Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2–60 mg. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites.
Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.

Distribution
The estimated volume of distribution in humans is 0.25 L/kg.
Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99%).

Biotransformation
Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.
In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man. Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone.

Elimination
Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

INDICATIONS
Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as **dual oral therapy in combination with**
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy in combination with**
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
- Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained

DOSAGE AND ADMINISTRATION
The usual dose is 15-30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary when used as monotherapy or with metformin or a sulfonylurea. Pioglitazone (Glitaz) may be taken with or without food.

CONTRAINDICATIONS
Pioglitazone is contraindicated in patients with:
- hypersensitivity to the active substance
- cardiac failure or history of cardiac failure (NYHA stages I to IV)
- hepatic impairment
- diabetic ketoacidosis
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria

PREGNANCY AND LACTATION

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding

Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

WARNINGS AND PRECAUTIONS

- Do not use pioglitazone in patients with active bladder cancer.
- 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.
- Monitor liver function before treatment and periodically thereafter, and cardiovascular disease for risk of heart failure
- Substitute insulin during perioperative period. Stop pioglitazone administration on morning of surgery and recommence when eating and drinking normally.

DRUG INTERACTIONS

Anti-diabetic drugs:

Sulfonylureas
- Glibenclamide
- Gliclazide, Tolbutamide, etc.

Sulfonylamides
- Glybuzole

Biguanides
- Metformin hydrochloride
- Buformin hydrochloride
- Nateglinide

α -Glucosidase inhibitors
- Voglibose, Acarbose

Insulin preparations

Beta-blockers: May mask warning signs of hypoglycemia when given concurrently with antidiabetic agents
Corticosteroids: May antagonize hypoglycemic effect of antidiabetic agents.
Diazoxide: May antagonize hypoglycemic effect of antidiabetic agents.
Diuretics: Hypoglycemic effect of antidiabetic agents may be antagonized by loop diuretics, thiazides and related diuretics;
Oestrogens: May antagonize hypoglycemic effect of antidiabetic agents
Progestogens: May antagonize hypoglycemic effect of antidiabetic agents
Testosterone: May enhance hypoglycemic effect of antidiabetic agents

ADVERSE EFFECTS

Common adverse effects include fluid retention and peripheral edema which may precipitate congestive heart failure (CHF) and upper respiratory tract infection. Other adverse events include heart failure, hematuria, anemia, myalgia, headache, fatigue, visual disturbances, sinusitis, pharyngitis, weight gain, impotence and increased CPK and increased transaminase levels.

OVERDOSE AND TREATMENT

In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

Hypoglycaemia may occur in combination with sulphonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

STORAGE CONDITION

Store at temperatures not exceeding 30̊C.

AVAILABILITY

Pioglitazone (Glitaz) 15 mg Tablet: Aluminum Foil Strip x 10's (Box of 100's)

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT

For suspected adverse drug reaction, report to the FDA:www.fda.gov.ph.
Seek advice from a healthcare professional at the first sign of any adverse drug reaction.

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