For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

METRIDE

1.Generic Name

Metformin Hydrochloride Prolonged-Release and Glimepiride Tablets I.P.

2. Qualitative and quantitative composition

METRIDE 1

Each uncoated inlay tablet contains:

Metformin Hydrochloride I.P...…… 500 mg

(In prolonged release form)

Glimepiride I.P……1 mg

Colour: Lake of Brilliant Blue

The excipients used are Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Brilliant Blue, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

METRIDE 2

Each uncoated inlay tablet contains:

Metformin Hydrochloride I.P...…… 500 mg

(In prolonged release form)

Glimepiride I.P……2 mg

Colour: Lake of Erythrosine

The excipients used are Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Erythrosine, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

3. Dosage form and strength

Dosage form: Uncoated inlay Tablet

Strength: Metformin Hydrochloride 500 mg, Glimepiride 1 and 2 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of patients with type 2 diabetes mellitus when diet, exercise & the single agent does not result in adequate glycemic control.

4.2 Posology and Method of Administration

Dose: As directed by the Physician.

4.3 Contraindications

Metformin Hydrochloride

• 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 <30mL/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.

Glimepiride I.P

METRIDE is contraindicated in patients with 1. Known hypersensitivity to the drug. 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

4.4 Special Warnings and Precautions for Use

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

Administration of iodinated contrast media:

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 with 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).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

Glimepiride

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY
The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an

adequate basis for this warning. The patient should be informed of the potential risks and advantages of METRIDE (glimepiride tablets) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with METRIDE or any other anti-diabetic drug. Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of METRIDE. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Combined use of glimepiride with insulin or metformin may increase the potential for hypoglycemia. Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with METRIDE or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including METRIDE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with METRIDE or metformin monotherapy, combined therapy with METRIDE and metformin or METRIDE and insulin may result in a response. Should secondary failure occur with combined METRIDE/metformin therapy, it may be necessary to initiate insulin therapy. Hemolytic anemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Since METRIDE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In postmarketing reports, hemolytic anemia has been reported in patients who did not have known G6PD deficiency.

Information for Patients

Patients should be informed of the potential risks and advantages of METRIDE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its

development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response.

Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

4.5 Drugs Interactions

Metformin Hydrochloride

Concomitant use not recommended

Alcohol

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

Iodinated contrast agents

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, see sections 4.2 and 4.4.

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 OCT 2.

Co-administration of metformin with

• Inhibitors of OCT 1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT 1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT 2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT 1 and OCT 2 (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.

Glimepiride

Carcinogenesis, Mutagenesis, and Impairment of Fertility Studies in rats at doses of up to 5000 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 which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 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, mouse micronucleus test). There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 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).

Pregnancy

Teratogenic Effects.

Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride. There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, METRIDE (glimepiride tablets) should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects.

In some studies, in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation. Pregnancy Teratogenic Effects. Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area).

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Nursing Mothers

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether METRIDE is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, METRIDE should be discontinued in nursing mothers. If METRIDE is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above Pregnancy, Nonteratogenic Effects.)

Pediatric Use

The safety and efficacy of METRIDE were evaluated in an active-controlled, single-blind (patients only), 24-week trial involving 272 pediatric patients, ranging from 8 to 17 years of age, with Type 2 diabetes. METRIDE (n=135) was administered at 1mg initially, and then titrated up to 2, 4 or 8 mg (mean last dose 4 mg) until the therapeutic goal of self-monitored fasting blood glucose < 7.0 mmol/L (< 126 mg/dl) was achieved. The active comparator metformin (n=137) was administered at 500 mg twice daily initially and titrated up to 1000 mg twice daily (mean last dose 1365 mg).

HbA1c (%)	Naïve Patients*		Previously Treated Patients*	
Baseline (mean)	Metformin	Glimepiride	Metformin	Glimepiride
Change from baseline (mean)+	69	72	57	55
Adjusted Treatment Difference**	8.2 -1.2	8.3 -1.0 0.2	9.0 -0.2	8.7 0.2 0.4

(95% CI)		(-0.3; 0.7)		(-0.4; 1.2)

* - Intent-to-treat population (METRIDE, n=127; metformin, n=126) + - Change from baseline means are least square means adjusting for baseline HbA1c and Tanner Stage ** - Difference is METRIDE – metformin with positive differences favouring metformin The profile of adverse reactions in pediatric patients treated with METRIDE was similar to that observed in adults. Hypoglycemic events, as documented by blood glucose values.

