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

AZULIX MF FORTE

1. Generic Name

Metformin Hydrochloride Prolonged Release and Glimepiride Tablets I.P.

2. Composition

AZULIX 3 MF FORTE

Each uncoated bilayered tablet contains:
Metformin Hydrochloride I.P. …….. 1000 mg
(in prolonged release form)
Glimepiride I.P. …… 3 mg
Excipients…….. q.s.
Colour: Ponceau 4R Lake

AZULIX 4 MF FORTE

Each uncoated bilayered tablet contains:
Metformin Hydrochloride I.P. …….. 1000 mg
(in prolonged release form)
Glimepiride I.P. …… 4 mg
Excipients…….. q.s.
Colour: Sunset Yellow Lake

Excipients used are Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Magnesium stearate, Polyvinyl pyrrolidone K-30, Sodium carboxy methyl cellulose, Lactose, calcium carboxy methyl cellulose, dichloromethane, colour Ponceau 4R Lake, Colour Sunset Yellow Lake.

3. Dosage form and strength

Dosage form: Uncoated bilayered prolonged release form
Strength: 1000 mg + 3 mg & 1000 mg + 4 mg

4. Clinical particulars

4.1 Therapeutic indication

AZULIX MF FORTE is indicated in the treatment of patients with type 2 diabetes mellitus when diet, exercise and the single agent do not result in adequate glycemic control.

4.2 Posology and method of administration

AZULIX MF FORTE should be given once daily with a full meal & should be started at a low dose.

Azulix MF FORTE should be taken as directed by the physician. Tablet to be swallowed whole and not to be chewed or crushed.

4.3 Contraindications

Glimepiride

Glimepiride is contraindicated in patients with the following conditions:

• hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the excipients
• insulin dependent diabetes,
• diabetic coma,
• ketoacidosis,
• severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a change over to insulin is required.

Metformin
• Hypersensitivity to metformin or to any of the excipients
• Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCL < 45 ml/min or eGFR < 45 mL/min/1.73m2).
• Acute conditions with the potential to alter renal function such as:
- dehydration,
- severe infection,
- shock
• Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
- decompensated heart failure,
- respiratory failure,
- recent myocardial infarction,
- shock
• Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Glimepiride

It 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 hypoglycaemia. Possible symptoms of hypoglycaemia 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 hypoglycaemic 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, hypoglycaemia may recur. Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to

cooperate,
- undernutrition, 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 haemoglobin is recommended.
Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with Glimepiride.
In stress-situations (e.g. accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.
No experience has been gained concerning the use of Glimepiride in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Metformin
Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality rate in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with impaired renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued.
Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction).
The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:
Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised immediately.
Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function:
As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:
• at least annually in patients with normal renal function,
• at least two to four times a year in patients with creatinine clearance levels at the lower limit of normal and in elderly subjects.
In case creatinine clearance CrCl is <45 ml/min (eGFR < 45 ml/min/1.73 m^2), metformin is contraindicated.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).
In these cases, it is also recommended to check renal function before initiating treatment with metformin.

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:
The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Surgery:
Metformin should be discontinued 48 hours before elective surgery with general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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.

4.5 Drugs interactions

Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic 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 hypoglycaemia may occur when one of the following medicinal products is taken, for example:
- phenylbutazone, azapropazone and oxyfenbutazone,
- 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, tetracyclines, quinolone antibiotics and clarithromycin,
- coumarin anticoagulants,
- fenfluramine,
- disopyramide,
- fibrates,
- ACE inhibitors,
- fluoxetine, MAO-inhibitors,
- allopurinol, probenecid, sulfinpyrazone,
- sympatholytics,
- cyclophosphamide, trophosphamide and iphosphamides,
- miconazole, fluconazole
- pentoxifylline (high dose parenteral),
- tritoqualine,

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_2 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 hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic 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.

Metformin

Concomitant use not recommended

Alcohol

Acute alcohol intoxication is associated with an 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 media

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precautions for use

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.

Diuretics, especially loop diuretics

They may increase the risk of lactic acidosis due to their potential to decrease renal function

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

Metformin

Pregnancy

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

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

When the patient plans to become pregnant and during pregnancy, it is recommended that 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.

4.7 Effects on ability to drive and use machines

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

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: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

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/µl and thrombocytopenic purpura

Immune system disorders

Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.
Not known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders

Rare: hypoglycaemia.
These hypoglycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic 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.

