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

ZUCATOR M

1. Generic Name

Remogliflozin Etabonate and Metformin Hydrochloride Tablets

2. Qualitative and quantitative composition

ZUCATOR M 500

Each film coated tablet contains:

Remogliflozin Etabonate……..…100 mg

Metformin Hydrochloride I.P. …500 mg

Excipients……q.s.

Colours: Ferric Oxide Yellow USPNF and Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Ferric oxide yellow, Croscarmellose sodium, Povidone K30, Magnesium Stearate, Hypromellose, Polyethylene Glycol/Macrogol and Titanium Dioxide.

ZUCATOR M 1000

Each film coated tablet contains:

Remogliflozin Etabonate…….100 mg Metformin Hydrochloride I.P. …1000 mg

Excipients……q.s.

Colours: Ferric Oxide Yellow USPNF and Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Ferric oxide yellow, Croscarmellose sodium, Povidone K30, Magnesium Stearate, Hypromellose, Polyethylene Glycol/Macrogol and Titanium Dioxide.

3. Dosage form and strength Dosage

form – Film coated tablet

Strength –

ZUCATOR M 500

Remogliflozin Etabonate - 100 mg, Metformin Hydrochloride I.P. - 500 mg

ZUCATOR M 1000

Remogliflozin Etabonate - 100 mg, Metformin Hydrochloride I.P. - 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

ZUCATOR M is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone.
- in patients already being treated with the combination of remogliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥90 ml/min)

The recommended dose is one tablet twice daily. The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 200 mg of remogliflozin, while not exceeding the maximum recommended daily dose of metformin. For patients insufficiently controlled on metformin the recommended starting dose should provide remogliflozin etabonate 100 mg twice daily (200 mg daily dose) and the dose of metformin similar to the dose already being taken. When ZUCATOR M is used in combination with a sulphonylurea and/or insulin, a lower dose of sulphonylurea and/or insulin may be required to reduce the risk of hypoglycemia. For patients switching from separate tablets or remogliflozin etabonate (200 mg total daily dose) and metformin to ZUCATOR M should receive the same daily dose of remogliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

For the different doses of metformin, ZUCATOR M is available in strengths of 100 mg remogliflozin etabonate plus 500 mg metformin hydrochloride and 100 mg remogliflozin etabonate plus 1000 mg metformin hydrochloride. Remogliflozin 100 mg, and Metformin 500 mg and 1000 mg in the combination are present in immediate release forms.

Special populations

Renal impairment

In a single dose study with subjects having mild and moderate renal impairment, there was no clinically meaningful impact on the plasma exposure or elimination $t_{1/2}$ of remogliflozin etabonate, remogliflozin and GSK 279782. Renal impairment also did not affect extent of plasma protein binding. However, Remogliflozin and Mettormin combination has not been studied in patients with moderate-to-severe renal impairment. Remogliflozin and Metformin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCI] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2). No dosage adjustment is indicated m patients with mild renal impairment. Remogliflozin should not be initiated in patients with GFR < 60 mL/min and should be discontinued at GFR below < 45 mL/min. A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. If no adequate strength of Remogliflozin and Metformin is available, individual monocomponents should be used instead of the mixed dose combination. Table1: Posology for renally impaired patients

GFR ml/min	Metformin	Remogliflozin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 200mg.
45-59	Maximum daily dose is 2000mg.	Remogliflozin should not be initiated. The

	The starting dose is almost half of the maximum dose.	dose should be adjusted to or maintained at a maximum daily dose of 200 mg.
30-44	Maximum daily dose is 1000mg. The starting dose is almost half of the maximum dose.	Remogliflozin is not recommended.
<30	Metformin is contraindicated	Remogliflozin is not recommended.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment. There is no clinical experience with Remogliflozin and Metformin in patients with hepatic impairment.

Elderly (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Because metformin is excreted by the kidney and elderly patients are more likely to have decreased renal function, Remogliflozin and Metformin should be used with caution in these patients. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Due to the limited therapeutic experience with remogliflozin in patients aged 75 years and older, initiation of therapy in this population is not recommended.

Paediatric population
The safety and efficacy of Remogliflozin and Metformin in children aged 0 to< 18 years have not yet been established. No data are available.

