เอกสารกำกับยาภาษาอังกฤษ

(เหมือนกันทุกขนาดบรรจุ)

1. Name of the medicinal product

PIOGOX Pioglitazone 15 mg tablet

PIOGOX Pioglitazone 30 mg tablet

2. Qualitative and quantitative composition

PIOGOX 15 mg tablet

Each tablet contains 15 mg of pioglitazone.

PIOGOX 30 mg tablets

Each tablet contains 30 mg of pioglitazone.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

PIOGOX 15: White, round, flat tablet, plain on both sides

PIOGOX 30: White, round, flat tablet, with scored on one side and plain on the other

4. Clinical Particulars

4.1 Therapeutic indications

(Reference 1: SmPC of Actos®. Topic (1) Therapeutic indications. Update 06 June 2019)

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 glycemic 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 glycemic 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 glycemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

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 HbA_{1c}). 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 (see section 4.4).

4.2 Posology and method of administration

(Reference 1: SmPC of Actos ®. Topic (2) Posology and method of administration. Update 06 June 2019)

Posology

Pioglitazone treatment 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 pioglitazone therapy. If patients report hypoglycemia, the dose of insulin should be decreased.

Special populations

Elderly

No dose adjustment is necessary for elderly patients (see section 5.2). Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly

when pioglitazone is used in combination with insulin (see section 4.4 Fluid retention and cardiac failure).

Renal impairment

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 mL/min) (see section 5.2). No information is available from dialyzed patients therefore pioglitazone should not be used in such patients.

Hepatic impairment

Pioglitazone should not be used in patients with hepatic impairment (see sections 4.3 and 4.4).

Pediatric population

The safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

4.3 Contraindication

(Reference 1: SmPC of Actos®. Topic (3) Contraindication. Update 06 June 2019)

Pioglitazone is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 hematuria

4.4 Special warning and precautions for use

(Reference 1: SmPC of Actos®. Topic (4) Special warnings and precautions for use. Update 06 June 2019)

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 or the elderly), 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 edema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported 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 edema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of edema. Post marketing cases of peripheral edema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. 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.

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

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12,506 patients, 0.15%) than in control groups

(7 cases from 10,212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, p=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.

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.

Monitoring of liver function

There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). 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, the medicinal product 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.

Hematology

There was a small reduction in mean hemoglobin (4% relative reduction) and hematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with hemodilution. Similar changes were seen in metformin (hemoglobin 3-4% and hematocrit 3.6–4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (hemoglobin 1–2% and hematocrit 1–3.2% relative reductions) treated patients in comparative controlled trials with pioglitazone.

Hypoglycemia

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 hypoglycemia, 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 edema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral edema. It is unclear whether or not there is a direct association between pioglitazone and macular edema but prescribers should be alert to the possibility of macular edema 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 reactions of bone fracture from randomized, 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 years 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%).

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.

The risk of fractures should be considered in the long-term care of patients treated with pioglitazone (see section 4.8).

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 (see section 4.6).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycemic control should

be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

PIOGOX tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

4.5 Interactions with other medicinal products and other forms of interactions

(Reference 1: SmPC of Actos®. Topic (5) Interactions with other medicinal products and other forms of interactions. Update 06 June 2019)

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 metabolized 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 events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycemic control should be considered (see section 4.4). 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 glycemic control should be considered (see section 4.4).

4.6 Fertility, pregnancy and lactation

(Reference 1: SmPC of Actos®. Topic (6) Fertility, pregnancy and lactation. Update 06 June 2019)

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. Fetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for fetal 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.

Fertility

In animal fertility studies there was no effect on copulation, impregnation or fertility index.

4.7 Effects on ability to drive and use machines

(Reference 1: SmPC of Actos®. Topic (7) Effects on ability to drive and use machines. Update 06 June 2019)

Pioglitazone has no or negligible influence on the ability to drive and use machines. However, patients who experience visual disturbance should be cautious when driving or using machines.

4.8 Undesirable effects

(Reference 1: SmPC of Actos®. Topic (8) Undesirable effects. Update 06 June 2019)

Tabulated list of adverse reactions

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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
	Monotherapy	Combination			
		with metformin	with sulpho-nylurea	with metformin and sulpho-nylurea	with insulin
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anemia		common			
Immune System Disorders					
hypersensitivity and allergic reactions[1]	not known	not known	not known	not known	not known
Metabolism and nutrition disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		

insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					
visual disturbance[2]	common	common	uncommon		
macular edema	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure[3]					common
Respiratory, thoracic and mediastinal disorders					
dyspnea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and connective tissue disorders					
fracture bone[4]	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
hematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			

General disorders and administration site conditions					
Oedema[5]					very common
fatigue			uncommon		
Investigations					
weight increased[6]	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydro-genase			uncommon		
alanine aminotransferase increased[7]	not known	not known	not known	not known	not known

Description of selected adverse reactions

[1] Postmarketing reports of hypersensitivity reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria.

[2] Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycemic treatments.

[3] In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study. In this study in patients receiving pioglitazone and insulin, a higher percentage of patients with heart failure was observed in patients aged ≥65 years compared with those less than 65 years (9.7% compared to 4.0%). In patients on insulin with no pioglitazone the incidence of heart failure was 8.2% in those ≥65 years compared to 4.0% in patients less than 65 years. Heart failure has been reported with marketing use of pioglitazone, and more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure (see section 4.4).

