



## METFORMIN HYDROCHLORIDE PIOGLITAZONE GLIMEPIRIDE

### TRIPRIDE-2

500 mg / 15 mg / 2 mg Tablet

ORAL BLOOD GLUCOSE LOWERING DRUG COMBINATION

↓ Front Side

#### PRODUCT NAME:

TRIPRIDE-2

#### DOSAGE FORM AND STRENGTH:

Tablets 2/15/500mg

#### PHARMACOLOGIC CATEGORY:

Drugs used in diabetes, Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives

#### PRODUCT DESCRIPTION

White/Pink uncoated tablet containing a white sustained release layer of Metformin HCl and Pink layer of Pioglitazone HCl and Glimepiride, which is plain on both surfaces.

#### FORMULATION/COMPOSITION:

Each uncoupled bilayered tablet contains:  
 Glimepiride USP ..... 2 mg  
 Pioglitazone Hydrochloride equivalent to Pioglitazone ..... 15 mg  
 Metformin Hydrochloride BP ..... 500 mg  
 (In sustained release form)

#### PHARMACODYNAMICS/PHARMACOKINETICS:

**Glimepiride:** Glimepiride is an orally active hypoglycemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

**Pioglitazone:** Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) and to a lesser extent PPAR- $\alpha$ .<sup>[14][15]</sup> 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 hemoglobin 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 PPAR $\gamma$ .

**Metformin:** Metformin is an oral antihyperglycemic drug used in the management of type 2 diabetes. It improves glucose tolerance in patients with type 2 diabetes (NIIDM), lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to sulphonylureas, thiazolidinediones, or  $\alpha$ -glycosidase inhibitors. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

#### Pharmacokinetics:

##### Glimepiride

**Absorption:** The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations ( $C_{max}$ ) are reached approx. 2.5 hours after oral intake (mean 0.3  $\mu$ g/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both  $C_{max}$  and AUC (area under the time/concentration curve).

**Distribution:** Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

**Biotransformation and elimination:** Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism (major enzyme is CYP2C9) - were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. There was no relevant accumulation.

##### 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 isozymes 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 isoenzyme 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.

##### Metformin

**Absorption:** The absolute bioavailability of a metformin 500-mg tablet given under fasting conditions is approximately 50–60%. Following a single oral dose of metformin extended release,  $C_{max}$  is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. At steady state, the AUC and  $C_{max}$  are less than dose proportional for extended release within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8  $\mu$ g/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from extended release at a 2000 mg once daily dose is similar to the same total daily dose administered as immediate release tablets 1000 mg twice daily. After repeated administration of extended release, metformin did not accumulate in plasma. Within subject variability in  $C_{max}$  and AUC of metformin from extended release is comparable to that with immediate release. Although the extent of metformin absorption (as measured by AUC) from the extended release tablet increased by approximately 50% when given with food, there was no effect of food on  $C_{max}$  and  $T_{max}$  of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of extended release.

**Distribution:** Distribution studies with metformin extended release have not been conducted. However, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654  $\pm$  358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24–48 hours and are generally <1  $\mu$ g/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5  $\mu$ g/mL, even at maximum doses.

**Metabolism:** Metabolism studies with metformin extended release have not been conducted. However, intravenous single-dose studies in normal subjects demonstrate that metformin immediate release is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

**Elimination:** Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance of metformin is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

#### 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 glycemic control in patients with type-2 diabetes.

#### DOSAGE AND MODE ROUTE 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=2g]. 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.

#### CONTRAINDICATIONS & PRECAUTION(S), WARNING(S)

- Initiation in patients with established NYHA Class III or IV heart failure.
- Renal impairment (e.g., serum creatinine levels  $\geq$  1.5 mg/dL [males],  $\geq$  1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of Pioglitazone & Metformin.
- Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function.

#### PRECAUTIONS & WARNINGS:

##### Glimepiride

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with Glimepiride may lead to hypoglycemia. Possible symptoms of hypoglycemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired

concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and Bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attack may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur.

Severe hypoglycemia or prolonged hypoglycemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasional hospitalization.