Weight (kg)	Metformin*	Glimepiride
Baseline (mean)	67.3	66.5
Change from baseline (mean)+	0.7	2.0
Adjusted Treatment Difference** (95% CI)		1.3
		(0.3; 2.3)

* - Safety population with on-treatment evaluation for weight (METRIDE, n=129; metformin, n=126) + - Change from baseline means are least square means adjusting for baseline HbA1c and Tanner Stage ** - Difference is METRIDE – metformin with positive differences favouring metformin

Geriatric Use in US clinical studies of METRIDE, 608 of 1986 patients were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Comparison of glimepiride pharmacokinetics in Type 2 diabetic patients ≤65 years (n=49) and those >65 years (n=42) was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups (see CLINICAL PHARMACOLOGY, Special Populations, Geriatric). The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents (see CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency; PRECAUTIONS, General; and DOSING AND ADMINISTRATION, Special Patient Population).

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Metformin Hydrochloride

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 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.

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.

Glimepiride

Pregnancy

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the 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 (hypoglycaemia) 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 hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

4.7 Effects On Ability to Drive and Use Machines

Metformin Hydrochloride

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use 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).

Glimepiride

No studies on the effects on the ability to drive and use machines have been performed.

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.8 Undesirable Effects

Metformin Hydrochloride

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 METRIDE.

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 an aetiology is recommended if a patient present 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

Glimepiride

Adult Patients

The incidence of hypoglycemia with METRIDE, as documented by blood glucose values <60 mg/dL, ranged from 0.9-1.7% in two large, well-controlled, 1-year studies. (See WARNINGS and PRECAUTIONS.)

METRIDE has been evaluated for safety in 2,013 patients in US controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with METRIDE are shown below.

Adverse Events Occurring in >1% METRIDE Patients

	METRIDE		**Placebo**	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including METRIDE.

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of METRIDE. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including METRIDE.

Hematologic Reactions

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including METRIDE.

Metabolic Reactions

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including METRIDE. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, including METRIDE, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of METRIDE. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of METRIDE, the incidence of blurred vision was placebo, 0.7%, and METRIDE, 0.4%.

Pediatric Patients

In a clinical trial, 135 pediatric patients with Type 2 diabetes were treated with METRIDE. The profile of adverse reactions in these patients was similar to that observed in adults.

4.9 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.

Glimepiride

Overdosage of sulfonylureas, including METRIDE, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of amore dilute (10%) glucose solution at a rate that will maintain the blood glucose

at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Metformin Hydrochloride

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 utilisation

• 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).

Glimepiride

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which METRIDE therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established. METRIDE is effective as initial drug therapy. In patients where monotherapy with METRIDE or metformin has not produced adequate glycemic control, the combination of METRIDE and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.

5.2 Pharmacodynamic Properties

Metformin Hydrochloride

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.

Clinical efficacy

The prospective randomised (UKPDS) study has established the long-term benefit of intensive

blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p=0.0023, and versus the combined sulphonylureas and insulin monotherapy groups (40.1 events/ 1000 patient-years), p=0.0034.

• a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, p=0.017;

• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years (p=0.011), and versus the combined sulphonylureas and insulin monotherapy groups 18.9 events/ 1000 patient-years (p=0.021);

• a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patients-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylureas, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Glimepiride

A mild glucose-lowering effect first appeared following single oral doses as low as 0.5-0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [Tmin]) was about 2 to 3 hours. In noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and HbA1c were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of METRIDE. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of METRIDE up to 8 mg once dail y. No difference in response was found when METRIDE was administered once or twice daily.

In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA1c for METRIDE (glimepiride tablets) patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebo-controlled study of Type 2 diabetic patients unresponsive to dietary management, METRIDE therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA1c. Efficacy results were not affected by age, gender, weight, or race.

