

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of pioglitazone (as hydrochloride) and 850 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, oblong, biconvex film-coated tablets debossed with '15/850' on one side and plain on the other side with the dimensions of 18.2mm x 7.1 mm x 10.1mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets is indicated as second line treatment of type 2 diabetes mellitus adult patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

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 (see section 4.4).

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR > 90mL/min)

The recommended dose of Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets is 30 mg/day pioglitazone plus 1700 mg/day of metformin hydrochloride (this dose is achievable with one tablet of Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets 15 mg/850 mg, taken twice a day).

Dose titration with pioglitazone (added to the optimal dose of metformin) should be considered before the patient is switched to Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets.

When clinically appropriate, direct change from metformin monotherapy to Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets may be considered.

Special populations

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should have their renal function monitored regularly (see sections 4.3 and 4.4).

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

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	Pioglitazone
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	No dose adjustment. Maximum daily dose is 45 mg
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
< 30	Metformin is contra-indicated	

Hepatic impairment

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should not be used in patients with hepatic impairment (see sections 4.3 and 4.4).

Paediatric population

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

Method of administration

Tablets should be swallowed with a glass of water. Taking Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets with, or just after food, may reduce gastrointestinal symptoms associated with metformin.

4.3 Contraindications

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Cardiac failure or history of cardiac failure (NYHA stages I to IV)
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock
- Hepatic impairment
- Acute alcohol intoxication, alcoholism
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min)
- Acute conditions with the potential to alter renal function such as:
 - Dehydration
 - Severe infection
 - Shock
- Intravascular administration of iodinated contrast agents (see section 4.4)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

There is no clinical experience of pioglitazone in triple combination with other oral antidiabetic medicinal products.

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever, heat, reduced fluid intake), Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see sections 4.3.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting treatment with a NSAID.

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 oedema; 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. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration of insulin and Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets may increase the risk of oedema. Post marketing cases of peripheral oedema 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 and Metformin hydrochloride 15 mg/850 mg film-coated tablets 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 12506 patients, 0.15%) than in control groups (7 cases from 10212 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 haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of liver function

There have been rare reports of elevated liver enzymes and hepatocellular dysfunction during post-marketing experience with pioglitazone (see section 4.8). Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

It is recommended, therefore, that patients treated with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets in all patients. Therapy with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets 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 and Metformin hydrochloride 15 mg/850 mg film-coated tablets, it is recommended that liver enzymes be monitored periodically according to clinical judgement. If ALT levels are increased to 3 X upper limit of normal during Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets 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 and Metformin hydrochloride 15 mg/850 mg film-coated tablets 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.

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) treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia

Patients receiving pioglitazone in dual oral therapy with a sulphonylurea may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea 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.

Surgery

As Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets contains metformin hydrochloride, it must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Polycystic ovarian syndrome

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).

Others

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double blind clinical trials (see section 4.8).

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.

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).

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 (see section 4.5).

Metformin may reduce vitamin B₁₂ serum levels. The risk of low vitamin B₁₂ levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B₁₂ deficiency. In case of suspicion of vitamin B₁₂ deficiency (such as anaemia or neuropathy), vitamin B₁₂ serum levels should be monitored. Periodic vitamin B₁₂ monitoring could be necessary in patients with risk factors for vitamin B₁₂ deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B₁₂ deficiency provided in line with current clinical guidelines.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for pioglitazone/metformin hydrochloride. The following statements reflect the information available on the individual active substances (pioglitazone and metformin).

Metformin

Concomitant use not recommended Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

Combinations requiring precautions for use

Some medicinal products that can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets, close monitoring of renal function is necessary.

Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

Pioglitazone

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 glycaemic 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 glycaemic control should be considered (see section 4.4).

Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. 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.

4.6 Fertility, pregnancy and lactation

For pioglitazone/metformin hydrochloride no preclinical or clinical data on exposed pregnancies or lactation are available.

Women of childbearing potential / Contraception in males and females

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets is not recommended in women of childbearing potential not using contraception. If a patient wishes to become pregnant, treatment with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should be discontinued.

Pregnancy

Risk related to pioglitazone

There are no adequate human data from the use of pioglitazone in pregnant women. Animal studies have not shown teratogenic effects but have shown fetotoxicity related to the pharmacologic action (see section 5.3).

Risk related to metformin

Animal studies have not revealed teratogenic effects. Small clinical trials have not revealed metformin to have malformative effects.

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should not be used during pregnancy. If a pregnancy occurs, treatment with Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets should be discontinued.

Breast-feeding

Both pioglitazone and metformin have been shown to be present in the milk of lactating rats. It is not known whether breast-feeding will lead to exposure of the infant to the medicinal product. Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets must therefore not be used in women who are breast-feeding (see section 4.3).

Fertility

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

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three

times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

Pioglitazone/metformin hydrochloride 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

Summary of the safety profile

Clinical trials have been conducted with pioglitazone/metformin hydrochloride tablets and co-administered pioglitazone and metformin (see section 5.1). At the initiation of the treatment abdominal pain, diarrhoea, loss of appetite, nausea and vomiting may occur, these reactions are very common but usually disappear spontaneously in most cases. Lactic acidosis is a serious reaction which may occur very rarely (< 1/10,000) (see section 4.4) and other reactions such as bone fracture, weight increase and oedema may occur commonly ($\geq 1/100$ to < 1/10) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in double-blind studies and post-marketing experience are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to < 1/10); uncommon ($\geq 1/1,000$ to < 1/100); rare ($\geq 1/10,000$ 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		
	Pioglitazone	Metformin	Pioglitazone/Metformin
Infections and infestations			
upper respiratory tract infection	common		common
sinusitis	uncommon		uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer	uncommon		uncommon
Blood and lymphatic system disorders			
anaemia			common
Immune system disorders			
hypersensitivity and allergic reactions ¹	not known		not known
Metabolism and nutrition disorders			

Vitamin B12 absorption decreased/ deficiency (see section 4.4).		common	common
lactic acidosis		very rare	very rare
Nervous system disorders			
hypo-aesthesia	common		common
insomnia	uncommon		uncommon
headache			common
taste disturbance		common	common
Eye disorders			
visual disturbance ²	common		common
macular oedema	not known		not known
Gastrointestinal disorders³			
abdominal pain		very common	very common
diarrhea		very common	very common
flatulence			uncommon
loss of appetite		very common	very common
nausea		very common	very common
vomiting		very common	very common
Hepatobiliary disorders			
Hepatitis ⁴		not known	not known
Skin and subcutaneous tissue disorders			
erythema		very rare	very rare
pruritis		very rare	very rare
urticaria		very rare	very rare
Musculoskeletal and connective tissue disorders			
bone fracture ⁵	common		common
arthralgia			common
Renal and urinary disorders			
haematuria			common
Reproductive system and breast disorders			
erectile dysfunction			common
General disorders and administration site conditions			
Oedema ⁶			common
Investigations			
weight increased ⁷	common		common

alanine aminotransferase increased ⁸	not known		not known
liver function tests abnormal ⁴		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.

3 Gastrointestinal disorders occur most frequently during initiation of therapy and resolve spontaneously in most cases.

4 Isolated reports: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

5 A pooled analysis was conducted of adverse reactions of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 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%; 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. The observed excess risk of fractures for women on pioglitazone in this study is therefore 0.5 fractures per 100 patient years of use. 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).

6 In active comparator controlled trials oedema was reported in 6.3% of patients treated with metformin and pioglitazone, whereas the addition of sulphonylurea to metformin treatment resulted in oedema in 2.2% of patients. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

7 In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2-3 kg over one year. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg.

8 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.

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

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.

A large overdose of metformin (or coexisting risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital.

The most effective method to remove lactate and metformin is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD05.

