SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Glimepiride, Pioglitazone and Metformin Tablets

TRIPRIDE 2

2. Qualitative and quantitative composition

Each uncoated bilayered tablet contains

Glimepiride USP 2mg

Pioglitazone Hydrochloride equivalent to Pioglitazone 15mg

Metformin HCI BP.....500mg

Each tablet contains 238.745 mg of lactose monohydrate. (as

sustained release form)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets

White, oblong shaped sustains released uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Glimepiride, Pioglitazone & Metformin Tablets are indicated once daily, as an adjunct to diet and exercise, to lower blood glucose. It is indicated as second-line therapy when diet, exercise, and the single agents or dual therapy do not result in adequate glycaemic control in patients with type-2 diabetes.

4.2 Posology and method of administration

Dosage should be individualized on the basis of both effectiveness and tolerability while not exceeding the maximum recommended daily dose [which is for glimepiride=8mg;

pioglitazone=45mg; metformin sustained-release=2000 mg]. The combination should be given once daily with meals and should be started at a low dose. The initial recommended dose is one tablet once daily.
Dosage should not exceed 3 tablets per day.

4.3 Contraindications

Glimepiride

Glimepiride is contraindicated in patients with a history of a hypersensitivity reaction to:
Glimepiride or any of the product's ingredients
Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to Glimepiride. Do not use Glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

Pioglitazone

Pioglitazone is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- cardiac failure or history of cardiac failure (NYHA stages I to IV)
- hepatic impairment
- diabetic ketoacidosis
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria

Metformin

Hypersensitivity to metformin or to any of the excipients listed in section 6.1

- 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

- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
  - decompensated heart failure,
  - respiratory failure,
  - recent myocardial infarction,
  - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Glimepiride

Hypoglycemia

All sulfonylureas, including Glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing Glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions

There have been Postmarketting reports of hypersensitivity reactions in patients treated with Glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue Glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia

Sulfonylureas can cause hemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because Glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also Postmarketting reports of hemolytic anaemia in patients receiving Glimepiride who did not have known G6PD deficiency.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pioglitazone

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. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration 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 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 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. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

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 hepatocellular dysfunction during post-marketing experience. It is recommended, therefore, that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT> 2.5 X upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain> 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued.

Weight gain

In clinical trials with pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure; therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with haemodilution.

Similar changes were seen in metformin (haemoglobin 3-4% and haematocrit 3.6–4.1% relative reductions) and to a lesser extent sulphonylureas and insulin (haemoglobin 1–2% and haematocrit 1–3.2% relative reductions) treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia

As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylureas or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylureas or insulin may be necessary.

Eye disorders

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with 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.

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 in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this data-set on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

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.

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

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

Metformin hydrochloride

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 or reduced fluid intake), metformin 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 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 of 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 metformin 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, 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 section 4.3.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

Administration of iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin 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.

Surgery:

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. 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.

Other precautions:

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

4.5 Interaction with other medicinal products and other forms of interaction

Glimepiride

Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require Glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including Glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors. When these medications are administered to a patient receiving Glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including Glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving Glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving Glimepiride, monitor the patient closely for hypoglycemia.

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of Glimepiride's glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of Glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Miconazole

A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

Cytochrome P450 2C9 Interactions

There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

Concomitant Administration of Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, Glimepiride should be administered at least 4 hours prior to colesevelam.

Pioglitazone

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylureas. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse 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.

Metformin

<u>Concomitant use not recommended</u>

Alcohol

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

Iodinated contrast agents

Metformin 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 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 metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed,

dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Pregnancy and lactation

Glimepiride

Pregnancy

Available data from a small number of published studies and Postmarketting experience with Glimepiride use in pregnancy over decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal outcomes. However, sulfonylureas (including glimepiride) cross the placenta and have been associated with neonatal adverse reactions such as hypoglycemia. Therefore, Glimepiride should be discontinued at least two weeks before expected delivery.

Lactation

Breastfed infants of lactating women using Glimepiride should be monitored for symptoms of hypoglycemia. It is not known whether glimepiride is excreted in human milk and there are no data on the effects of glimepiride on milk production. Glimepiride is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Glimepiride and any potential adverse effects on the breastfed child from Glimepiride or from the underlying maternal condition.

Pioglitazone

Pregnancy

There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Lactation

Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women.

Fertility

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

Metformin

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycaemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effect on the child.

Fertility

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

It 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.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

Glimepiride

The following serious adverse reactions are discussed in more detail below and elsewhere in the labeling:

Hypoglycemia

Hemolytic anemia

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson Syndrome
- Hemolytic anemia in patients with and without G6PD deficiency
- Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may
- progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia
- Thrombocytopenia (including severe cases with platelet count less than 10,000/μL) and
- thrombocytopenic purpura
- Hepatic porphyria reactions and disulfiram-like reactions

- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone.

