

**AZULIX MV**

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**1. Generic Name**

Metformin Hydrochloride (SR), Glimepiride and Voglibose Tablets

**2. Qualitative and quantitative composition**

**AZULIX MV 1/0.3**

Each uncoated bilayered tablet contains:

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

(in Sustained release form)

Glimepiride I.P. .... 1 mg

Voglibose I.P..... 0.3 mg

Excipients.....q.s.

Colour: Sunset Yellow Lake

The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Sunset Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

**AZULIX MV 2/0.3**

Each uncoated bilayered tablet contains:

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

(in Sustained release foam)

Glimepiride I.P. .... 2 mg

Voglibose I.P..... 0.3 mg

Excipients.....q.s.

Colour: Quinoline Yellow Lake

The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Quinoline Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

**AZULIX MV 1/0.2**

Each uncoated bilayered tablet contains:

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

(in Sustained release foam)

Glimepiride I.P. .... 1 mg

Voglibose I.P..... 0.2 mg

Excipients.....q.s.

Colour: Sunset Yellow FCF

The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Magnesium Stearate, Lactose, Starch, Croscarmellose sodium, Hydroxy Propyl Cellulose, Lake Sunset Yellow, Crospovidone.

### **AZULIX MV 2/0.2**

Each uncoated bilayered tablet contains:

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

(in Sustained release foam)

Glimepiride I.P. .... 2 mg

Voglibose I.P. .... 0.2 mg

Excipients.....q.s.

Colour: Ferric oxide USP NF Yellow and Ferric Oxide USP NF Red

The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Magnesium Stearate, Lactose, Starch, Croscarmellose sodium, Crospovidone, Ferric oxide USP NF Red, Ferric oxide USP NF Yellow.

### **3. Dosage form and strength**

**Dosage form:** Uncoated Bilayered Tablets

**Strengths:**

Metformin Hydrochloride 500 mg, Glimepiride 1 mg and Voglibose 0.3 mg,

Metformin Hydrochloride 500 mg, Glimepiride 2 mg and Voglibose 0.3 mg

Metformin Hydrochloride 500 mg, Glimepiride 1 mg and Voglibose 0.2 mg

Metformin Hydrochloride 500 mg, Glimepiride 2 mg and Voglibose 0.2 mg

### **4. Clinical particulars**

#### **4.1 Therapeutic indication**

It is indicated as an adjunct to diet and exercise in type 2 diabetes mellitus patients, when monotherapy is not able to achieve glycemic control.

#### **4.2 Posology and method of administration**

**Posology**

The daily recommended dose is as directed by the Physician.

**Method of administration**

AZULIX MV tablets should be administered orally. Do not crush or chew the tablet. Swallow as a whole.

**Recommendations for Use in Renal Impairment**

Assess renal function prior to initiation of AZULIX MV and periodically thereafter.

AZULIX MV is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m<sup>2</sup>. Initiation of AZULIX MV in patients with an eGFR between 30-45 mL/minute/1.73 m<sup>2</sup> is not recommended. In patients taking AZULIX MV whose eGFR later falls below 45-mL/min/1.73 m<sup>2</sup>, assess the benefit risk of continuing therapy. Discontinue AZULIX MV if the patient's eGFR later falls below 30-mL/minute/1.73 m<sup>2</sup>.

## Paediatrics

The dosage of AZULIX MV must be individualized on the basis of both effectiveness and tolerability. Safety and effectiveness of AZULIX MV in paediatric patients have not been established.

### 4.3 Contraindications

- Hypersensitivity to metformin or to glimepiride or other sulfonylureas or sulphonamides or voglibose or to any of the excipients
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (GFR < 30 mL/min/1.73m<sup>2</sup>).
- 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.
- insulin dependent diabetes
- diabetic coma
- ketoacidosis
- severe renal or hepatic function disorders.
- In case of severe renal or hepatic function disorders, a changeover to insulin is required.

### 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 antihypertensives, 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.

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

### 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 agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

### Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

### Paediatric population

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

### **Children aged between 10 and 12 years**

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

### 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 does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

## **Glimepiride**

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with "Glimepiride Tablets" 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
- overdosage with Glimepiride Tablets
- 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 (see section 4.5)

Treatment with glimepiride tablets 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 tablets

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 tablets 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.

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

### **Voglibose**

- All patients should continue their dietary restriction 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. Patients should be instructed and explained to recognize hypoglycemic symptoms and its management.