[4] A pooled analysis was conducted of adverse reactions of bone fractures from randomized, comparator controlled, double blind clinical trials in over 8,100 patients in the pioglitazone-treated groups and 7,400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Post-marketing, bone fractures have been reported in both male and female patients (see section 4.4)

[5] Edema was reported in 6–9% of patients treated with pioglitazone over one year in controlled clinical trials. The edema rates for comparator groups (sulphonylurea, metformin) were 2–5%. The reports of edema were generally mild to moderate and usually did not require discontinuation of treatment.

[6] In active comparator-controlled trials mean weight increase with pioglitazone given as monotherapy was 2–3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.

[7] In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

(Reference 1: SmPC of Actos®. Topic (9) Overdose. Update 06 June 2019)

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.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

(Reference 1: SmPC of Actos®. Topic (10) Pharmacodynamic properties. Update 06 June 2019)

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.

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 glycemic control is improved in patients with type 2 diabetes mellitus. The improved glycemic 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, glycemic control (defined as HbA1c < 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, glycemic 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.

In a placebo-controlled trial, patients with inadequate glycemic control despite a three-month insulin optimization period were randomized to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in HbA_{1c} of 0.45% compared with those continuing on insulin alone, and a reduction of insulin dose in the pioglitazone treated group.

HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.

In one year, clinical trials, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy vs. placebo) was studied in a small 18-week trial in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased, while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with small, but not clinically significant increases in LDL-cholesterol levels.

In clinical trials of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL cholesterol levels compared with placebo, whilst reductions were observed with

metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced post prandial hypertriglyceridemia through an effect on both absorbed and hepatically synthesized triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significantly different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5,238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomized to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medicinal products (beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, acetylsalicylic acid, statins, fibrates).

Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularization and leg revascularization, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of edema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with pioglitazone in all subsets of the pediatric population in type 2 diabetes mellitus. See section 4.2 for information on pediatric use.

5.2 Pharmacokinetic properties

(Reference 1: SmPC of Actos®. Topic (11) Pharmacokinetic properties. Update 06 June 2019)

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 (see section 4.5).

Elimination

Following oral administration of radiolabeled pioglitazone to man, recovered label was mainly in feces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or feces. 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.

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.

5.3 Preclinical safety data

(Reference 1: SmPC of Actos®. Topic (12) Preclinical safety data. Update 06 June 2019)

In toxicology studies, plasma volume expansion with hemodilution, anemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Fetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal

hyperinsulinemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for fetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumors (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumorigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumors. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumorigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumor multiplicity in the colon. The relevance of this finding is unknown.

Environmental Risk Assessment (ERA):

No environmental impact is anticipated from the clinical use of pioglitazone.

6. Pharmaceutical particulars

6.1 List of excipients

PIOGOX 15

Croscarmellose sodium, Microcrystalline cellulose PH101, Lactose monohydrate, Polysorbate 80, Magnesium stearate, Colloidal silicon dioxide, Hydroxy propyl cellulose, Sodium starch glycolate

PIOGOX 30

Croscarmellose sodium, Microcrystalline cellulose PH101, Lactose monohydrate, Polysorbate 80, Magnesium stearate, Colloidal silicon dioxide, Hydroxy propyl cellulose, Sodium starch glycolate

6.2 Incompatibilities

(Reference 1: SmPC of Actos®. Topic (13) Incompatibilities. Update 06 June 2019)

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

(Reference 1: SmPC of Actos®. Topic (14) Special precautions for storage. Update 06 June 2019)

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PIOGOX 15

Tablets with packed in PVC-aluminium blister pack of 10, 12, 14, and 15 tablets and packed in paper box of 3 and 10 blisters.

Tablets with packed in aluminium strip pack of 10, 12, 14, and 15 tablets and packed in paper box of 3 and 10 blisters.

Tablets with packed in aluminium-aluminium blister pack of 10 tablets and packed in paper box of 3 and 10 blisters.

PIOGOX 30

Tablets with packed in PVC-aluminium blister pack of 10 tablets and packed in paper box of 3, 5, 10, 25, and 100 blisters.

Tablets with packed in aluminium strip pack of 10 tablets and packed in paper box of 3, 5, 10, 25 and 10 blisters.

Tablets with packed in aluminium-aluminium blister pack of 10 tablets and packed in paper box of 3, 5, 10, 25 and 10 blisters.

6.6 Special precautions for disposal and other handling

(Reference 1: SmPC of Actos®. Topic (15) Special precautions for disposal and other handling. Update 06 June 2019)

No special requirements for disposal.

7. Marketing authorization holder

Millimed Co., Ltd.

193 Moo 1, Pak Khlong Bang Plakot, Phra Samut Chedi,

Samut Prakan 10290 Thailand

Tel. +66 2461 1027

8. Marketing authorization number(s)

PIOGOX 15

XXXXXXXX

PIOGOX 30

XXXXXXXX

9. Date of first authorization/renewal of the authorization

XX.XX.XX

10. Date of revision of the text

25 July 2020