Method of administration
ZUCATOR M should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet. It a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken on the same time. In that case, the missed dose should be skipped. No sex or age related effect was identified in glucose lowering effect of remogliflozin etabonate.

4.3 Contraindications
Hypersensitivity to the active substance 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).

- 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 impairment, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Remogliflozin and Metformin is contraindicated in patients with GFR<45 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function. Remogliflozin and Metformin should not be initiated in patients with moderate to severe renal impairment (glomerular filtration rate [GFR] < 60 mL/min). The safety and efficacy of Remogliflozin Metformin in patients with hepatic impairment has not been established. Remogliflozin and Metformin is not recommended for use in patients with hepatic impairment Use in patients at risk for adverse reactions related to volume depletion Due to its mechanism of action, remogliflozin etabonate produces glycosuria and an osmotic diuresis. Consequently there may be a decrease in intravascular volume that could result in hypotension, hemoconcentration, or electrolyte abnormalities. Initiation of Remogliflozin etabonate and Metformin in patients receiving concomitant diuretics should be undertaken cautiously and where appropriate dose reduction to diuretics considered based upon clinical presentation or laboratory results.

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 acidot1c dyspnoea, abdominal pain, muscle cramps, asthma 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.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors. No moderate to severe events of DKA were reported in clinical studies with remogliflozin. The risk of DKA must be considered in the event of non-specific

symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with remogliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with Remogliflozin and Metformin may be restarted once the patient's condition has stabilised. Before initiating Remogliflozin and Metformin, factors in the patient history that may predispose to ketoacidosis should be considered. Patients who may be at a higher risk of DKA include patients with a lowbeta-cell function reserve (e.g. dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients. Restarting SGLT2 inhibitor treatment in patients with previous OKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. The safety and efficacy of Remogliflozin and Metformin in patients with type 1 diabetes have not been established and Remogliflozin and Metformin should not be used for treatment of patients with type 1 diabetes Limited data from clinical trials suggest that OKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Administration of iodinated contrast agent

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.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chrome heart failure, Remogliflozin and Metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Remogliflozin and Metformin is contra1nd1cated due to the metformin component. There is no experience in clinical studies with remogliflozin in patients with cardiac failure.

Surgery

As Remogliflozin and Metformin contains metformin, Remogliflozin and 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.

Urinary tract infections

Urinary tract infections were reported for remogliflozin up to 24 weeks. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of remogliflozin should be considered when treating urinary tract infections.

Lower limb amputations

An increase in cases of lower limb amputation (pr1manly of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. No event of limb amputation has been reported in clinical studies with remogliflozin. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Necrotising fasciitis of the perineum (Fournier's gangrene)

In patients with diabetes mellitus receiving other SGLT2 inhibitors. reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and lifethreatening necrotizing infection requiring urgent surgical intervention, have been identified in post marketing surveillance. Cases have been reported In both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with Remogliflozin and Metformin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement Discontinue Remogliflozin and Metformin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.

Elderly

The effect of remogliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Therapeutic experience in patients aged 85 years and older is limited. Initiation of therapy in this population is not recommended. Caution should be exercised in patients who have potential for complex metabolic abnormalities with intercurrent illnesses and who experience significant volume depletion or significant hypoglycemia.

Urine laboratory assessments

Due to its mechanism of action, patients taking Remogliflozin and Metformin will test positive for glucose in their urine.

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. Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with remogliflozin etabonate.

4.5 Drugs interactions

Co-administration of multiple doses of Remogliflozin and Metformin does not meaningfully alter the pharmacokinetics of either remogliflozin or metformin in healthy subjects. Two studies have been conducted in subjects with T2DM 10 evaluate the combination of Remogliflozin etabonate and metformin. The first study (Study KG2105246) evaluated Remogliflozin etabonate 500 mg BID and metformin 500 mg

BID adminisrered together over a 3-day dosing period. The second study (Study KG2110243) evaluated Remogliflozin etabonate 500 mg BID and 750 mg BID added on to metformin at total daily doses ≥2000 mg for 2 weeks. There was no effect of Remogliflozin etabonate on metformin PK parameters in either study: metformin area under the plasma concentration versus time curve at steady state, C_{max} and T_{max} were similar when given alone or when given with Remogliflozin etabonate. The following statements reflect the information available on the individual active substances.