## **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 *Iodinated contrast agents*

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

#### Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

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

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

##### *Organic cation transporters (OCT)*

Metformin is a substrate of both transporters OCT1 and 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, trimethoprim, 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**

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.

Potential 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 dosages) and nicotinic acid derivatives
- laxatives (long term use)
- phenytoin, diazoxide
- glucagon, barbiturates and rifampicin
- acetazolamide

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

Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to 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 gastrointestinal 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.

### **Voglibose**

When Voglibose is used in combination with derivative(s) of sulfonamide, sulfonylurea or biguanide, or with insulin, hypoglycemic symptoms may occur. Therefore, when used in combination with any of these drugs, care should be taken, such as starting the administration at a low dose.

When Voglibose is administered concomitantly with drugs that enhance or diminish the hypoglycemic action of antidiabetic drugs, caution should be taken as this might additionally delay the action of Voglibose on the absorption of carbohydrates. Examples of drugs enhancing the hypoglycemic action of antidiabetic drugs:  $\alpha$ -blockers, salicylic acid preparations, monoamine oxidase inhibitors, and fibrate derivatives. Examples of drugs diminishing the hypoglycemic action of antidiabetic drugs: epinephrine, adrenocortical hormone, and thyroid hormone.

Voglibose does not affect the pharmacokinetics of warfarin; hence it can be safely administered along with warfarin.



#### **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 foetal development, parturition or postnatal development.

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

###### 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, breast-feeding 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 effects 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. Reported 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.

###### Breast-feeding

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.

## Voglibose

### Pregnancy

Voglibose should be administered to pregnant women or women having possibilities of being pregnant only if the expected therapeutic benefit is thought to outweigh any possible risk. The safety of this drug in pregnant women has not been established.

### Lactation

It is desirable to avoid the administration of this drug to nursing mothers. However, if the administration is indispensable, nursing should be discontinued. Animal studies (rats) have revealed a suppressive action of this drug on body weight increase in newborns, presumably due to suppression of milk production resulting from inhibition of carbohydrate absorption in mother animals.

### **Paediatrics**

The safety of AZULIX MV in children has not been established (no clinical experience).

#### **4.7 Effects on ability to drive and use machines**

AZULIX MV tablets have no direct influence on the ability to drive and use machines but may cause hypoglycaemia.

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 signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

#### **4.8 Undesirable effects**

##### **Metformin Hydrochloride**

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

The following adverse reactions may occur under treatment with AZULIX MV. Frequencies are defined as follows: very common:  $\geq 1/10$ ; 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.

<b>Metabolism and nutrition disorders</b>	
Very rare	Lactic acidosis
	Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
<b>Nervous system disorders</b>	
Common	Taste disturbance
<b>Gastrointestinal disorders</b>	
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. To prevent them, it is recommended that metformin be taken

	in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.
<b>Hepatobiliary disorders</b>	
Very rare	Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation
<b>Skin and subcutaneous tissue disorders</b>	
Very rare	Skin reactions such as erythema, pruritus, urticaria

### **Glimepiride**

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

<b>Blood and lymphatic system disorders</b>	
Rare	Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.
Not known	Severe thrombocytopenia with platelet count less than 10,000/ $\mu$ l and thrombocytopenic purpura.
<b>Immune system disorders</b>	
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.
<b>Metabolism and nutrition disorders</b>	
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 dosage.
<b>Eye disorders</b>	
Not known	Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.
<b>Gastrointestinal disorders</b>	
Very rare	Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.
<b>Hepato-biliary disorders</b>	
Very rare	Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.
Not known	hepatic enzymes increased
<b>Skin and subcutaneous tissue disorders</b>	
Not known	Hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.
<b>Investigations</b>	
Very rare	Blood sodium decrease.

## **Voglibose**

Gastrointestinal adverse effects such as diarrhoea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting, or heartburn may occur with the use of Voglibose. Also abdominal distention, increased flatus, and intestinal obstruction like symptoms due to an increase in intestinal gas, may occur with use of Voglibose.

When Voglibose is administered to patients with serious liver cirrhosis, hyper ammonia may worsen with the development of constipation followed by disturbance of consciousness. Elevation of GOT (glutamate oxaloacetate), GPT (glutamate pyruvate transaminase), LDH (lactate dehydrogenase), aGPT (aglutamate pyruvate) or alkaline phosphatase may infrequently occur.