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

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.
The following adverse reactions may occur with AZULIX MF FORTE SR.
Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Metabolism and nutrition disorders
Very rare:
• Lactic acidosis
• 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 presents with megaloblastic anaemia.
Nervous system disorders
Common:
• Taste disturbance
Gastrointestinal disorders
Very common:
• Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary disorders
Very rare
• Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders
Very rare:

• Skin reactions such as erythema, pruritus, urticaria

4.9 Overdose

Glimepiride

Symptoms

After ingestion of an overdose hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdose hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular, when treating hypoglycaemia due to accidental intake of Glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

Metformin

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5 Pharmacological properties

5.1 Mechanism of Action

Glimepiride

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.

Metformin

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).

5.2 Pharmacodynamic properties

Glimepiride

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives. ATC Code: A10B B12.

Glimepiride is an orally active hypoglycaemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus.

Insulin release

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results - by opening of calcium channels - in an increased influx of calcium into the cell.
This leads to insulin release through exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylurea binding site.

Extrapancreatic activity

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.
The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2, 6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether the medicinal product was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.
Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect.

Combination therapy with metformin
Improved metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum dosage of metformin has been shown in one study.

Combination therapy with insulin
Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. In two studies, the combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

Special populations
Paediatric population
An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride -0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of non-inferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.
Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

Metformin
ORAL ANTI-DIABETICS
(A10BA02: Gastrointestinal tract and metabolism)
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

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 sulphonylurea 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 sulphonylurea 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 patient-years (p=0.01)
For metformin used as second-line therapy, in combination with a sulphonylurea, 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.

5.3 Pharmacokinetic properties

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 (Cmax) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both Cmax 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.

Special populations
Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Paediatric population
A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.

Metformin
Absorption
After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

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

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

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

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

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

Following a single oral administration of 1500 mg of Metformin SR750 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 SR750 mg was shown to be bioequivalent to Metformin SR500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin SR1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin SR1000 mg was shown to be bioequivalent to Metformin SR500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.
When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax is slightly prolonged by about 1 hour).

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

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

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

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.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

Metformin

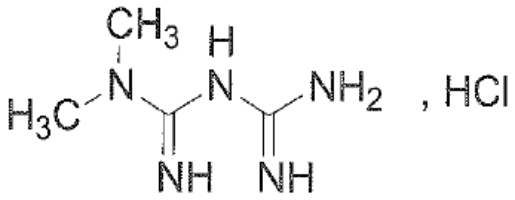
Preclinical data reveal no special hazard for humans based on conventional studies on

safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

7 Description

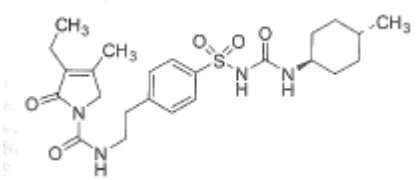
Metformin

Metformin Hydrochloride is 1, 1- dimethylbiguanide hydrochloride. Metformin Hydrochloride is a white or almost white crystalline powder. It is freely soluble in water; slightly soluble in ethanol (95 per cent); practically insoluble in acetone, in chloroform, in dichloromethane and in ether. The molecular formula is C4H11N5, Hcl and the molecular weight is 165.6 g/mol The structural formula is:



Glimepiride

Glimepiride is 1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl] sulphonyl]-3 -trans-(4-methylcyclohexyl)urea. 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. The molecular formula is C24H34N4O5S, Hcl and the molecular weight is 490.6 g/mol The structural formula is:



AZULIX 3 MF FORTE is White & Pink coloured, elongated, biconvex, bilayered, uncoated tablets, plain on both sides AZULIX 4 MF FORTE is White & light Orange coloured, elongated, biconvex, bilayered, uncoated tablet, plain on both sides. AZULIX 3 MF FORTE and AZULIX 4 MF FORTE contain excipients are Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Magnesium stearate, Polyvinyl pyrrolidone K-30, Sodium carboxy methyl cellulose, Lactose, calcium carboxy methyl cellulose, dichloromethane, colour Ponceau 4R Lake, Colour Sunset Yellow Lake.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

AZULIX 3 MF FORTE and AZULIX 4 MF FORTE are available in Blister strip of 10 Tablets.

8.4 Storage and handing instructions

Store at temperature below 25°C. Protect from Moisture.
Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- 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 you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet

What is in this leaflet

9.1 What AZULIX MF FORTE is and what it is used for

AZULIX MF FORTE contains the active ingredients Metformin Hydrochloride, belongs to a group of medicines called biguanides, which works by making the body more sensitive to insulin and helps return to normal the way body uses glucose and Glimepiride, belongs to a blood sugar lowering group of medicines called sulfonylureas, which works by increasing the amount of insulin released from your pancreas. The insulin then lowers your blood sugar levels.

AZULIX MF FORTE is used in the treatment of patients with type 2 diabetes mellitus when diet, exercise and the single agent do not result in adequate glycemic control.

