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

Voglitor MF

1. Generic Name

Voglibose and Metformin Hydrochloride Tablets

2. Qualitative and quantitative composition

VOGLITOR MF 0.2
Each uncoated tablet contains:
Voglibose I.P……..... 0.2 mg
Metformin Hydrochloride I.P. ……..… 500 mg

VOGLITOR MF 0.3
Each uncoated tablet contains:
Voglibose I.P. ……..0.3 mg
Metformin Hydrochloride I.P. ……500 mg

Other inactive ingredients are povidone, iso propyl alcohol, microcrystalline cellulose, magnesium stearate.

3. Dosage form and strength

Dosage form: Uncoated Tablets
Strength: Voglibose 0.2 mg, Metformin Hydrochloride 500 mg

Voglibose 0.3 mg, Metformin Hydrochloride 500 mg

4. Clinical particulars

4.1 Therapeutic indication

As 2nd line treatment of Type II Diabetes mellitus when diet, exercise and the single agent do not result in adequate glycemic control.

4.2 Posology and method of administration

Dosage: To be taken as directed by the physician

Posology

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with Voglibose and Metformin any other pharmacologic agent. Dosage of **VOGLITOR MF** must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses.

VOGLITOR MF should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to **VOGLITOR MF** and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately 3 months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of VOGLITOR MF, either when used as monotherapy or in combination with sulfonylurea or insulin.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of **VOGLITOR MF** may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

VOGLITOR MF tablets must be swallowed whole and never crushed or chewed.

Occasionally, the inactive ingredients of **VOGLITOR MF** will be eliminated in the feces as a soft, hydrated mass.

Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of **VOGLITOR MF** and periodically thereafter. **VOGLITOR MF** is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 $m^{2.}$ Initiation of **VOGLITOR MF** in patients with an eGFR between 30 – 45 mL/minute/1.73 m^2 is not recommended. In patients taking **VOGLITOR MF** whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy. Discontinue **VOGLITOR MF** if the patient's eGFR later falls below 30 mL/minute/1.73 m^2

Pediatrics

The dosage of **VOGLITOR MF** must be individualized on the basis of both effectiveness and tolerability. Safety and effectiveness of **VOGLITOR MF** in pediatric patients have not been established.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue **VOGLITOR MF** at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart **VOGLITOR MF** if renal function is stable.

Combination with insulin

Voglitor MF and insulin may be used in combination therapy to achieve better blood glucose control. Insulin dosage is adjusted on the basis of blood glucose measurements.

Specific Patient Populations

Elderly

Since elderly patients generally have a physiological hypo function, it is desirable that such caution be taken as starting the administration at a low dose. Furthermore, this drug should be carefully administered under close observation, through the course of the disease condition, with careful attention to the blood sugar level and the onset of gastrointestinal symptoms and dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

In Pregnant Women

VOGLITOR MF are not recommended for use in pregnancy. **VOGLITOR MF** is not recommended in patients below the age of 10 years. **VOGLITOR MF** is not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of **VOGLITOR MF** should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function.

4.3 Contraindications

- Hypersensitivity to active substances or to any of the excipients of this product
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
- Acute conditions with the potential to alter renal function such as: dehydration, shock
- Severe infection, before and after operation or with serious trauma
- Gastrointestinal obstruction or predisposed to it

4.4 Special warnings and precautions for use

General

The administration of Voglitor MF Tablets should be limited to patients who have established diabetes, as there are certain other disease conditions such as abnormal glucose tolerance and positive urinary sugar that represent diabetes-like symptoms (renal glycosuria, senile abnormal glucose tolerance, abnormal thyroid function, etc).

Voglitor MF Tablets should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite adequate attempts at dieting, exercise and weight reduction.

When a patient stabilised on any oral hypoglycaemic medicinal product is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue the therapy and treat with insulin on a temporary basis.

Voglibose tablets should be administered with caution to the following patients:

- Patients with history of laparotomy or ileus
- Patients with chronic intestinal disease accompanied by disturbance in digestion and absorption
- Patients with aggravating symptoms due to increased generation of intestinal gas (eg, roemheld syndrome, severe hernia, and stenosis and ulcer of the large intestine)
- Patients with serious hepatic or renal disorders.

Lactic acidosis

Reported postmarketing cases of lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of Voglitor MF associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Voglitor MF associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence **of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL (see PRECAUTIONS).**

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g. carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided.