In a reported study When Voglibose is used in combination with other antidiabetic drugs, hypoglycemia may occur (0.1% to <5%). Hypersensitivity: Rash and pruritus may rarely occur. In such a case, Voglibose tablets should be discontinued.

Psychoneurologic: Headache may rarely occur.

Hematologic: Anemia; thrombocytopenia, and leucopenia may rarely occur.

Others: Numbness, edema of face, blurred vision, hot flushes, malaise, weakness, hyperkalemia, increased serum amylase, decreased HDL cholesterol, diaphoresis or alopecia, and perspiration.

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

[https://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting).

## **4.9 Overdose**

### **Metformin Hydrochloride**

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

#### **Symptoms**

After ingestion of an overdosage 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) overdosage 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.

### **Voglibose**

Voglibose competitively and reversibly inhibits the  $\alpha$ -glucosidase enzymes (glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestine, which delays the hydrolysis of complex carbohydrates. It is unlikely to produce hypoglycemia in overdose, but abdominal discomfort and diarrhoea may occur.

## **5 Pharmacological properties**

### **5.1 Mechanism of Action**

#### **Metformin Hydrochloride**

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

#### **Glimepiride**

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent (type 2) diabetes mellitus.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulphonylureas 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 sulphonylureas.

#### **Voglibose**

Voglibose is an alpha glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of  $\alpha$ -glucosidase in the intestinal brush border. Inhibition of this enzyme catalyzes the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects resulting in improvement of post prandial hyperglycemia and various disorders caused by hyperglycemia.  $\alpha$ -Glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. These agents may be considered as monotherapy in elderly patients or in patients with predominantly post prandial hyperglycemia.  $\alpha$ -Glucosidase

inhibitors are typically used in combination with other oral antidiabetic agents and/or insulin. Voglibose should be administered at the start of a meal as it is poorly absorbed.

## 5.2 Pharmacodynamic properties

### Metformin Hydrochloride

Pharmacotherapeutic group: Blood glucose lowering drugs, Biguanides

ATC code: A10BA02

In reported clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

#### Clinical efficacy

The prospective randomised reported study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

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 sulfonylurea 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 sulfonylurea 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 ( $p=0.01$ ).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

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.

#### Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

### 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 sulphonylurea group. It may be used in non-insulin dependent (type 2) diabetes mellitus.

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

#### 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 sulfonylureas 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 glycolipogenesis 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 daily 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.

#### **Voglibose**

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, and excl. insulins

ATC code: A10BF03

In a reported randomized double-blind trial comprising 1780 Japanese individuals with impaired glucose tolerance, who were treated for an average of 48.1 weeks (standard deviation, SD =36.3), Ryuzo Kawamori et al reported Voglibose to be better than placebo (p=0.0026). It was noted that Voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance.

Kazuhisa Takami et al examined the effects of dietary modification / restriction alone and dietary modification/restriction with Voglibose or glyburide on abdominal adiposity and metabolic abnormalities in 36 Japanese patients with type 2 diabetes. In newly diagnosed patients who were relatively lean but had excess visceral adipose tissue area (VAT), dietary modification/restriction (with or without Voglibose or glyburide) effectively reduced VAT. Decrease in VAT was closely associated with improvement of glycemic control through diet. Additional use of Voglibose or low dose glyburide had no detrimental effects on abdominal adiposity and had beneficial effects on insulin sensitivity and the acute insulin response. In another reported trial, treatment with Voglibose in diabetes mellitus patients demonstrated improved post prandial blood glucose levels, a significant decline of triglyceride level, and an elevation of high density lipoprotein (HDL) cholesterol and apolipoprotein A-1. As compared to acarbose, Voglibose was more effective and had fewer side effects. In a reported meta-analysis comparing miglitol and Voglibose, no significant differences in post prandial glucose were observed between the 2 groups.

### **5.3 Pharmacokinetic properties**

#### **Metformin Hydrochloride**

##### Absorption

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration ( $C_{max}$ ) is reached in approximately 2.5 hours ( $t_{max}$ ). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.



After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels ( $C_{max}$ ) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

### Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ( $V_d$ ) 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.

#### Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration ( $C_{max}$ ) and systemic exposure (AUC<sub>0-t</sub>) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

## **Glimepiride**

### Absorption

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only the absorption rate is slightly diminished. Maximum serum concentrations (C<sub>max</sub>) 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 C<sub>max</sub> 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 intra individual 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<sub>(0-last)</sub>, C<sub>max</sub> and t<sub>1/2</sub> similar to that previously observed in adults.