Pioglitazone and Metformin hydrochloride 15 mg/850 mg film-coated tablets combines two antihyperglycaemic active substances with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: pioglitazone, a member of the thiazolidinedione class and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones act primarily by reducing insulin resistance and biguanides act primarily by decreasing endogenous hepatic glucose production.

Pioglitazone and metformin combination

The fixed dose combination tablet of pioglitazone 15 mg/metformin 850 mg BID (N=201), pioglitazone 15 mg BID (N=189), and metformin 850 mg BID (N=210) were evaluated in type 2 diabetes mellitus patients with mean baseline HbA1c of 9.5% in a randomised double-blind, parallel-group study. Previous anti-diabetic medication was discontinued for 12 weeks prior to baseline measurements. After 24 weeks of treatment, the primary endpoint of mean change from baseline in HbA1c

was -1.83% in the combination group versus -0.96% in the pioglitazone group ($p < 0.0001$) and -0.99% in the metformin group ($p < 0.0001$).

The safety profile seen in this study reflected the known adverse reactions seen with the individual products and did not suggest any new safety issues.

Pioglitazone

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 $HbA1c \geq 8.0\%$ 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 $HbA1c < 8.0\%$) 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, glycaemic control measured as mean change from baseline in $HbA1c$ was similar between treatment groups after one year. The rate of deterioration of $HbA1c$ during the second year was less with pioglitazone than with gliclazide.

In a placebo controlled trial, patients with inadequate glycaemic control despite a three month insulin optimisation period were randomised to pioglitazone or placebo for 12 months. Patients receiving pioglitazone had a mean reduction in $HbA1c$ 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 postprandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of

pioglitazone's effects on glycaemia and were statistically significantly different to glibenclamide.

In PROactive, a cardiovascular outcome study, 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised 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, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, 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 revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidence of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes mellitus. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), $p=0.0023$, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), $p=0.0034$

-a significant reduction of the absolute risk of any diabetes-related mortality: metformin

7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, $p=0.017$

-a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, ($p=0.011$), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years ($p=0.021$)

-a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, ($p=0.01$).

Paediatric population

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

5.2 Pharmacokinetic properties

Pioglitazone/metformin hydrochloride

Bioequivalence studies in healthy volunteers have shown pioglitazone/metformin hydrochloride to be bioequivalent to the administration of pioglitazone and metformin given as separate tablets.

Food had no effect on the AUC and C_{max} of pioglitazone when pioglitazone/metformin hydrochloride was administered to healthy volunteers. However, in the case of metformin, in the fed state the mean AUC and C_{max} were lower (13% and 28% respectively). T_{max} was delayed by food by approximately 1.9 h for pioglitazone and 0.8 h for metformin.

The following statements reflect the pharmacokinetic properties of the individual active substances of pioglitazone/metformin hydrochloride.

Pioglitazone

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 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.

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.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 $\mu\text{g/ml}$. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 $\mu\text{g/ml}$, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

No animal studies have been conducted with the combined products in pioglitazone/metformin hydrochloride. The following data are findings in studies performed with pioglitazone or metformin individually.

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia, 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 \leq 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 hyperinsulinaemia 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 tumours (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 tumourigenic 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 tumours. 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 tumourigenic findings in the male rat cannot be excluded.

There was no tumourigenic 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 tumour multiplicity in the colon. The relevance of this finding is unknown.

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Povidone K30

Croscarmellose sodium

Magnesium stearate

Coating

Hypromellose 2910 (E464)

Macrogol 8000 (E1521)

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions; store in the original package to protect from light.

6.5 Nature and contents of container

Aluminium/aluminium blister packs of 14, 28, 30, 50, 56, 60, 90, 98, 112, 180, 196 (2 x 98) tablets or 60 x 1 tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clydesdale Pharma Ltd

Unit 3-5 Campbell Court

Campbell Road

Tadley

RG26 5EG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 51718/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/04/2019

10 DATE OF REVISION OF THE TEXT

22/12/2025