If Voglitor MF -associated lactic acidosis is suspected, immediately discontinue Voglitor MF and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Other Precautions:

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.

Metformin

Lactic acidosis

There have been reported postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Voglitor MF. In Voglitor MF treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue Voglitor MF and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal impairment—

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include.

- Before initiating Metformin obtain an estimated glomerular filtration rate (eGFR) Metformin is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2. Initiation of Metformin is not recommended in patients with eGFR between 30-45 mL/min/1.73 m2 .

- Obtain an eGFR at least annually in all patients taking Metformin. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking Metformin whose eGFR falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.
- *Drug interactions*—The concomitant use of Metformin with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation. Consider more frequent monitoring of patients.
- *Age 65 or greater*—the risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
- *Radiologic studies with contrast*—Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and Metformin if renal function is stable.
- *Surgery and other procedures*—withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. Metformin should be temporarily discontinued while patients have restricted food and fluid intake.
- *Hypoxic states*—several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue Metformin
- *Excessive alcohol intake*—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Metformin
- *Hepatic impairment*—Patients with hepatic impairment have developed cases of metformin associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of **Metformin** in patients with clinical or laboratory evidence of hepatic disease.

  Vitamin B12 levels—In reported controlled clinical trials of **Metformin** of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of **Metformin or** vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on **Metformin any** apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2-to 3-year intervals may be useful.

Hypoglycemia—Hypoglycemia does not occur in patients receiving **Metformin** alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Macrovascular outcomes—there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin or any other antidiabetic drug.

4.5 Drugs interactions

Voglibose

When Voglibose is used in combination with derivative(s) of sulfonylamide, 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: α-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.

Metformin

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with Metformin)

Glyburide—in a single-dose interaction reported study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain

Furosemide—A single-dose, metformin-furosemide drug interaction reported study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%,

without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine—A single-dose, metformin-nifedipine drug interaction reported study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Drugs that reduce metformin clearance—Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single-and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Other—Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

Carbonic anhydrase inhibitors—Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Alcohol—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving metformin

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

Pregnancy

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

A limited amount of reported data in pregnant women does not indicate an increased risk of congenital abnormalities. Reported 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 Voglitor MF 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

Studies in lactating rats show that Metformin is excreted into human breast milk. Similar studies have not been conducted in nursing mothers because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If Voglitor MF is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and effectiveness of Metformin for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of Metformin in this age group is supported by evidence from adequate and well-controlled studies of Metformin in adults with additional data from a controlled clinical reported study in pediatric patients ages 10 to 16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. . In this study, adverse effects were similar to those described in adults. A maximum daily dose of 2000 mg is recommended. Safety and effectiveness of Metformin in pediatric patients have not been established.

Geriatric Use

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients

4.7 Effects on ability to drive and use machines

Voglitor MF 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

In a reported double-blind clinical study of Metformin in patients with type 2 diabetes, a total of 141 patients received Metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the Metformin patients, and that were more common in Metformin -than placebo-treated

Patients, are listed in.

Table 11: Most Common Adverse Reactions (>5.0 Percent) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Adverse Reaction	**Metformin Monotherapy (n=141)**	**Placebo (n=145)**
	% of patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

Reactions that were more common in Metformin -than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 6% of patients treated with Metformin. Additionally, the following adverse reactions were reported in ≥1.0% to ≤5.0% of Metformin patients and were more commonly reported with Metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

In reported worldwide clinical trials over 900 patients with type 2 diabetes have been treated with Metformin in placebo-and active-controlled studies. In placebo-controlled trials, 781 patients were administered Metformin and 195 patients received placebo. Adverse reactions reported in greater than 5% of the Metformin patients, and that were more common in Metformin -than placebo-treated patients, are listed in Table 12**.**

Table 12: Most Common Adverse Reactions (>5.0 Percent) in Placebo-Controlled Studies of Metformin*

Adverse Reaction	**Metformin (n=781)**	**Placebo (n=195)**
	% of Patients	
Diarrhea	9.6	2.6
Nausea/Vomiting	6.5	1.5

Reactions that were more common in Metformin -than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 0.6% of patients treated with Metformin. Additionally, the following adverse reactions were reported in ≥1.0% to ≤5.0% of Metformin patients and were more commonly reported with Metformin than placebo: abdominal pain,

constipation, distention abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.

Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with postmarketing use of metformin

Pediatric Patients

In reported clinical trials with Metformin in pediatric patients with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

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:
http://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.

4.9 Overdose

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected..

Voglibose competitively and reversibly inhibits the α-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

Voglibose

Voglibose is an alpha glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-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 post-prandial 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. α-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. α-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.

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacodynamic properties

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 mo d i f i c a t i o n / r e s t r i c t i o n a l o n e a n d d i e t a r y 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.

Metformin

5.3 Pharmacokinetic properties

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.

Metformin

Absorption and Bioavailability

In The reported absolute bioavailability of a Metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin 500 to 1500 mg, and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of Metformin, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of Metformin, however, the extent of absorption (as measured by AUC) is similar to Metformin.

At steady state, the AUC and Cmax are less than dose proportional for Metformin within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from Metformin at a 2000 mg once-daily dose is similar to the same total daily dose administered as Metformin tablets 1000 mg twice daily. After repeated administration of Metformin, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from Metformin is comparable to that with Metformin.

Although the extent of metformin absorption (as measured by AUC) from the Metformin tablet increased by approximately 50% when given with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of Metformin.

Distribution

According to the reported study, the apparent volume of distribution (V/F) of metformin following single oral doses of Metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin , steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 μg/mL. During controlled clinical trials of Metformin, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination

In a reported study, intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see **Table 1**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single-or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of Metformin in patients with type 2 diabetes are comparable to those in healthy normal adults.

Renal Impairment

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and renal clearance is decreased

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

In the reported study limited data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Table 1: Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of metformin.

Subject Groups: GL dose[a] (number of subjects)	**Cmax [b] (µg/mL)**	**Tmax [c] (hrs)**	**Renal Clearance (mL/min)**
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)d	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dos[e] (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults: 850 mg single dose			
Mild (CLcr g 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CLcr 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57) 130
Severe (CLcr 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	(±90)

a All doses given fasting except the first 18 doses of the multiple dose studies

b Peak plasma concentration

cTime to peak plasma concentration

d Combined results (average means) of five studies: mean age 32 years (range 23-59 years)

e.Kinetic study done following dose 19, given fasting

F.Elderly subjects, mean age 71 years (range 65-81 years)

g CLcr = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

After administration of a single oral Metformin 500 mg tablet with food, geometric mean metformin Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients

(12-16 years of age) and gender-and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16).

Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of Metformin was comparable in males and females.

Race

According to reported study, no studies of metformin pharmacokinetic parameters according to race have been performed. In reported controlled clinical studies of Metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Clinical Studies

Metformin

In a reported double-blind, placebo-controlled, multicenter US clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with **Metformin** (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and hemoglobin A1c (HbA1c) of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to the placebo group (see **Table 2**).

Table 2: Metformin vs Placebo Summary of Mean Changes from Baseline* in Fasting Plasma Glucose, HbA1c, and Body Weight, at Final Visit (29-week study)

	Metformin (n=141)	**Placebo (n=145)**	**p-Value**
FPG (mg/dL) Baseline Change at FINAL VISIT	241.5 –53.0	237.7 6.3	NS** 0.001
Hemoglobin A1c (%) Baseline Change at FINAL VISIT	8.4 –1.4	8.2 0.4	NS** 0.001
Body Weight (lbs) Baseline Change at FINAL VISIT	201.0 –1.4	206.0 – 2.4	NS** NS**

* All patients on diet therapy at Baseline ** Not statistically significant

A reported 29-week, double-blind, placebo-controlled study of **Metformin** and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see **Table 3**). Patients randomized to the combination arm started therapy with **Metformin** 500 mg and glyburide 20 mg. At the end of each week of the first 4 weeks of the trial, these patients had their dosages of **Metformin** increased by 500 mg if they had failed to reach target fasting plasma glucose. After week 4, such dosage adjustments.

Were made monthly, although no patient was allowed to exceed **Metformin** 2500 mg. Patients in the **Metformin** only arm (metformin plus placebo) followed the same titration schedule. At the end of the trial, approximately 70% of the patients in the combination group were taking **Metformin** 2000 mg/glyburide 20 mg or **Metformin** 2500 mg/glyburide 20 mg. Patients

randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG, and HbA1c of 14 mg/dL, 3 mg/dL, and 0.2%, respectively. In contrast, those randomized to **Metformin** (up to 2500 mg/day) experienced a slight improvement, with mean reductions in FPG, PPG, and HbA1c of 1 mg/dL, 6 mg/dL, and 0.4%, respectively. The combination of **Metformin** and glyburide was effective in reducing FPG, PPG, and HbA1c levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to results of glyburide treatment alone, the net differences with combination treatment were –77 mg/dL, –68 mg/dL, and –1.9%, respectively.

	Comb (n=213)	**Glyb (n=209)**	**GLU (n=210)**	p-values		
				Glyb vs Comb	**GLU vs Comb**	**GLU vs Glyb**
Baseline Change at FINAL VISIT	250.5 –63.5	247.5 13.7	253.9 –0.9	NS** 0.001	NS** 0.001	NS** 0.025
Hemoglobin A1c (%)						
Baseline Change at FINAL VISIT	8.8 –1.7	8.5 0.2	8.9 –0.4	NS** 0.001	NS** 0.001	0.007 0.001
Body Weight (lbs)						
Baseline Change at FINAL VISIT	202.2 0.9	203.0 –0.7	204.0 –8.4	NS** 0.011	NS** 0.001	NS** 0.001

All patients on glyburide, 20 mg/day, at Baseline ** Not statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of Metformin Tablets therapy was proportional to the level of fasting hyperglycemia. Patients with type 2 diabetes with higher fasting glucose concentrations experienced greater declines in plasma glucose and glycosylated hemoglobin.

In clinical studies, Metformin, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol, and LDL cholesterol levels, and had no adverse effects on other lipid levels (see **Table 4**).

Table 4: Summary of Mean Percent Change from Baseline of Major Serum Lipid Variables at Final Visit (29-week studies)

	Metformin vs Placebo		**Combined Metformin /Glyburide vs Monotherapy**		
	Metformin (n=141)	**Placebo (n=145)**	**Metformin (n=210)**	**Metformin / Glyburide (n=213)**	**Glyburide (n=209)**
Total Cholesterol (mg/dL) Baseline Mean	211.0 –5%	212.3 1%	213.1 –2%	215.6 –4%	219.6 1%

% Change at FINAL VISIT					
Total Triglycerides (mg/dL) Baseline Mean % Change at FINAL VISIT	236.1 –16%	203.5 1%	242.5 –3%	215.0 –8%	266 .1 4%
LDL-Cholesterol (mg/dL) Baseline Mean % Change at FINAL VISIT	135.4 –8%	138.5 1%	134.3 –4%	136.0 –6%	137 .5 3%
HDL-Cholesterol (mg/dL) Baseline Mean % Change at FINAL VISIT	39.0 2%	40.5 – 1%	37.2 5%	39.0 3%	37. 0 1%

In contrast to sulfonylureas, body weight of individuals on Metformin tended to remain stable or even decrease somewhat (see **Tables 2** and **3**).

A 24-week, double-blind, placebo-controlled reported study of Metformin plus insulin versus insulin plus placebo was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone (see **Table 5**). Patients randomized to receive Metformin plus insulin achieved a reduction in HbA1c of 2.10%, compared to a 1.56%

Reduction in HbA1c achieved by insulin plus placebo. The improvement in glycemic control was achieved at the final study visit with 16% less insulin, 93.0 U/day vs 110.6 U/day, Metformin plus insulin versus insulin plus placebo, respectively, p=0.04.

Table 5: Combined Metformin /Insulin vs Placebo/Insulin Summary of Mean Changes from Baseline in HbA1c and Daily Insulin Dose

Metformin / Insulin (n=26) Placebo/ Insulin (n=28)	**Metformin / Insulin (n=26)**	**Placebo/ Insulin (n=28)**	**Treatment Difference Mean ± SE**
Hemoglobin A1c (%) Baseline Change at FINAL VISIT	8.95 –2.10	9.32 –1.56	–0.54 ± 0.43a
Insulin Dose (U/day) Baseline Change at FINAL VISIT	93.12 –0.15	94.64 15.93	–16.08 ± 7.77b

[a] Statistically significant using analysis of covariance with baseline as covariate (p=0.04)

Not significant using analysis of variance (values shown in table)

[b] Statistically significant for insulin (p=0.04)

A second double-blind, placebo-controlled reported study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA1c of 7.46 ± 0.97%, the addition of Metformin maintained similar glycemic control (HbA1c 7.15 ± 0.61 vs 6.97 ± 0.62 for Metformin plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68 ± 30.22 vs an increase of 0.43 ± 25.20 units for Metformin plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the combination of Metformin plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs, compared to an increase of 1.30 ± 6.08 lbs for placebo plus insulin, p=0.01.

Pediatric Clinical Studies

In a double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 182.2 mg/dL), treatment with **Metformin** (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 64.3 mg/dL, compared with placebo (see **Table 10**). **Table 10: Metformin vs Placebo (Pediatrics[a]) Summary of Mean Changes from Baseline* in Plasma Glucose and Body Weight at Final Visit**

	Metformin	**Placebo**	**p-Value**
FPG (mg/dL) Baseline Change at FINAL VISIT	**(n=37)** 162.4 –42.9	**(n=36)** 192.3 21.4	<0.001
Body Weight (lbs) Baseline Change at FINAL VISIT	**(n=39)** 205.3 –3.3	**(n=38)** 189.0 –2.0	NS**

a Pediatric patients mean age 13.8 years (range 10-16 years)

* All patients on diet therapy at Baseline ** Not statistically significant

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Metformin

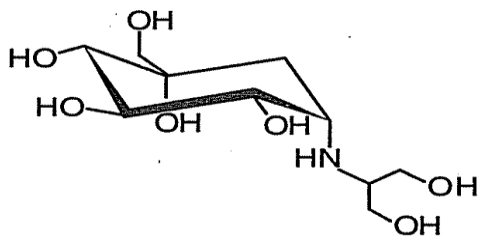
According to reported study, recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Metformin should not be used during pregnancy unless clearly needed.

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.

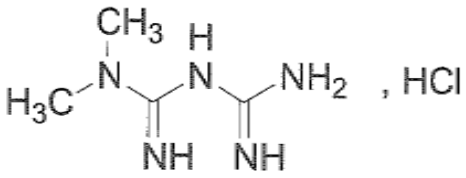
7. Description

Voglibose is 3,4-dideoxy-4-[[2-hydroxy-l-(hydroxymethyl) ethyl]amino]-2-C-(hydroxymethyl)-D-epiinositol. Having molecular formula C10H21NO7 and Molecular weight 267.3. The chemical structure is:



Voglibose is a white to off white crystalline powder.

Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. Having molecular formula C4H11N5HCL and molecular weight 165.6. The chemical structure is:



Metformin Hydrochloride is a white or almost white crystalline powder.

Product Description:

Voglitor MF 0.2

White to off white, round shaped, flat faced beveled edge, uncoated tablets plain on both sides.

Voglitor MF 0.3

White to off white, round shaped, flat faced beveled edge, uncoated tablets with break line on one side and plain on other side..

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
Voglitor MF available in 10 BLISTER STRIPS OF 10 TABLETS EACH

8.4 Storage and handing instructions
STORE BELOW 30ºC IN A DRY PLACE, PROTECTED FROM LIGHT.

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 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?

9.4. Possible side effects
9.5. How to store Voglitor MF
9.6. Contents of the pack and other information

9.1 What Voglitor MF is and what it is used for

Voglitor MF is a fixed dose combination of two active ingredients, Voglibose and Metformin, the medicines to treat diabetes. They belong to group of medicines called an alpha glucosidase inhibitors and biguanides, respectively.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use.

If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Voglitor MF helps to lower your blood glucose to as normal a level as possible.

If you are an overweight adult, taking Voglitor MF over a long period of time also helps to lower the risk of complications associated with diabetes. Voglitor MF is associated with either a stable body weight or modest weight loss.

Voglitor MF is used to treat type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take GLUCOPHAGE or GLUCOPHAGE XR, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

Voglitor MF is used in 2nd line treatment of Type II 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 use Voglitor MF

Do not use Voglitor MF if:

- You are allergic to Voglibose or Metformin or to any of the other ingredients of this medicine.
- you have liver problems
- you have severely reduced kidney function
- You have lactic acidosis 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 Voglitor MF

  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 Voglitor MF 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

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

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.

During treatment with Voglitor MF, 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.

Other medicines and Voglitor MF
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Voglitor MF can affect the way some other medicines work. Also some medicines can affect the way Voglitor MF works.

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

You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Voglitor MF. 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 Voglitor MF in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib, olaparib).
- Other medicines used to treat diabetes.

Voglitor MF with alcohol
Avoid excessive alcohol intake while taking Voglitor MF since this may increase the risk of lactic acidosis.

Taking tablets with food and drink
Do not drink alcohol while taking Voglitor MF tablets. This is because it may make you feel dizzy or sleepy.

Pregnancy and breast-feeding
During pregnancy, you need insulin to treat your diabetes. Tell your doctor if you are, you think you might be or are planning to become pregnant, so that he or she may change your treatment.

This medicine is not recommended if you are breast-feeding or if you are planning to breast-feed your baby.

Driving and using machines

Voglitor MF can cause hypoglycaemia. 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 use Voglitor MF

Always take Voglitor MF exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Carefully read the label from the pharmacist. Ask your pharmacist if you are not sure about the dose to take. The medicine should be taken for the prescribed number of days.

Voglitor MF cannot replace the benefits of a healthy lifestyle. Continue to follow any advice about diet that your doctor has given you and get some regular exercise.

If you have reduced kidney function, your doctor may prescribe a lower dose.

If you take insulin too, your doctor will tell you how to start Voglitor MF.

Monitoring

- Your doctor will perform regular blood glucose tests and will adapt your dose of Voglitor MF to your blood glucose levels. Make sure that you talk to your doctor regularly. This is particularly important if you are an older person.
- Your doctor will also check at least once a year how well your kidneys work. You may need more frequent checks if you are an older person or if your kidneys are not working normally.

How to take Voglitor MF

Take Voglitor MF with or after a meal. This will avoid you having side effects affecting your digestion.

Do not crush or chew the tablets. Swallow each tablet with a glass of water.

• If you take one dose a day, take it in the morning (breakfast)

• If you take two divided doses a day, take them in the morning (breakfast) and evening (dinner)

• If you take three divided doses a day, take them in the morning (breakfast), at noon (lunch) and in the evening (dinner)

If, after some time, you think that the effect of Voglitor MF is too strong or too weak, talk to your doctor or pharmacist.

If you take more Voglitor MF than you should
If you have taken more Voglitor MF 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 Voglitor MF immediately and contact a doctor or the nearest hospital straight away.

If you forget to take Voglitor MF
Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time.

Children and Adolescents:
This medicine should not be given to children or adolescents.

If you stop taking Voglitor MF

Do not stop taking this medicine without talking to your doctor. You should not stop taking Voglitor MF just because you feel better.

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

9.4 Possible Side Effects

Like all medicines, these tablets can cause side effects, although not everybody gets them.

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

Very Rare (affects less than 1 in 10,000 people)

- 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.

- 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 Voglitor MF 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.

Common (affects 1 in 10 people)

- Changes in taste

Very Common (affects 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 Voglitor MF. It helps if you spread the doses over the day and if you take Voglitor MF with or straight after a meal. If symptoms continue, stop taking Voglitor MF and talk to your doctor.

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

- Face Swelling
- A high level of the electrolyte potassium in the blood.
- Loose stools, constipation, anorexia, heartburn, abdominal distension, increased flatus, intestinal obstruction like symptoms (due to increased intestinal gas)
- Excessive swearing
- Sudden hair loss (alopecia)
- Numbness
- Hot Flushes, Malaise, weakness

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:
http://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 Voglitor MF

Keep out of the sight and reach of children.

Store below 30ºC in a dry place, protected from light.

Do not use Voglitor MF after the expiry date which is stated on the carton or the bottle or the blister after 'EXP'. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What Voglitor MF contains:
The active substance in this product is Voglibose and Metformin.

The other ingredients are povidone, iso propyl alcohol, microcrystalline cellulose, magnesium stearate.

10. Details of manufacturer
Manufactured by:
TORRENT PHARMACEUTICALS LTD.
32 No, Middle Camp, NH-10,
East District, Gangtok, Sikkim-737 135

OR

Windlas Biotech Limited (Plant-2)

Khasra No. 141 to 143 & 145,

Mohabewala Industrial Area,

Dehradun – 248110, Uttarakhand.

11. Details of permission or licence number with date
M/563/2010 issued on 06.12.2021

OR

47/UA/2009 issued on 14.09.2020

12. Date of revision
AUG-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/VOGLITOR MF 0.2+1000, 0.3+1000/Aug-2022/02/PI