Piodiab®

Pioglitazone Hydrochloride

FORMS AND PRESENTATION
Piodiab® 15: Tablets: Box of 30.
Piodiab® 30: Tablets: Box of 30.
COMPOSITION:
Piodiab® 15: Each tablet contains: Pioglitazone Hydrochloride eq. to Pioglitazone 15 mg.
Piodiab® 30: Each tablet contains: Pioglitazone Hydrochloride eq. to Pioglitazone 30 mg.
Excipients: lactose, starch, croscarmellose sodium, povidone, magnesium stearate, colloidal silicone dioxide, sodium starch glycolate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
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 $HbA_{1c} \geq 8.0\%$ 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 $HbA_{1c} < 8.0\%$) was sustained in 69% of patients treated with Pioglitazone, compared with 50% of patients on gliclazide. In a two-year study of combination therapy comparing Pioglitazone with gliclazide when added to metformin, glycaemic control measured as mean change from baseline in HbA_{1c} was similar between treatment groups after one year. The rate of deterioration of HbA_{1c} during the second year was less with Pioglitazone than with gliclazide.
Pharmacokinetic Properties
Absorption: Following oral administration, Pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged Pioglitazone are usually achieved 2 hrs 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%).
Metabolism: 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 hrs and for its total active metabolites 16 to 23 hrs.
Elderly: Steady state pharmacokinetics are similar in patients age 65 and over and young subjects.
Patients with renal impairment: In patients with renal impairment, plasma concentrations of Pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) Pioglitazone concentration is unchanged.
Patients with hepatic impairment: Total plasma concentration of Pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of Pioglitazone.
INDICATIONS
Piodiab® is indicated in the treatment of type 2 diabetes mellitus:
As monotherapy: in 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 patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.
- a sulphonylurea, only in 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 patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
Piodiab® is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.
CONTRAINDICATIONS
Pioglitazone is contraindicated in patients with: hypersensitivity to the active substance or to any of the excipients, cardiac failure or history of cardiac failure (NYHA stages I to IV), hepatic impairment, diabetic ketoacidosis.
PRECAUTIONS
Elderly: Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.
In light of age- related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.
Bladder Cancer: Risk factors for bladder cancer should be assessed before initiating Pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic hematuria should be investigated before starting Pioglitazone therapy.
Patients should be advised to promptly seek the attention of their physician if macroscopic hematuria or other symptoms such as dysuria or urinary urgency develop during treatment.
Fluid retention and cardiac failure: Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema particularly those with reduced cardiac reserve. There have been cases of cardiac failure reported from the market when Pioglitazone was used in combination with insulin or in patients with a history of cardiac failure; patients should be observed for signs and symptoms of heart failure, weight gain and oedema when Pioglitazone is used in combination with insulin. Since insulin and Pioglitazone are associated with fluid retention, concomitant administration may increase the risk of oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.
A cardiovascular outcome study of Pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study. Caution should be exercised in patients over 75 years because of the limited experience in this patient group.
Monitoring of liver function: There have been rare reports of hepatocellular dysfunction during post-marketing experience. It is recommended, therefore, that patients treated with Pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Pioglitazone in all patients. Therapy with Pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.
Following initiation of therapy with Pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during Pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with Pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.
Weight gain: In clinical trials with Pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.
Haematology: There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with Pioglitazone, consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3 - 4% and haematocrit 3.6 – 4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (haemoglobin 1 – 2% and haematocrit 1 – 3.2% relative reductions) treated patients in comparative controlled trials with Pioglitazone.
Hypoglycaemia: As a consequence of increased insulin sensitivity, patients receiving Pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.
Eye disorders: Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including Pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between Pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.
Others: An increased incidence in bone fractures in women was seen in a pooled analysis of adverse effects reports of bone fracture from randomised, controlled, double blind clinical trials in over 8100 Pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.