## **Voglibose**

### Absorption

Voglibose is poorly absorbed after oral doses. Plasma concentrations after oral doses have usually been undetectable. After an 80 mg dose (substantially higher than recommended dose), peak plasma levels of about 20 ng/mL were observed in 1 to 1.5 hours. When Voglibose tablets were repeatedly administered to healthy male adults (6 subjects) in a single dose of 0.2 mg, 3 times a day, for 7 consecutive days, Voglibose was not detected in plasma or urine. Similarly, when Voglibose was administered to healthy male adults (10 subjects) as a single dose of 2 mg, Voglibose was not detected in plasma or urine.

### Distribution

After ingestion of Voglibose (and other glucosidase inhibitors), the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity.

### Metabolism

Voglibose is metabolized by intestinal enzymes and by the microbial flora.

### Elimination

Voglibose is excreted in the urine and feces. In a reported study in which a single dose of 1 mg/kg of C14-Voglibose was administered to rats, the transfer of Voglibose to the fetus and to mother's milk was observed, and the rates of excretion into urine and feces were about 5% and 98%, respectively.

## **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 and reproductive toxicity.

#### **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.

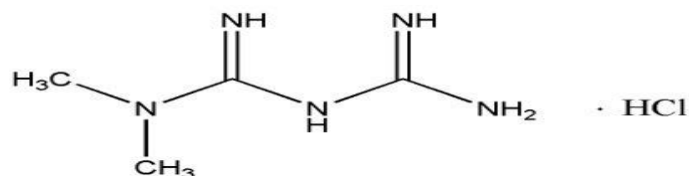
#### **Voglibose**

Reported animal studies (rats) have revealed a suppressive action of Voglibose on body weight increase in new-borns presumably due to suppression of milk production in mother animals resulting from suppression of carbohydrate absorption. Therefore, it is desirable not to give Voglibose tablets to women during lactation. When the administration is unavoidable, nursing should be avoided.

## 7. Description

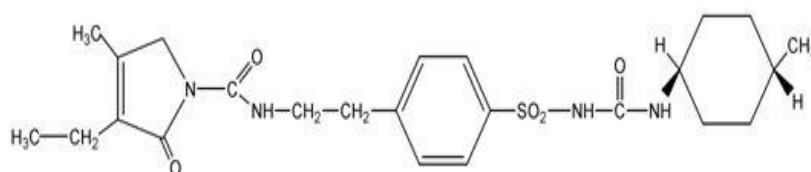
### Metformin Hydrochloride

Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. Having molecular formula  $C_4H_{11}N_5HCl$  and molecular weight 165.6. The chemical structure is:



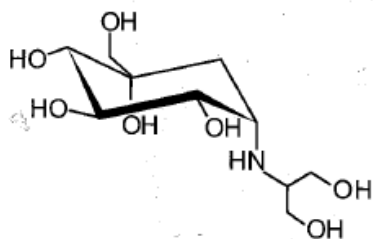
### Glimepiride

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:



### Voglibose

Voglibose is 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epiinositol. Voglibose is a white to off white crystalline powder. The molecular formula is  $C_{10}H_{21}NO_7$  and the molecular weight is 267.3 g/mol. The structural formula is:



### AZULIX MV 1/0.3:

Orange & white coloured, bilayered, elongated, biconvex, uncoated tablets plain on both side. The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Sunset Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

### AZULIX MV 2/0.3:

Yellow & white coloured, bilayered, elongated, biconvex, uncoated tablets plain on both side. The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Quinoline Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

### **AZULIX MV 1/0.2:**

Bilayered capsule shaped uncoated tablets, one layer with Orange colour with break line and the other layer with white colour. The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Quinoline Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

### **AZULIX MV 2/0.2:**

Bilayered capsule shaped uncoated tablets, one layer with brown colour with break line and the other layer with white colour. The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Magnesium Stearate, Lactose, Starch, Croscarmellose sodium, Crospovidone, Ferric oxide USP NF Red, Ferric oxide USP NF Yellow.

## **8. Pharmaceutical particulars**

### **8.1 Incompatibilities**

None Stated

### **8.2 Shelf-life**

Do not use later than the date of expiry.

### **8.3 Packaging information**

AZULIX MV 1/0.3 and AZULIX MV 2/0.3 are available in 10 blister strip of 10 Tablets.