9.2 What you need to know before you are given AZULIX MF FORTE

Do not take AZULIX MF FORTE and tell your doctor if:

- 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.
- You are allergic to metformin. An allergic reaction may cause a rash, itching or shortness of breath.
- 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 severe kidney disease.
- You have a severe liver disease
- 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 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 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 (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.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking AZULIX MF FORTE.

Warnings and precautions

Talk to your doctor or pharmacist before taking AZULIX MF FORTE

- 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 AZULIX MF FORTE

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 AZULIX MF FORTE, 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 AZULIX MF FORTE 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 AZULIX MF FORTE
is not recommended for use in children under 18 years of age.

Other medicines and AZULIX MF FORTE:
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 AZULIX MF FORTE if you are taking other medicines, which may weaken or strengthen the effect of AZULIX MF FORTE on the level of sugar in your blood.

The following medicines can increase the blood sugar lowering effect of AZULIX MF FORTE . 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 AZULIX MF FORTE. 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 heart beat, 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 (rifampicine)
- Medicines to treat increased pressure in the eye (azetazolamide)

The following medicinal products can increase or decrease the blood sugar lowering effect of AZULIX MF FORTE :
- 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) AZULIX MF FORTE 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 AZULIX MF FORTE . To avoid this effect, you should be advised to take AZULIX MF FORTE at least 4 hours before colesevelam.

AZULIX MF FORTE with food and drink:
Alcohol intake may increase or decrease the blood sugar lowering action of AZULIX

MF FORTE in an unpredictable way

Risk of lactic acidosis
AZULIX MF FORTE 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 a 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 AZULIX MF FORTE 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 AZULIX MF FORTE 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 AZULIX MF FORTE during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with AZULIX MF FORTE.

During treatment with AZULIX MF FORTE, 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.

If you are older than 75 years, treatment with AZULIX MF FORTE should not be started to lower the risk of developing type 2 diabetes.

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 AZULIX MF FORTE
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, in the context of an X-ray or scan, you must stop taking AZULIX MF

FORTE before or at the time of injection. Your doctor will decide when you must stop and when to restart your treatment with AZULIX MF FORTE.

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 AZULIX MF FORTE. 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 AZULIX MF FORTE in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

Pregnancy, breast-feeding and fertility:
Pregnancy
AZULIX MF FORTE 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
AZULIX MF FORTE may pass into breast milk. AZULIX MF FORTE 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

AZULIX MF FORTE contains lactose
If you have been told by your doctor that you cannot tolerate some sugars, contact your doctor before taking this medicinal product.

9.3 How AZULIX MF FORTE is given
Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure

Taking this medicine

- Should be given once daily with a full meal & should be started at a low dose.
- Tablet to be swallowed whole and not to be chewed or crushed.

If you take more AZULIX MF FORTE than you should

If you happen to have taken too much AZULIX MF FORTE 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.

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 heart beat. If you experience some of these symptoms, you should immediately seek medical attention, as lactic acidosis may lead to coma. Stop taking AZULIX MF FORTE immediately and contact a doctor or the nearest hospital straightaway.

If you forget to take AZULIX MF FORTE

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

If you stop taking AZULIX MF FORTE

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 AZULIX MF FORTE until your doctor tells you to stop.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

9.4 Possible side effects

Like all medicines, AZULIX MF FORTE can cause side effects, although not everybody gets them. The following side effects may occur:

- AZULIX MF FORTE 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 AZULIX MF FORTE and**

contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

- AZULIX MF FORTE may cause abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice (may affect up to 1 user in 10,000). 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
- 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)
- Decreased vitamin B12 levels
- Skin rashes including redness, itching and hives.

These problems generally get better after you stop taking AZULIX MF FORTE

Very rare side effects (may affect up to 1 in 10,000 people):

- 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 AZULIX MF FORTE . This is due to changes in blood sugar levels and should soon improve
- Increased liver enzymes
- Severe unusual bleeding or bruising under the skin

9.5 How to store AZULIX MF FORTE

- Keep this medicine out of the sight and reach of children
- Store at temperature below 25°C. Ptotect from Moisture.
- Do not use this medicine after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.
- Do not use this medicine if you notice visible signs of deterioration.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

10 Details of manufacturer

Windlas Biotech Pvt. Limited (Plant-2),
Khasra No. 141-143 & 145,
Mohabewala Industrial Area,
Dehradun - 248 110, Uttarakhand

11 Details of permission or licence number with date

34/UA/2013 issued on 19.04.2018

12 Date of revision

July 2019

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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Ahmedabad-380 009, INDIA

IN/AZULIX MF FORTE 3,4,1000mg/JUL-2019/02/PI