In long-term extension trials with previously-treated patients, no meaningful deterioration inmean fasting blood glucose (FBG) or HbA1c levels was seen after 2 1/2 years of METRIDE therapy.

Combination therapy with METRIDE and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was >130% of their ideal bodyweight. Initially, 5-10 units of insulin were administered with the main evening meal and

titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FP G levels but the METRIDE/insulin therapy group used approximately 38% less insulin.

METRIDE therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for Type 2 diabetes.

5.3 Pharmacokinetic Properties

Metformin Hydrochloride

Absorption

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.

The bioequivalent product shows the following properties:

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 tablets 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).

Metformin absorption from the prolonged release formulation is not altered by meal composition.

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

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 volume of distribution (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.

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

Metabolism and elimination

The terminal elimination half-life of clonidine has been found to range from 5 to 25.5 hours. It can be prolonged in patients with severely impaired renal function up to 41 hours.

About 70% of the dose administered is excreted with the urine mainly in form of the unchanged parent drug (40-60% of the dose). The main metabolite p-hydroxy-clonidine is pharmacologically inactive. Approximately 20% of the total amount is excreted with the faeces. There is no definitive data about food or race effects on the pharmacokinetics of clonidine.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/ml in patients with normal renal function. The hypotensive effect is attenuated or decreases with plasma concentrations above 2.0 ng/ml.

Glimepiride

Absorption. After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean Tmax (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

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

Metabolism. Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1is clinically meaningful is not clear.

Excretion. 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 feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Pharmacokinetic Parameters. The pharmacokinetic parameters of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dos e-proportionality (4 and 8 mg) study in patients with Type 2 diabetes are summarized below:

Volunteers	**Patients with Type 2 diabetes**	
Single Dose	(Day 1) Single Dose	Multiple Dose (Day 10)
Mean±SD	**Mean±SD M**	**Mean±SD**

Cmax (ng/ml)			
1 mg	103 ± 34 (12)	——	——
2 mg	177 ± 44 (12)	——	——
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	551± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
Tmax (h)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL/f (mL/min)	52.1 ± 16.0 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
Vd/f (L)	21.8 ± 13.9 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
T1/2 (h)	5.3 ± 4.1 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

() = No. of subjects

CL/f=Total body clearance after oral dosing

Vd/f=Volume of distribution calculated after oral dosing

These data indicate that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in Type 2 diabetic patients. Oral clearance of glimepiride did not change over the 1-8-mg dose range, indicating linear pharmacokinetics.

Variability. In normal healthy volunteers, the intra-individual variabilities of Cmax, AUC, and CL/f for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively.

Special Populations

Geriatric. Comparison of glimepiride pharmacokinetics in Type 2 diabetic patients ≤65 years and those >65 years was performed in a study using a dosing regimen of 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 about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatric. The pharmacokinetics of glimepiride (1 mg) were evaluated in a single dose study conducted in 30 Type 2 diabetic patients (Male = 7; Female = 23) between ages 10 and 17 years. The mean $AUC_{(0\text{-last})}$ (338.8±203.1 ng•hr/mL), Cmax (102.4±47.7 ng/mL) and T1/2(3.1±1.7 hours) were comparable to those previously reported in adults ($AUC_{(0\text{-last})}$ 315.2±95.9 ng•hr/mL, Cmax 103.2±34.3 ng/mL and T1/2 5.3±4.1 hours).

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 pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of METRIDE (glimepiride tablets) in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n = 536), blacks (n = 63), and Hispanics (n = 63)

Renal Insufficiency. A single-dose, open-label study was conducted in 15 patients with renal impairment. METRIDE (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLcr); (Group I, CLcr = 77.7 mL/min, n = 5), (Group II, CLcr = 27.7 mL/min, n = 3), and (Group III, CLcr = 9.4 mL/min, n = 7). METRIDE was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased

2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life (T1/2) 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 percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

A multiple-dose titration study was also conducted in 16 Type 2 diabetic patients with renal impairment using doses ranging from 1-8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLcr less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg METRIDE may be given to Type 2 diabetic patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.