Factors favoring hypoglycemia include:

- Unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- Under nutrition, irregular mealtimes or missed meals or periods of fasting,
- Alterations in diet,
- Imbalance between physical exertion and carbohydrate intake,
- Consumption of alcohol, especially in combination with skipped meals,
- Impaired renal function,
- Serious liver dysfunction,
- Overdose with Glimepiride,
- Certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency),
- Concurrent administration of certain other medicinal products.

Treatment with Glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated hemoglobin is recommended.

Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with Glimepiride.

Glimepiride 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 on pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing Antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure; however this did not lead to an increase in mortality in this study.

**Elderly:** Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

**Bladder Cancer:** Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P<0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. 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 hematuria should be investigated before starting pioglitazone therapy.

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

**Monitoring of liver function:** There have been rare reports of hepatocellular dysfunction during post-marketing experience. 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 judgment. 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 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. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

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

**Hypoglycemia:** As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylureas or in dual therapy with insulin may be at risk for dose-related hypoglycemia, 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 thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

**Others:** An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomized, controlled, double-blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

**Size: 280 (L) x 400 (H) mm**  
**Folding size: 140 x 25 mm**  
**Carton size: 61 x 20 x 90 mm**  
**65 x 34 x 94 mm**

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## ↓ Back Side

blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

### Risk related to glimepiride

There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycemia) of glimepiride. Consequently, glimepiride should not be used during the whole pregnancy.

In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

**Lactation:** The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

### 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.

**Metformin:** 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 foetal development, parturition or postnatal development.

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

**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.

**Metformin:** Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted on nursing mothers.

### INTERACTIONS:

#### Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor. Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from an *in vivo* interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulfonylureas the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycemia may occur when one of the following medicinal products is taken, for example:

- Phenylbutazone, azapropazone and oxyphenbutazone,
- Insulin and oral antidiabetic products, such as metformin,
- Salicylates and p-amino-salicylic acid,
- Anabolic steroids and male sex hormones,
- Chloramphenicol, certain long acting sulfonamides, tetracycline, quinolone antibiotics and clarithromycin
- Coumarin anticoagulants,
- Fenfluramine,
- Disopyramide,
- Fibrates,
- ACE inhibitors,
- Fluoxetine, MAO-inhibitors
- Allopurinol, Probenecid, sulfapyrazone,
- Sympatholytic,
- Cyclophosphamide, trophosphamide and iphosphamides,
- Miconazole, fluconazole,
- Pentoxifylline (high dose parenteral),
- Tritroqualine.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken, for example:

- Oestrogens and progestogens,
- Saluretics, thiazide diuretics,
- Thyroid stimulating agents, glucocorticoids,
- Phenothiazine derivatives, chlorpromazine,
- Adrenaline and sympathicomimetics,
- Nicotinic acid (high doses) and nicotinic acid derivatives,
- Laxatives (long term use),
- Phenytoin, diazoxide,
- Glucagon, barbiturates and rifampicin,
- Acetazolamide.

H<sub>2</sub> antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before 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 metabolized by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycemic control should be considered. Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycemic control should be considered.

#### Metformin

Individual combinations

Alcohol: Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- Fasting or malnutrition,
- Hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents: Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Associations requiring precautions for use:

Glucocorticoids (systemic and local routes), beta- $\alpha$ -agonists, and diuretics have intrinsic hyperglycemic activity. Inform the patient and perform more frequent blood glucose monitoring especially at the beginning of treatment. If necessary, adjust the dosage of the Antidiabetic drug during therapy with the other drug and upon its discontinuation. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the Antidiabetic drug during therapy with the other drug and upon its discontinuation.

### ADVERSE EFFECTS:

#### Glimepiride

The following adverse reactions from clinical investigations were based on experience with Glimepiride and other sulfonylureas, were listed below by system organ class and in order of decreasing incidence (very common:  $\geq 1/10$ ; common:  $\geq 1/100$  to  $<1/10$ ; uncommon:  $\geq 1/1,000$  to  $<1/100$ ; rare:  $\geq 1/10,000$  to  $<1/1,000$ ; very rare:  $<1/10,000$ , not known (cannot be estimated from the available data).

#### Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication. Not known: severe thrombocytopenia with platelet count less than 10,000/ $\mu$ l and thrombocytopenic purpura.

#### Immune system disorders

Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnea, fall in blood pressure and sometimes shock.

Not-known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

#### Metabolism and nutrition disorders

Rare: hypoglycemia.

These hypoglycemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycemic therapies, on individual factors such as dietary habits and dose.

#### Eye disorders

Not known: visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

#### Gastrointestinal disorders

Very rare: nausea, vomiting, Diarrhoea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

#### Hepato-biliary disorders

Not known: hepatic enzymes increased.

Very rare: hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.

#### Skin and subcutaneous tissue disorders

Not known: hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

#### Investigations

Very rare: blood sodium decrease.

#### Pioglitazone

Adverse reaction	Frequency of adverse reactions of pioglitazone by treatment regimen				
	Mono-therapy	Combination	with sulphonylurea	with metformin and sulphonylurea	with insulin
<b>Infections and infestations</b>					
upper respiratory tract infection	common	common	common	common	common
bronchitis					common
sinusitis	uncommon	uncommon	uncommon	uncommon	uncommon
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon
<b>Blood and lymphatic system disorders</b>					
anemia		common			

<b>Immune System Disorders</b>	not known	not known	not known	not known	not known
<b>Metabolism and nutrition disorders</b>					
hypo-glycaemia			uncommon	very common	common
appetite increased			uncommon		
<b>Nervous system disorders</b>					
hypo-aesthesia	common	common	common	common	common
headache		common	uncommon		
dizziness			common		
insomnia	uncommon	uncommon	uncommon	uncommon	uncommon
<b>Eye disorders</b>					
visual disturbance <sup>2</sup>	common	common	uncommon		
macular oedema <sup>3</sup>	not known	not known	not known	not known	not known
<b>Ear and labyrinth disorders</b>					
vertigo			uncommon		
<b>Cardiac disorders</b>					
heart failure <sup>4</sup>					common
<b>Respiratory, thoracic and mediastinal disorders</b>					
dyspnea					common
<b>Gastrointestinal disorders</b>					
flatulence		uncommon	common		
<b>Skin and subcutaneous tissue disorders</b>					
sweating			uncommon		
<b>Musculoskeletal and connective tissue disorders</b>					
fracture bone <sup>5</sup>	common	common	common	common	common
arthralgia		common		common	common
back pain					common
<b>Renal and urinary disorders</b>					
hematuria		common			
glycosuria			uncommon		
proteinuria			uncommon		
<b>Reproductive system and breast disorders</b>					
erectile dysfunction		common			
<b>General disorders and administration site conditions</b>					
oedema					very common
fatigue			uncommon		
<b>Investigations</b>					
weight increased <sup>6</sup>	common	common	common	common	common
blood creatine phospho-kinase increased				common	
increased lactic dehydrogenase				uncommon	
alanine aminotransferase increased <sup>7</sup>	not known	not known	not known	not known	not known

#### Metformin

During treatment initiation, the most common adverse reactions are nausea, vomiting, Diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common:  $\geq 1/10$ ; common:  $\geq 1/100$ ,  $<1/10$ ; uncommon:  $\geq 1/1,000$ ,  $<1/100$ ; rare:  $\geq 1/10,000$ ,  $<1/1,000$ ; very rare:  $<1/10,000$ .

<b>MICRO LABS LIMITED, BANGALORE, INDIA</b>					
1	Product Name	Tripride-2		<u>Colours Used</u>	
2	Strength	500 mg, 15 mg & 2 mg		<input checked="" type="checkbox"/> BLACK	
3	Component	Leaflet			
4	Category	Export - Philippines			
5	Dimension	280 (L) x 400 (H) mm			
6	Artwork Code	EXG-ML05I-0219/B			
7	Pharma Code	N/A		<input type="checkbox"/> Colours not for Printing <input type="checkbox"/> Keylines	
8	Reason for Change	Text revised from Customer			
		Prepared by (DTP)	Checked by (PD)	Approved by	
				Head CQA	Head Production/ Packing (Site)
Sign	Kantharaju L.				
Date	24-04-2023				