Fractures were observed in 2.6% of women taking Pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with Pioglitazone (1.3%) versus comparator (1.5%).
The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with Pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on Pioglitazone is therefore 0.8 fractures per 100 patient years of use.
In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of Pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with Pioglitazone (1.7%) versus comparator (2.1%).
The risk of fractures should be considered in the long term care of women treated with Pioglitazone.
As a consequence of enhancing insulin action, Pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment 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). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.
Piodiab tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
Ability to drive and use machines: No effects on ability to drive and use machines have been observed.
PREGNANCY AND LACTATION
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.
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.
DRUG INTERACTIONS
Interaction studies have shown that Pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of Pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. In vitro studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.
Co-administration of Pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of Pioglitazone. Since there is a potential for an increase in dose related adverse effects, a decrease in the dose of Pioglitazone may be needed when gemfibrozil is concomitantly administered.
Close monitoring of glycaemic control should be considered. Co-administration of Pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of Pioglitazone. The Pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered.
ADVERSE EFFECTS
Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving Pioglitazone in double-blind studies are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common >1/10; common > 1/100, < 1/10; uncommon > 1/1000, < 1/100; rare > 1/10000, < 1/1000; very rare <1/10000; not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Pioglitazone monotherapy:
Eye disorders: Common: visual disturbance.
Infection and infestations: Common: upper respiratory tract infection; Uncommon: sinusitis.
Investigations: Common: weight increased.
Nervous system disorders: Common: hypoaesthesia; Uncommon: insomnia.
Pioglitazone in combination therapy with metformin:
Blood and lymphatic system disorders: Common: anaemia.
Eye disorders: Common: visual disturbance.
Gastrointestinal disorders: Uncommon: flatulence.
Investigations: Common: weight increased.
Musculoskeletal system and connective tissue disorders: Common: arthralgia.
Nervous system disorders: Common: headache.
Renal and urinary disorders: Common: haematuria.
Reproductive system and breast disorders: Common: erectile dysfunction.
Pioglitazone in combination therapy with sulphonylurea:
Ear and labyrinth disorders: Uncommon: vertigo.
Eye disorders: Uncommon: visual disturbance.
Gastrointestinal disorders: Common: flatulence.
General disorders and administration site conditions: Uncommon: fatigue.
Investigations: Common: weight increased; Uncommon: increased lactic dehydrogenase.
Metabolism and nutritional disorders: Uncommon: appetite increased, hypoglycaemia.
Nervous system disorders: Common: dizziness; Uncommon: headache.
Renal and urinary disorders: Uncommon: glycosuria, proteinuria.
Skin and subcutaneous tissue disorders: Uncommon: sweating.
Pioglitazone in triple oral combination therapy with metformin and sulphonylurea:
Investigations: Common: weight increased, blood creatine phosphokinase increased.
Metabolism and nutrition disorders: Very common: hypoglycaemia.
Musculoskeletal and connective tissue disorders: Common: arthralgia.
Pioglitazone in combination therapy with insulin:
Metabolism and nutrition disorders: Common: hypoglycaemia.
General disorders and administration site conditions: Very common: oedema.
Infections and infestations: Common: bronchitis.
Investigations: Common: weight increase.
Musculoskeletal system and connective tissue disorders: Common: back pain, arthralgia.
Respiratory, thoracic and mediastinal disorders: Common: dyspnoea.
Cardiac disorders: Common: heart failure.
DOSAGE AND ADMINISTRATION
Piodiab® tablets are taken orally once daily with or without food.
Piodiab® may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily. In combination with insulin, the current insulin dose can be continued upon initiation of Piodiab® therapy. If patients report hypoglycaemia, the dose of insulin should be decreased.
Elderly: No dosage adjustment is necessary for elderly patients.
Patients with renal impairment: No dosage adjustment is necessary in patients with impaired renal function (Cl_{cr} > 4 ml/min). No information is available from dialysed patients therefore Piodiab® should not be used in such patients.
Patients with hepatic impairment: Piodiab® should not be used in patients with hepatic impairment.
Children and adolescents: There are no data available on the use of Piodiab® in patients under 18 years of age, and therefore its use is not recommended in this age group.
OVERDOSAGE
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 CONDITIONS
Store below 30°C
Keep in original pack in intact conditions.
Date of revision: May 2015.

This is a medicament
- A 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
- Medicament: keep out of reach of children

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