Hepatic Insufficiency. No studies were performed in patients with hepatic insufficiency.

Other Populations. There were no important differences in glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine. The pharmacokinetics of glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower Cmax and AUC. However, since neither Cmax nor AUC values were normalized for body surface area, the lower values of Cmax and AUC for the obese patients were likely the result of their excess weight and not due to a difference in the kinetics of glimepiride.

Drug Interactions. The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs, clarithromycin and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving METRIDE, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving METRIDE, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving METRIDE, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving METRIDE, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin (1 g tid) and METRIDE led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean Cmax had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of METRIDE did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and METRIDE significantly increased Cmax, AUC, and T1/2 of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving

propranolol and placebo. Pooled data from clinical trials in patients with Type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of METRIDE (glimepiride tablets) (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. METRIDE treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during METRIDE treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg METRIDE were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with Type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (e.g. fluconazole) and inducers (e.g. rifampicin) of cytochrome P450 2C9.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Metformin Hydrochloride

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

Glimepiride

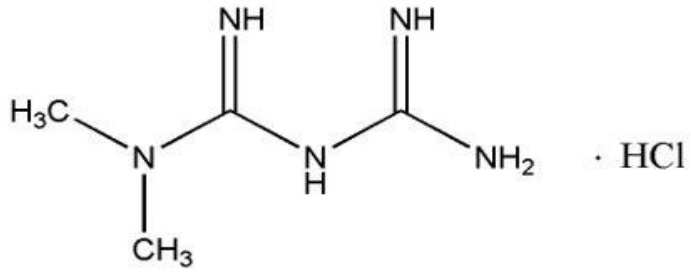
Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to 320 mg glimepiride/kg/day for 12 months (approximately 1,000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataract genic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture**.**

7. DESCRIPTION

Metformin Hydrochloride Prolonged-Release and Glimepiride Tablets is indicated for the treatment of patients with type 2 diabetes mellitus when diet, exercise & the single agent does not result in adequate glycaemic control.

Metformin Hydrochloride

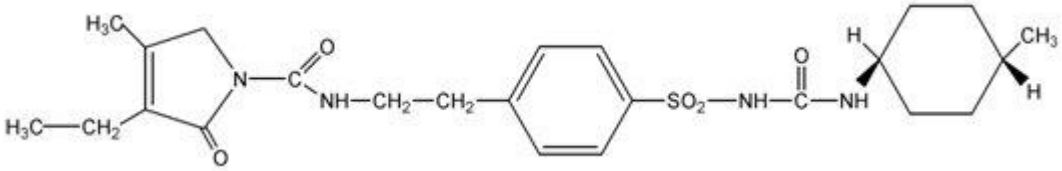
Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula of Metformin Hydrochloride is ($C_4H_{11}N_5$, HCl) and its molecular weight is 165.6. Its structural formula is:



Metformin Hydrochloride is a white or almost white crystalline powder. It is freely soluble in water; slightly soluble in ethanol (95%); practically insoluble in acetone, in chloroform, in dichloromethane and in ether.

Glimepiride

Glimepiride is identified as 1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl)urea having an empirical formula of $C_{24}H_{34}N_4O_5S$ with a molecular weight of 490.62. Its structural formula is:



Glimepiride is a white or almost white powder. It is soluble in dimethylformamide; sparingly soluble in dichloromethane; slightly soluble in methanol; practically insoluble in water.

Metride 1

Metformin Hydrochloride Prolonged-Release and Glimepiride Tablets is white to off-white flat capsule shaped uncoated tablets having one blue round inlay tablet near the centre of one side. The excipients used are Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Brilliant Blue, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

Metride 2

Metformin Hydrochloride Prolonged-Release and Glimepiride Tablets is white to off-white flat capsule shaped uncoated tablets having one pink round inlay tablet near the centre of one side. The excipients used are Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Erythrosine, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

METRIDE is available in blister strips of 15 tablets each.