Pioglitazone

Adverse reaction	**Frequency of adverse reactions of pioglitazone by treatment regimen**				
	Mono-therapy	**Combination**			
		with metformin	**with sulpho-nylurea**	**with metformin and sulpho-nylurea**	**with insulin**
Infections and infestations					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
Blood and lymphatic system disorders					
anaemia		common			
Immune System Disorders					
hypersensitivity and allergic reactions[1]	not known	not known	not known	not known	not known
Metabolism and nutrition					

disorders					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
Nervous system disorders					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
Eye disorders					
visual disturbance[2]	common	common	uncommon		
macular oedema[3]	not known	not known	not known	not known	not known
Ear and labyrinth disorders					
vertigo			uncommon		
Cardiac disorders					
heart failure[4]					common
Respiratory, thoracic and mediastinal disorders					
dyspnoea					common
Gastrointestinal disorders					
flatulence		uncommon	common		
Skin and subcutaneous tissue disorders					
sweating			uncommon		
Musculoskeletal and					

connective tissue disorders					
fracture bone[5]	common	common	common	common	common
arthralgia		common		common	common
back pain					common
Renal and urinary disorders					
haematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
Reproductive system and breast disorders					
erectile dysfunction		common			
General disorders and administration site conditions					
oedema					very common
fatigue			uncommon		
Investigations					
weight increased[6]	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydrogenase			uncommon		
alanine aminotransferase increased[7]	not known	not known	not known	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] Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic treatments.

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

[4] *A pooled analysis was conducted of adverse reactions of bone fractures from 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%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of **female** *patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus*

comparator (2.1%). Post-marketing, bone fractures have been reported in both male and female patients (see section 4.4)

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

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

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

Metformin

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin SR was similar in nature and severity to that reported in patients treated with Metformin immediate release.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur with Metformin SR.

Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Very rare:

- Lactic acidosis (see 4.4. Special warnings and precautions for use).
- Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders

Common:

- Taste disturbance

Gastrointestinal disorders

Very common:

- Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

- Skin reactions such as erythema, pruritus, urticaria

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 Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Glimepiride

An over dosage of Glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma,

seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

Pioglitazone

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.

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

Metformin hydrochloride

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis 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

Glimepiride

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives

ATC Code: A10B B12

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

Pharmacodynamics

In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2–3 hours after single oral doses of Glimepiride. The effects of Glimepiride on HbA , fasting plasma glucose, and post-prandial glucose have been assessed in clinical trials.

Pioglitazone

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

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α.[14][15] It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream. Although not clinically significant, pioglitazone decreases the level of triglycerides and increases that of high-density lipoproteins (HDL) without changing low-density lipoproteins (LDL) and total cholesterol in patients with disorders of lipid metabolism, although statins are the drug of choice for this.

More recently, pioglitazone and other active TZDs have been shown to bind to the outer mitochondrial membrane protein mitoNEET with affinity comparable to that of pioglitazone for PPARγ.

Metformin

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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.

<u>Mechanism of action</u>

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis

- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects

In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

5.2 Pharmacokinetic properties

Glimepiride

Absorption

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C_{max}) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean C_{max} and AUC (area under the curve) were decreased by 8% and 9%, respectively. Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics. In healthy subjects, the intra- and inter-individual variability's of glimepiride pharmacokinetic parameters were 15–23% and 24–29%, respectively.

Distribution

After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Biotransformation and elimination

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faeces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special populations

Glimepiride

Special populations

Geriatric Patients: A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤65 years and those >65 years was evaluated in a multiple-dose study using Glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was approximately 11% higher than that for the younger patients.

Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Race: No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of Glimepiride in patients with type 2 diabetes, the reduction in HbA_{1C} was comparable in Caucasians (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal Impairment: A single-dose, open-label study Glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CLcr): Group I consisted of 5 patients with mild renal impairment (CLcr > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CLcr = 20–50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CLcr < 20 mL/min). Although, glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life (T) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

Hepatic Impairment: It is unknown whether there is an effect of hepatic impairment on Glimepiride pharmacokinetics because the pharmacokinetics of Glimepiride has not been adequately evaluated in patients with hepatic impairment.

Obese Patients: The pharmacokinetics of glimepiride and its metabolites were measured in a single dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the t , clearance, and volume of distribution of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower C_{max} and AUC than those of normal body weight. The mean C_{max}, AUC , AUC values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours·ng/mL vs. 2820 ± 1110 hours·ng/mL and 4000 ± 1320 hours·ng/mL vs. 3280 ± 1360 hours·ng/mL, respectively.

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 states 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 is 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 the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of Metformin SR 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin SR 750 mg was shown to be bioequivalent to Metformin SR 500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin SR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin SR 1000 mg was shown to be bioequivalent to Metformin SR 500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax is slightly prolonged by about 1 hour).

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.

Metabolism

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 hours.

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.

Special populations

Metformin

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

5.3 Preclinical safety data

Glimepiride

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation. No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46–54 mg/kg body weight/day. This is at least 28 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,500 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

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 tumorigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of 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 tumorigenic findings in the male rat cannot be excluded.

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

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

Environmental Risk Assessment (ERA):

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

Metformin

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Hypromellose

Dibasic calcium phosphate

Povidone (K 30)

Colloidal anhydrous silica

Talc

Magnesium stearate

Low sub hydroxypropyl cellulose

Lactose

Sodium starch glycollate

Ferric oxide (YELLOW)

Ferric oxide (RED)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store below 30°C. Keep out of 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

H2010/20807210

9. Date of first Authorization /renewal of the authorization:

30/06/2026

10. Date of revision of text: