National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Pioglitazone Hydrochloride & Metformin Hydrochloride Sustained Release Tablets

PIONORM M

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated bilayered tablet contains:

Pioglitazone Hydrochloride equivalent to Pioglitazone 15rng

Metformin Hydrochloride BP 500mg

(in sustained release form)

Excipients: Each tablet contains 255.640mg lactose monohydrate.

Each uncoated bilayered tablet contains:

Pioglitazone Hydrochloride equivalent to Pioglitazone 35rng

Metformin Hydrochloride BP 500mg

(in sustained release form)

For the full list of excipients, see section 6.1.

Excipients: Each tablet contains 229.280 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Pionorm M 15:

White/Orange colored oblong shaped uncoated, bilayered sustain release tablets with 'MICRO' engraved on both the sides

Pionorm M 30:

White/blue colored oblong shaped uncoated, bilayered sustain release tablets with 'MICRO' engraved on both the sides

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Pioglitazone Hydrochloride & Metformin Hydrochloride 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.

4.2 Posology and method of administration

Pioglitazone Hydrochloride & Metformin Hydrochloride should be taken with meals to reduce the gastrointestinal side effects associated with metformin.

If therapy with a combination tablet containing pioglitazone and metformin is considered appropriate the recommended starting dose is:

- 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- For patients with New York Heart Association (NYHA) Class I or Class II congestive heart failure: 15 mg/500 mg or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- For patients inadequately controlled on metformin monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once or twice daily (depending on the dose of metformin already being taken) and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- For patients inadequately controlled on pioglitazone monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability.
- For patients who are changing from combination therapy of pioglitazone plus metformin as separate tablets: it should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken.

It may be titrated up to a maximum daily dose of 45 mg of pioglitazone and 2550 mg of metformin. Metformin doses above 2000 mg may be better tolerated given three times a day.

After initiation of Pioglitazone Hydrochloride & Metformin Hydrochloride or with dose increase, monitor patients carefully for adverse reactions related to fluid retention such as weight gain, edema, and signs and symptoms of congestive heart failure. Liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) should be obtained prior to initiating Pioglitazone Hydrochloride & Metformin Hydrochloride. Routine periodic monitoring of liver tests during treatment with Pioglitazone Hydrochloride & Metformin Hydrochloride is not recommended in patients without liver disease.

Concomitant Use with an Insulin Secretagogue or Insulin

If hypoglycemia occurs in a patient coadministered Pioglitazone Hydrochloride & Metformin Hydrochloride and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced.

If hypoglycemia occurs in a patient coadministered Pioglitazone Hydrochloride & Metformin Hydrochloride and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.

Coadministration with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone (one of the ingredients in Pioglitazone Hydrochloride & Metformin Hydrochloride and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of Pioglitazone Hydrochloride & Metformin Hydrochloride is 15 mg/850 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors.

4.3 Contraindications

Pioglitazone Hydrochloride & Metformin Hydrochloride 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
- Breast-feeding

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 Hydrochloride & Metformin Hydrochloride should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensive, diuretics and nonsteroidal anti-inflammatory drugs (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.

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterized by acidotic Dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Pioglitazone Hydrochloride & Metformin Hydrochloride 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.

Renal function

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

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 Hydrochloride & Metformin Hydrochloride 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 Hydrochloride & Metformin Hydrochloride 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 macro vascular 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 elevated liver enzymes and hepatocellular dysfunction during post-marketing experience with pioglitazone. 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 Hydrochloride & Metformin Hydrochloride undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with Pioglitazone Hydrochloride & Metformin Hydrochloride in all patients. Therapy with Pioglitazone Hydrochloride & Metformin Hydrochloride 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 Hydrochloride & Metformin Hydrochloride , it is recommended that liver enzymes be monitored periodically according to clinical judgment. If ALT levels are increased to 3 x upper limit of normal during Pioglitazone Hydrochloride & Metformin Hydrochloride 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 Hydrochloride & Metformin Hydrochloride should be guided by clinical judgment 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.