Remogliflozin

No clinically meaningful effect of food on the exposures of either remogliflozin etabonate, remogliflozin, or metabolites (i.e. GSK279782, GSK333081) has been observed The risk of drug in1eractions with cytochrome P450 (GYP) inhibitors is low due to the multiple pathways (GYP and non-GYP) of elimination. Following coadministration of remoglifloz1n etabonate with ketoconazole, a potent CYP3A4 inhibitor, clinically meaningful effect was not observed on the systemic exposure of remogliflozin and its metabolites. In a clinical pharmacology study, low levels of ethinylestradiol and norethindrone were observed probably due to sporadic lack of absorption in women receiving the oral contraceptive (Brevicon) in combination with remogliflozin etabonate. As the effectiveness of oral contraceptives may be negatively impacted. Therefore, patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with remogliflozin etabonate. Both remoglifloz1n etabonate and remogliflozin are P-glycoprotein {P-gp) substrates whereas neither are P-gp inhibitors. It is unlikely that P-gp inhibitors will have a clinically relevant effect as more than 90% of the dose is absorbed in humans. In a clinical study, serum concentrations of metformin were not altered by co-administration of remogliflozin etabonate and similarly, serum levels of remogliflozin etabonate, remogliflozin, and GSK279782 were not affected by co-administration of metformin. Co-administration of remogliflozin etabonate with diuretics did not have clinically meaningful effect on serum electrolytes Concomitant administration of remogliflozin etabonate and bupropion does not affect the steady state PK of remogliflozin or bupropion and has no impact on urine glucose excretion. There is a potential for GYP inducers to alter the pharmacokinetics of remogliflozin and its metabolites In a 2-week repeat dose oral toxicity study in rats, incidence of hypoglycemia was seen when Remogliflozin etabonate was co-administered with glimepiride accompanied by increased level of glimepiride. Increased risk of hypoglycemia is known when sulfonylurea such as glimepiride is co-administered with SGLT2 inhibitors. However, in 24-weekphase III clinical trial in subjects with type 2 diabetes mellitus no adverse event of hypoglycemia was reported in 36 patients when sulfonylurea was concomitantly administered with remogliflozin etabonate and metformin.

<u>Paediatric population</u>

No interaction studies have been performed in paediatric population.

Metformin

<u>Concomitant use not recommended</u>

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

Iodinated contrast agents
Metformin must be discontinued prior to or at the time of1he 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 func1ion 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. Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin (see sections 4.2 and 4.8).

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and focal 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 respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with:-
- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (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.

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

Pregnancy

No clinical studies with remogliflozin etabonate have been conducted in pregnant or lactating women and it is not known if remogliflozin etabonate or remogliflozin (active moiety) is secreted in human breast milk. Remogliflozin etabonate is not recommended during pregnancy and breastfeeding. Pregnancy should be excluded prior to administration of remogliflozin etabonate and .appropriate contraceptive measures should be followed by women of childbearing potential. Due to a potential effect pf remoglifloz1n etabonate on absorption, oral hormonal contraceptives may not provide effective contraception and an appropriate alternative method for avoiding pregnancy should be utilized (see section 4.5). 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 this medicinal product but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation

No studies in lactating animals have been conducted with the combined active substances of Remogliflozin and Metformin. It 1s unknown whether remogliflozin and/or its metabolites are excreted in human milk. Metformin is excreted into human breast milk in small amounts. A risk to newborns/infants cannot be excluded. Remogliflozin and Metformin should no\ be used during breast-feeding.