8.4 Storage and Handing Instructions

Store at a temperature not exceeding 30ºC, protected from light and moisture.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

METRIDE

Read all of this leaflet carefully before you start taking this medicine.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you. Do not pass it on to others. It may

harm them, even if their symptoms are the same as yours.

• If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT METRIDE IS AND WHAT IT IS USED FOR

METRIDE Tablets is combination of medicines called metformin hydrochloride (belong to a group of medicines called biguanides, used in the treatment of diabetes) and. Glimepiride (Glimepiride is an orally active blood sugar lowering drug. This drug belongs to a blood sugar lowering group of medicines called sulfonylureas. Glimepiride works by increasing the amount of insulin released from your pancreas. The insulin then lowers your blood sugar levels.)

METRIDE IS FOR

The medicine is used for the treatment of patients with type 2 diabetes mellitus when diet, exercise & the single agent does not result in adequate glycemic control.

2. BEFORE YOU TAKE METRIDE TABLETS

Do not take METRIDE TABLETS if:

you are allergic to metformin or any of the other ingredients of this medicine. An allergic reaction may cause a rash, itching or shortness of breath.

You are allergic (hypersensitive) to Glimepiride or other sulfonylureas (medicines used to lower your blood sugar such as glibenclamide) or sulfonamides (medicines for bacterial

infections such as sulfamethoxazole) or any of the other ingredients of this medicine (listed in section 6 what Glimepiride tablets contains).

- You have insulin dependent diabetes (type 1 diabetes mellitus)

- You have diabetic ketoacidosis (a complication of diabetes when your acid level is raised in your body and you may have some of the following signs: fatigue, feeling sick (nausea), frequent urination and muscular stiffness)

- You are in a diabetic coma. • you have uncontrolled diabetes with for example severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see ‘‘Risk of lactic acidosis’’ below) or ketoacidosis.

Ketoacidosis is a condition in which substances called ‘ketone bodies’ accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

• you have liver problems

• you have severely reduced kidney function

• you have a severe infection, such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis.

• you have lost too much water from your body (dehydration). Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see ‘Warnings and precautions’).

• you have been treated for acute heart problems or have recently had a heart attack or have severe circulatory problems or breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see 'Warnings and precautions’).

• you are a heavy drinker of alcohol.

• you are under 18 years of age.

Warnings and precautions

Talk to your doctor or pharmacist before taking METRIDE Tablets

 If you are recovering from an injury, operation, infections with fever, or from other forms of stress, inform your doctor as temporary change of treatment may be necessary

 If you have severe liver or kidney disorder If you are not sure if any of these apply to you, talk to your doctor or pharmacist before taking Glimepiride containing Tablets Lowering of the haemoglobin level and breakdown of red blood cells (haemolytic anemia) can occur in patients missing the enzyme glucose-6-phoshate dehydrogenase. Important information about hypoglycaemia (low blood sugar) When you take Glimepiride tablets, you may get hypoglycaemia (low blood sugar). Please see below for additional information about hypoglycaemia, its signs and treatment.

Following factors could increase the risk of you getting hypoglycaemia:

 Undernourishment, irregular meal time, missed or delayed meal or period of fasting

 Changes to your diet

 Taking more Glimepiride tablets than needed

 Having kidneys that do not work properly

 Having severe liver disease

 If you suffer from particular hormone-induced disorders (disorders of the thyroid glands, of the pituitary gland or adrenal cortex)

 Drinking alcohol (especially when you skip a meal)

 Taking certain other medicines (See Taking other medicines below)

 If you increase the amount of exercise you do and you don't eat enough food or eat food containing less carbohydrate than usual.

Signs of hypoglycaemia include:

Hunger pangs, headache, nausea, vomiting, sluggishness, sleepiness, problems sleeping, restlessness, aggression, problems with concentration, reduced alertness and reaction time, depression, confusion, problems with your speech and sight, slurred speech, shakiness, partial paralysis, dizziness, helplessness.

The following signs may also occur:

sweating, clammy skin, anxiety, fast or increased heartbeat, high blood pressure, awareness of your heart beat, sudden strong pain in the breast that may radiate into neighbouring areas (angina pectoris and cardiac arrhythmias)

If blood sugar levels continue to drop you may suffer from considerable confusion (delirium), develop fits, lose self-control, breathing may be shallow and your heart beat slowed down, you may fall into unconsciousness. The clinical picture of a severe reduced blood sugar level may resemble that of a stroke.

Treating hypoglycaemia:

In most cases the signs of reduced blood sugar vanish very quickly when you consume some form of sugar, e.g. sugar cubes, sweet juice, sweetened tea.

You should therefore always take some form of sugar with you (e.g. sugar cubes). Remember that artificial sweeteners are not effective. Please contact your doctor or go to the hospital if taking sugar does not help or if the symptoms recur.

Laboratory Tests

The level of sugar in your blood or urine should be checked regularly. Your doctor may also take blood tests to monitor your blood cell levels and liver function.

Children and adolescents

Glimepiride containing Tablets is not recommended for use in children under 18 years of age.

Risk of lactic acidosis

METRIDE may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above apply to you, talk to your doctor for further instructions.

Stop taking METRIDE for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions. **Stop taking METRIDE and contact a doctor or the nearest hospital**

immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

• vomiting

• stomach ache (abdominal pain)

• muscle cramps

• a general feeling of not being well with severe tiredness

• difficulty in breathing

• reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

If you need to have major surgery you must stop taking METRIDE during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with METRIDE.

During treatment with METRIDE, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet. You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.

Do not stop taking this medicine without speaking to your doctor

Other medicines and Glimepiride tablets: Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. Your doctor may wish to change your dose of Glimepiride tablets if you are taking other medicines, which may weaken or strengthen the effect of Glimepiride tablets on the level of sugar in your blood.

The following medicines can increase the blood sugar lowering effect of Glimepiride tablets. This can lead to a risk of hypoglycaemia (low blood sugar):

 Medicines to treat pain and inflammation (phenylbutazone, azopropazone, oxyphenbutazone, aspirin like medicines)

 Other medicines to treat diabetes mellitus (such as insulin or metformin)

 Medicines supporting muscle build up (anabolics)

 Medicines to inhibit blood clotting (coumarin derivatives such as warfarin)

 Medicines used to reduce weight (fenfluramine)

 Medicines called anti-arrhythmic agents used to control abnormal heart beat (disopyramide)

 Medicines lowering high cholesterol level (fibrates)

 Medicines lowering high blood pressure (ACE inhibitors)

 Medicines to treat depression (fluoxetine, MAO inhibitors)

 Medicines to treat gout (allopurinol, probenecid, sulfinpyrazone)

 Medicines to treat cancer (cyclophosphamide, ifosfamide, trofosfamide)

 Medicines to treat bacterial and fungal infections (tetracyclines, chloramphenicol, fluconazole, miconazole, quinolones, clarithromycin)

 Medicines to treat nasal allergies such as hay fever (tritoqualine)

 Medicines to increase circulation when given in a high dose intravenous infusion (pentoxifylline)

 Medicines to treat urinary infections (such as some long acting sulfonamides)

 Medicines used for male sex hormone replacement therapy

 Medicines called sympatholytics to treat high blood pressure, heart failure, or prostate symptoms

The following medicines may decrease the blood sugar lowering effect of Glimepiride Tablets. This can lead to a risk of hyperglycaemia (high blood sugar level):

 Medicines containing female sex hormones (oestrogens, progestogens)

 Medicines to treat high blood pressure called thiazide diuretics (water tablets)

 Medicines used to stimulate the thyroid gland (such as levothyroxine)

 Medicines to treat allergies and inflammation (glucocorticoids)

 Medicines to treat severe mental disorders (chlorpromazine and other phenothiazine derivatives

 Medicines used to raise heartbeat, to treat asthma or nasal congestion, coughs and colds, used to reduce weight, or used in life-threatening emergencies (adrenaline and sympathomimetics)

 Medicines to treat high cholesterol level (nicotinic acid)

 Medicines to treat constipation when they are used long term (laxatives)

 Medicines to treat fits (phenytoin)

 Medicines to treat high blood pressure or lowering blood sugar (diazoxide)

 Medicines to treat severe low blood sugar levels (glucagon)

 Medicines to treat nervousness and sleep problems (barbiturates)

 Medicines to treat infections, tuberculosis (rifampicin)

 Medicines to treat increased pressure in the eye (azetazolamide)

The following medicinal products can increase or decrease the blood sugar lowering effect of Glimepiride Tablets:

 Medicines to treat high blood pressure or heart failure such as beta-blockers, clonidine, guanethidine and reserpine. These can also hide the signs of hypoglycaemia, so special care is needed when taking these medicines.

 Medicines to treat stomach ulcers (called H2 antagonists)

Glimepiride tablets may either increase or weaken the effects of the following medicines:

 Medicines inhibiting blood clotting (coumarin derivatives such as warfarin)

 Colesevelam, a medicine used to reduce cholesterol, has an effect on the absorption of Glimepiride Tablets. To avoid this effect, you should be advised to take Glimepiride Tablets at least 4 hours before colesevelam

If you need to have an injection of contrast medium that contains iodine into your bloodstream, in the context of an X-ray or scan, you must stop taking METRIDE before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with METRIDE.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests or your doctor may need to adjust the dosage of METRIDE. It is especially important to mention the following:

• Medicines which increase urine production (diuretics (water tablets) such as furosemide)

• Medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).

• Certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists.

• Steroids such as prednisolone, mometasone, beclometasone.

• Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.

• Medicines that may change the amount of METRIDE in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

METRIDE with food, drink and alcohol:

You should take medicine as suggested by your physician.

Avoid excessive alcohol intake while taking METRIDE since this may increase the risk of lactic acidosis Alcohol intake may increase or decrease the blood sugar lowering action of Glimepiride Tablets in an unpredictable way.

Pregnancy, breast-feeding and fertility:

Pregnancy

METRIDE Tablets should not be taken during pregnancy. Tell your doctor if you are, you think you might be or are planning to become pregnant.

Breast feeding

Glimepiride may pass into breast milk. METRIDE should not be taken during breast feeding.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines:

Your ability to concentrate or react may be reduced if your blood sugar is lowered (hypoglycaemia), or raised (hyperglycaemia) or if you develop visual problems as a result of such conditions. Bear in mind that you could endanger yourself or others (e.g. when driving a car or using machines). Please ask your doctor whether you can drive a car if you:

- have frequent episodes of hypoglycaemia
- have fewer or no warning signals of hypoglycaemia

3. HOW TO TAKE METRIDE TABLETS

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Swallow the tablets whole with a glass of water; do not chew.

Recommended dose

As directed by the Physician.

If you take more METRIDE TABLETS than you should

If you take extra tablets by mistake you need not worry, but if you have unusual symptoms, contact your doctor. If the overdose is large, lactic acidosis is more likely. Symptoms of lactic acidosis are non-specific, such as vomiting, bellyache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. If you experience some of these symptoms, you should immediately seek medical attention, as lactic acidosis may lead to coma. Stop taking Metride Tablets immediately and contact a doctor or the nearest.

If you happen to have taken too much Metride Tablets or an additional dose there is a danger of hypoglycaemia and therefore you should instantly consume enough sugar (e.g. a small bar of sugar cubes, sweet juice, sweetened tea) and inform a doctor immediately. When treating hypoglycaemia due to accidental intake in children, the quantity of sugar given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Persons in a state of unconsciousness must not be given food or drink. Since the state of hypoglycaemia may last for some time it is very important that the patient is carefully monitored until there is no more danger. Admission into hospital may be necessary, also as a measure of precaution. Show the doctor the package or remaining tablets, so the doctor knows what has been taken. Severe cases of hypoglycaemia accompanied by loss of consciousness and coma are cases of medical emergency requiring immediate medical treatment and admission into hospital. It may be helpful to tell your family & friends to call a doctor immediately if this happens to you.

hospital straightaway.

Taking this medicine

• Take this medicine as directed by the Physician.

If you forget to take METRIDE TABLETS

If you forget to take a dose, do not take a double dose to make up for forgotten doses.