AZULIX MV 1/0.2 and AZULIX MV 2/0.2 are available in 10 Alu - PVC/PVDC (clear) blister of 10 Tablets.

### **8.4 Storage and handing instructions**

Store at a temperature below 25°C, Protect from light and moisture.

Keep all medicines out of reach of children. Tablet to be swallowed whole and not to be chewed or crushed.

## **9. Patient Counselling Information**

### **AZULIX MV**

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

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness 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 MV** is and what it is used for

9.2. What you need to know before you take **AZULIX MV**

9.3. How to take **AZULIX MV**

9.4. Possible side effects

9.5. How to store **AZULIX MV**

9.6. Contents of the pack and other information

### **9.1 What AZULIX MV is and what it is used for**

AZULIX MV is a combination Metformin Hydrochloride, Glimpiride and Voglibose. Metformin Hydrochloride belongs to a group of medicines called biguanides. Glimpiride belongs to a blood sugar lowering group of medicines called sulfonylureas. Voglibose is an alpha glucosidase inhibitors.

AZULIX MV is used as an adjunct to diet and exercise in type 2 diabetes mellitus patients, when monotherapy is not able to achieve glycemic control.

### **9.2 What you need to know before you take AZULIX MV**

#### **Do not take AZULIX MV Tablets:**

- you are allergic to Metformin Hydrochloride or Glimpiride or Voglibose or to any of the other ingredients of this medicine.
- you have liver problems
- you have severely reduced kidney function
- You have insulin dependent diabetes (type 1 diabetes mellitus)
- 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 lost too much water from your body (dehydration), such as due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. 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 are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have 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 drink a lot of alcohol
- you have a gastrointestinal condition in which digested material is prevented from passing normally through the bowel (Gastrointestinal obstruction).

**Do not take this medicine if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking AZULIX MV.**

Make sure you ask your doctor for advice, if:

- you need to have an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your bloodstream
- you need to have major surgery

You must stop taking AZULIX MV for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor's instructions precisely.

## **Warnings and precautions**

### Risk of lactic acidosis

AZULIX MV 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 MV 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 MV 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 MV during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with AZULIX MV.

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

During treatment with AZULIX MV, 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 not sure if any of these apply to you, talk to your doctor or pharmacist before taking AZULIX MV.

Lowering of the haemoglobin level and breakdown of red blood cells (haemolytic anemia) can occur in patients missing the enzyme glucose-6-phosphate dehydrogenase.

AZULIX MV on its own does not cause hypoglycaemia (a blood glucose level which is too low). However, if you take AZULIX MV together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitinides), there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart beating, vision disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

Important information about hypoglycaemia (low blood sugar) When you take AZULIX MV, 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 MV 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

AZULIX MV Tablets is not recommended for use in children under 18 years of age

### **Other medicines and AZULIX MV**

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking AZULIX MV before or at the time of injection. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of AZULIX MV.

It is especially important to mention the following:

- medicines which increase urine production (diuretics).
- 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).
- beta-2 agonists such as salbutamol or terbutaline (used to treat asthma).
- corticosteroids (used to treat a variety of conditions, such as severe inflammation of the skin or in asthma).
- medicines that may change the amount of AZULIX MV in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).
- other medicines used to treat diabetes.

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

- Medicines to treat pain and inflammation (phenylbutazone, azopropazone, oxyphenbutazone, aspirinlike 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 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 MV 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 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 MV 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)
- AZULIX MV 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 AZULIX MV Tablets. To avoid this effect, you should be advised to take AZULIX MV Tablets at least 4 hours before colesevelam

### **AZULIX MV with alcohol**

Avoid excessive alcohol intake while taking AZULIX MV since this may increase the risk of lactic acidosis (see section ‘Warnings and precautions’).

## **Pregnancy, breast-feeding and fertility:**

### Pregnancy

AZULIX MV 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

AZULIX MV may pass into breast milk. AZULIX MV should not be taken during breast feeding. Ask your doctor or pharmacist for advice before taking this medicine.

## **Driving and using machines**

AZULIX MV on its own does not cause hypoglycaemia (a blood glucose level which is too low). This means that it will not affect your ability to drive or use machines. However, take special care if you take AZULIX MV together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitinides). Symptoms of hypoglycaemia include weakness, dizziness, increased sweating, fast heartbeat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.