Haematologic

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 thiazolidinedione's, 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 Hydrochloride & Metformin Hydrochloride 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 Hydrochloride & Metformin Hydrochloride 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.

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.

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 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.

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

This medicinal product 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.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Pioglitazone Hydrochloride & 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 Hydrochloride & Metformin Hydrochloride 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.

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 cyclooxygenase (COX) II inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Pioglitazone Hydrochloride & Metformin Hydrochloride , 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. 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.

Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dose 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 dose 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 Hydrochloride & Metformin Hydrochloride no preclinical or clinical data on exposed pregnancies or lactation are available.

Women of childbearing potential / Contraception in males and females

Pioglitazone Hydrochloride & Metformin Hydrochloride is not recommended in women of childbearing potential not using contraception. If a patient wishes to become pregnant, treatment with Pioglitazone Hydrochloride & Metformin Hydrochloride 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.

Risk related to metformin

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

Pioglitazone Hydrochloride & Metformin Hydrochloride should not be used during pregnancy. If a pregnancy occurs, treatment with Pioglitazone Hydrochloride & Metformin Hydrochloride should be discontinued.

Lactation

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 Hydrochloride & Metformin Hydrochloride must therefore not be used in women who are breast-feeding.

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 Hydrochloride & 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 Hydrochloride & Metformin Hydrochloride tablets and co-administered pioglitazone and metformin. 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) and other reactions such as bone fracture, weight increase and oedema may occur commonly (≥ 1/100 to < 1/10)

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 (≥ 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**		
	Pioglitazone	**Metformin**	**Pioglitazone Hydrochloride & Metformin Hydrochloride**
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[2]		very rare	very rare

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[3]	common			common
macular oedema	not known			not known
Gastrointestinal disorders[4]				
abdominal pain		very common		very common
diarrhoea		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[5]		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[6]	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[7]			common
Investigations			
weight increased[8]	common		common
alanine aminotransferase increased[9]	not known		not known
liver function tests abnormal[5]		not known	not known

Description of selected adverse reactions

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

[2] Long term treatment of metformin has been associated with a decrease of vitamin B12 absorption with decrease of serum levels. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

[3] 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.

[4] Gastrointestinal disorders occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[5] Isolated reports: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

[6] A pooled analysis was conducted of adverse reactions of bone fractures from randomised, 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%; 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.

[7] 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.

[8] 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.

[9] 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 macro vascular 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.

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 hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pioglitazone Hydrochloride & Metformin Hydrochloride 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. Thiazolidinedione 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 HbA_{1c} of 9.5% in a randomised double-blind, parallel-group study. Previous anti-diabetic medicinal products were discontinued for 12 weeks prior to baseline measurements. After 24 weeks of treatment, the primary endpoint of mean change from baseline in HbA_{1c} 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.

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 utilization
- 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.

5.2 Pharmacokinetic properties

Pioglitazone Hydrochloride & Metformin Hydrochloride

Bioequivalence studies in healthy volunteers have shown Pioglitazone Hydrochloride & 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 Hydrochloride & 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 Hydrochloride & 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.

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 µg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/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 V_d 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 Hydrochloride & 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 ≤ 4 times the clinical exposure. Foetal 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 foetal 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 thiazolidinedione 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:

Pionorm M 15

Hypromellose

Carmellose sodium

Dibasic calcium phosphate

Povidone

Colloidal anhydrous silica

Talc

Magnesium Stearate

Low-substituted Hydroxy propyl cellulose

Lactose

Carmel lose calcium

Sunset yellow lake

Pionorm M 30

Hypromellose

Carmellose sodium

Dibasic calcium phosphate

Povidone

Colloidal anhydrous silica

Talc

Magnesium Stearate

Low-substituted Hydroxy propyl cellulose

Lactose

Carmel lose calcium

Brilliant blue color lake

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 Months from the date of Manufacturing.

6.4 Special precautions for storage:

Store below 30°C. Keep out from the reach of children

6.5 Nature and contents of container:

Blister pack of 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

MICRO LABS LIMITED

#31, Race Course Road

Bangalore-560001

INDIA

8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of text

July 2021