If you stop taking METRIDE TABLETS

If you interrupt or stop the treatment you should be aware that the desired blood sugar lowering effect is not achieved or that the disease will get worse again. Keep taking METRIDE TABLETS until your doctor tells you to stop.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following, stop taking METRIDE TABLETS and see your doctor immediately:

METRIDE TABLETS may cause a very rare (may affect up to 1 user in 10,000) but very serious side effect called lactic acidosis (see section 'Warnings and precautions'). If this happens you must **stop taking METRIDE TABLETS and contact a doctor or the nearest hospital immediately,** as lactic acidosis may lead to coma.

• Abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice. If you develop yellowing of the eyes and/or skin contact your doctor immediately.

 Allergic reactions (including inflammation of blood vessels, often with skin rash) which may develop into serious reactions with difficulty in breathing, fall in blood pressure and sometimes progressing to shock

 Abnormal liver function including yellowing of the skin and eyes (jaundice), problems with the bile flow (cholestasis), inflammation of the liver (hepatitis) or liver failure

 Allergy (hypersensitivity) of the skin such as itching, rash, hives and increased sensitivity to sun. Some mild allergic reactions may develop into serious reactions

 Severe hypoglycaemia including loss of consciousness, seizures or coma

Other possible side effects are listed by frequency as follows:

Very common (affects more than 1 person in 10):

• Diarrhoea, nausea, vomiting, stomach ache or loss of appetite. If you get these, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks. It helps if you take the tablets with or immediately after a meal.

Common (affects less than 1 person in 10, but more than 1 person in 100):

• Taste disturbance

Rare side effects (may affect up to 1 in 1000 people)

• Lower blood sugar than normal (hypoglycaemia)

• Decrease in the number of blood cells: Blood platelets (which increases risk of bleeding or bruising) White blood cells (which makes infections more likely) Red blood cells (which can make the skin pale and cause weakness or breathlessness) These problems generally get better after you stop taking Metride Tablets

Very rare (affects less than 1 person in 10,000):

• Decreased vitamin B12 levels

• Skin rashes including redness, itching and hives.

• Allergic reactions (including inflammation of blood vessels, often with skin rash) which may develop into serious reactions with difficulty in breathing, fall in blood pressure and sometimes progressing to shock. If you experience any of these symptoms, tell your doctor immediately.
• Abnormal liver function including yellowing of the skin and eyes (jaundice), impairment of the bile flow (cholestasis), inflammation of the liver (hepatitis) or liver failure. If you experience any of these symptoms, tell your doctor immediately.

• Feeling or being sick, diarrhoea, feeling full or bloated, and abdominal pain

• Decrease in the amount of sodium level in your blood (shown by blood tests)

Not known (frequency cannot be estimated from the available data)

• Allergy (hypersensitivity) of the skin may occur such as itching, rash, hives and increased sensitivity to sun. Some mild allergic reactions may develop into serious reactions with swallowing or breathing problems, swelling of your lips, throat or tongue. Therefore, in the event of one of these side effects, tell your doctor immediately.

• Allergic reactions with sulfonylureas, sulfonamides, or related drugs may occur

• Problems with your sight may occur when beginning treatment with Glimepiride Tablets. This is due to changes in blood sugar levels and should soon improve

• Increased liver enzymes

• Severe unusual bleeding or bruising under the skin

5. HOW TO STORE METRIDE TABLETS

Store at a temperature not exceeding 30ºC, protected from light and moisture.

Keep out of reach of children

6. FURTHER INFORMATION

What METRIDE TABLETS contains

• The active substance are Metformin Hydrochloride and Glimepiride

Metride 1

• The other ingredients are: Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Brilliant Blue, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

Metride 2

• The other ingredients are: Hydroxy Propyl Methyl Cellulose, Povidone, Isopropyl Alcohol, Magnesium Stearate, Lactose, Starch, Lake of Erythrosine, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide.

10. DETAILS OF MANUFACTURER

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Licence No.: M/563/2010 issued on 17.12.2018

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ METRIDE 500,1 and 2 mg/JUN-19/01/PI