

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 15mg.

Piodiab®30: Each tablet contains: Pioglitazone Hydrochloride eq. to Pioglitazone 30 mg.

Excipients: lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, magnesium stearate.

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. gliziclate as monotherapy was extended to two years in order to assess time to treatment failure (defined as appearance of HbA_{1c} ≥ 8.0% after the first six months of therapy). Kaplan-Meier analysis showed shorter time to treatment failure in patients treated with gliziclate, 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 gliziclate. In a two-year study of combination therapy comparing Pioglitazone with gliziclate 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 lower with Pioglitazone than with gliziclate.

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-II 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 major 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 plasma concentrations are similar in patients aged 65 and over and young subjects.

Patients with renal impairment: In patients with 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 in the treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

After initiation of therapy with Piodiab®, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA_{1c}). In patients who fail to show an adequate response, Piodiab® should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of Piodiab® is maintained.

CONTRAINDICATIONS

Piodiab® 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, current bladder cancer or a history of bladder cancer, uninvestigated macroscopic haematuria.

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.

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 - 3.6% 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.

Qthres: 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 may 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

Pioglitazone should not be used in pregnancy.

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 effects 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.

Piodiab® monotherapy:

Infections and infestations: upper respiratory tract infection (common); sinusitis (uncommon). **Neoplasms benign, malignant and unspecified (including cysts and polyps):** bladder cancer (uncommon).

Eye disorders: visual disturbance (common); macular oedema (not known).

Immune system disorders: hypersensitivity and allergic reactions (not known).

Investigations: weight increased (common); alanine aminotransferase increased (not known).

Musculoskeletal and connective tissue disorders: fracture bone (common).

Nervous system disorders: hypoaesthesia (common); insomnia (uncommon).

Piodiab® in combination therapy with metformin:

Infections and infestations: upper respiratory tract infection (common); sinusitis (uncommon). **Neoplasms benign, malignant and unspecified (including cysts and polyps):** bladder cancer (uncommon).

Blood and lymphatic system disorders: anaemia (common).

Immune system disorders: hypersensitivity and allergic reactions (not known).

Eye disorders: visual disturbance (common); macular oedema (not known).

Gastrointestinal disorders: flatulence (uncommon).

Investigations: weight increased (common); alanine aminotransferase (not known).

Musculoskeletal system and connective tissue disorders: fracture bone, arthralgia (common).

Nervous system disorders: hypoaesthesia, headache (common); insomnia (uncommon).

Renal and urinary disorders: haematuria (common).

Reproductive system and breast disorders: erectile dysfunction (common).

Piodiab® in combination therapy with sulphonylurea:

Infections and infestations: upper respiratory tract infection (common); sinusitis (uncommon).

Neoplasms benign, malignant and unspecified (including cysts and polyps): bladder cancer (uncommon).

Immune system disorders: hypersensitivity and allergic reactions (not known).

Metabolism and nutritional disorders: appetite increased, hypoglycaemia (uncommon).

Nervous system disorders: hypoaesthesia, dizziness (common); headache, insomnia (uncommon).

Eye disorders: visual disturbance (common); macular oedema (not known).

Ear and labyrinth disorders: vertigo (uncommon).

Gastrointestinal disorders: flatulence (common).

Skin and subcutaneous tissue disorders: sweating (uncommon).

Musculoskeletal system and connective tissue disorders: arthralgia (common).

Renal and urinary disorders: glycosuria, proteinuria (uncommon).

General disorders and administration site conditions: fatigue (uncommon).

Investigations: weight increased (common); increased lactate dehydrogenase (uncommon); alanine aminotransferase increased (not known).

Piodiab® in triple oral combination therapy with metformin and sulphonylurea:

Infections and infestations: upper respiratory tract infection (common); sinusitis (uncommon).

Neoplasms benign, malignant and unspecified (including cysts and polyps): bladder cancer (uncommon).

Immune system disorders: hypersensitivity and allergic reactions (not known).

Metabolism and nutrition disorders: hypoglycaemia (very common).

Nervous system disorders: hypoaesthesia (common); insomnia (uncommon).

Eye disorders: macular oedema (not known).

Musculoskeletal system and connective tissue disorders: fracture bone, arthralgia (common).

Investigations: weight increased, blood creatine phosphokinase increased (common), alanine aminotransferase increased (not known).

Piodiab® in combination therapy with insulin:

Infections and infestations: upper respiratory tract infection, bronchitis (common); sinusitis (uncommon).

Neoplasms benign, malignant and unspecified (including cysts and polyps): bladder cancer (uncommon).

Immune system disorders: hypersensitivity and allergic reactions (not known).

Metabolism and nutrition disorders: hypoglycaemia (common).

Nervous system disorders: hypoaesthesia (common); insomnia (uncommon).

Eye disorders: macular oedema (not known).

Cardiac disorders: heart failure (common).

Respiratory, thoracic and mediastinal disorders: dyspnoea (common).

Musculoskeletal system and connective tissue disorders: fracture bone, arthralgia, back pain (common).

General disorders and administration site conditions: oedema (very common).

Investigations: weight increase (common); alanine aminotransferase increased (not known).

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 stable conditions.

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Marketing Authorization Holder and Manufacturer:

Benta SAL

Dubych - Lebanon

(BPI)

This is a medication
(A medication 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 medication
- 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

Consult of Arab Health Ministries
Union of Arab Pharmacies