## **9.3 How to take AZULIX MV**

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

- Take this medicine by mouth just before or with the first main meal of the day (usually breakfast). If you do not have breakfast you should take the product on schedule as prescribed by your doctor. It is important not to leave out any meal when you are on AZULIX MV Tablets
- Swallow the tablets whole with at least half glass of water. Do not crush or chew the tablets

### **If you take more AZULIX MV than you should**

If you have taken more AZULIX MV than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as vomiting, bellyache (abdominal pain) 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 seek immediately medical attention, as lactic acidosis may lead to coma. Stop taking AZULIX MV immediately and contact a doctor or the nearest hospital straight away.

### **If you forget to take AZULIX MV Tablets**

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

### **If you stop taking AZULIX MV 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 AZULIX MV Tablets 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 MV can cause side effects, although not everybody gets them. The following side effects may occur: AZULIX MV 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'). as lactic acidosis may lead to coma

Tell your doctor immediately if you experience any of the following symptoms :

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.

### **Very common side effects (in more than 1 in 10 people)**

digestive problems, such as feeling sick (nausea), being sick (vomiting), diarrhoea, bellyache (abdominal pain) and loss of appetite.

These side effects most often happen at the beginning of the treatment with AZULIX MV. It helps if you spread the doses over the day and if you take AZULIX MV with or straight after a meal. If symptoms continue, stop taking AZULIX MV and talk to your doctor

### **Common side effects (in less than 1 in 10 people)**

- changes in taste.

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

- Lower blood sugar than normal (hypoglycaemia) (See Section 2)
- 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 AZULIX MV tablets

### **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)

- Lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. Symptoms of lactic acidosis are non-specific (see section ‘Warning and precautions’)
- abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, stop taking AZULIX MV and talk to your doctor.
- skin reactions such as redness of the skin (erythema), itching or an itchy rash (hives).
- low vitamin B12 levels in the blood.

**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 sulfonyleureas, sulfonamides, or related drugs may occur
- Problems with your sight may occur when beginning treatment with AZULIX MV 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

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

[https://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting). By reporting side effects, you can help provide more information on the safety of this medicine

**9.5 How to store AZULIX MV**

Store at a temperature below 25°C, Protect from light and moisture.

**9.6 Contents of the pack and other information**

What **AZULIX MV** contains

The active substances **AZULIX MV** is Metformin Hydrochloride 500 mg/Glimepiride 1 mg/Voglibose 0.3 mg, Metformin Hydrochloride 500 mg/Glimepiride 2 mg/Voglibose 0.3 mg, Metformin Hydrochloride 500 mg/Glimepiride 1 mg/Voglibose 0.2 mg and Metformin Hydrochloride 500 mg/Glimepiride 2 mg/Voglibose 0.2 mg.

**AZULIX MV 1/0.3:** The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Sunset Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

**AZULIX MV 2/0.3:** The excipients used are HPMC, Sodium Carboxymethyl Cellulose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Quinolione Yellow Lake, Lactose, Calcium Carboxymethylcellulose, Dichloromethane and Purified Water.

**AZULIX MV 1/0.2:** The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Magnesium Stearate, Lactose, Starch, Croscarmellose sodium, Hydroxy Propyl Cellulose, Lake Sunset Yellow, Crospovidone.

**AZULIX MV 2/0.2:** The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Magnesium Stearate, Lactose, Starch, Croscarmellose sodium, Crospovidone, Ferric oxide USP NF Red, Ferric oxide USP NF Yellow.

#### **10. Details of manufacturer**

**AZULIX MV 1/0.3 and AZULIX MV 2/0.3:**

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

**AZULIX MV 1/0.2 and AZULIX MV 2/0.2:**

Manufactured by:  
Hetero Labs Limited (Unit-II)  
Kalyanpur (Village), Chakkan Road,  
Baddi (Tehsil), Solan (Distt),  
Himachal Pradesh - 173 205

#### **11. Details of permission or licence number with date**

**AZULIX MV 1/0.3 and AZULIX MV 2/0.3:**

Mfg Lic No. 34/UA/2013 issued on 20.08.2014

**AZULIX MV 1/0.2 and AZULIX MV 2/0.2:**

Mfg Lic No. MNB/09/780 issued on 24.03.2015

#### **12. Date of revision**

Not Applicable

#### **MARKETED BY**



TORRENT PHARMACEUTICALS LTD.

**IN/AZULIX MV 500, 1, 0.3 mg, 500, 2, 0.3 mg, 500, 1, 0.2 mg and 500, 2, 0.2 mg/Feb-21/01/PI**