Fertility

The effect of Remogliflozin and Metformin on fertility in humans has not been studied. Remogliflozin etabonate had no effect on male (200, 600 and 1200 mg/kg/day, oral) and female (200, 600 and 1000 mg/kg/day; oral) fertility 1n rats and the no-observedadverse-effect level (NOAEL) were 1200 mg/kg/day (approximately 58 times the maximum recommended human dailydose (MRHDD) of 100 mg twice daily (200 mg/day) on body surface area (mg/ml basis) and 1000 mg/kg/day (approximately 49 times the MRHDD of 200 mg/day on mg/m^2 basis), respectively. Remogliflozin etabonate was not teratogenic in rats (200, 600 and 1000 mg/kg/day) and rabbits (125,250 and 500 mg/kg/day) at oral doses of .1000 and 500 mg/kg/day (approximately 49 times the MAHDD of 200 mg/day on mg/m^2 basis), respectively. In pre- and postnatal developmental study in rats (200, 600 and 1000 mg/kg/day; oral), no treatmentrelated effects were noted in pregnant/lactating females and on development of the conceptus and the offspring following exposure up to 1000 mg/kg/day (approximately 49 times the MRHDD of 200 mg/day on mg/m^2 basis). Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose of 2000 mg/day

(Remogliflozin etabonate + metformin (100 + 1000 mg) twice daily based on mg/m^2 comparisons.

4.7 Effects on ability to drive and use machines

Currently, there is no information available to assess any possible effect of remogliflozin on the ability to drive or use machinery. Patients should be alerted to the risk of hypoglycaemia when remogliflozin issued in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Remogliflozin

Summary of the safety profile

In a 24-week, randomised double-blind, double-dummy parallel-group, multi-centre,

active-controlled (dapagliflozin 10 mg) phase III study, 906 subjects with type 2 diabetes mellitus were treated with Remogliflozin etabonate in addition to ongoing metformin treatment with doses 2:1500 mg (2:1000 mg per day in sub1ects not tolerating higher doses of metformin). Commonly reported adverse reaction were urinary tract infection (1.84%).

Tabulated list of adverse reactions

The following adverse reactions have been identified in the active-controlled clinical trial.

Adverse reactions listed below are classified according to tendency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare(≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 2· Summary of Frequency Categories of TEAEs considered related to Remogliflozin etabonate (Safety Population)

System organ class	**Common**	**Uncommon**
Blood and lymphatic system disorders		Anaemia
Ear and labyrinth disorders		Vertigo
Gastrointestinal disorders		Abdominal pain Constipation Diarrhoea Gastritis
General disorders and administration site conditions		Asthma Fatigue Pyrexia
Infections and infestations	Urinary tract infection	Bacteriuria, Genital infection fungal Vulvovaginal candidiasis Vulvovaginitis
Investigations		Blood bicarbonate abnormal Blood creatinine increased Blood/acne acid increased Glomerular filtration rale decreased Weight decreased

Metabolism and nutrition disorders		Diabeticketoacidos1s Dys!ip1daemia Hypercholesterolaemia Hyperlactacidaemia Hypertriglyceridaemia Hypoglycaemia Lactic acidosis
		Polydipsia
Musculoskeletal and connective tissue disorders		Pain in extremity
Nervous system disorders		Dizziness Headache
Renal and urinary disorders		Dysuria Ketonuria Pollakiuria Polyuria Renal failure
Reproductive system and breast disorders		Pruritus genital Vaginal discharge Vulvovaginal pruritus
Skin and subcutaneous tissue disorders		Hyperhidrosis lntertrigo Urticaria
Vascular disorders		Orthostatic hypotension

Note: (1) Remogliflozin 100 mg and 250 mg are pooled to have TEAE frequencies only for Remogliflozin, not for Dapagliflozin. Percentages are based on the total number of subjects in safety population in both Remogroups, irrespective of relationship to the study drug.

(2) System organ class and preferred terms are coded using the MedDRA Version 20.0 or latest available dictionary

(3)If a subject experienced more than one episode of aTEAE, the subject is counted once for that event.

Description of selected adverse reactions Hypoqlvcemia
In the randomized controlled study of remogliflozin etabonate as add-on to metformin, the frequency of adverse events of hypoglycaemia was similar (<2%) between treatment groups. Major events of hypoglycaemia were comparable between the groups treated with remogliflozin etabonate or control arm treatment.

Vulvovaginitis batanitis and related genital infections
Vulvovaginltis, balanitis and related genital infections were reported in 1.7%.and 1.1% of subjects who received remogliflozin etabonate 100 mg and remoglifloz1n etabonate

250 mg, respectively and 2.5% in subjects who received control arm treatment. All the infections were mild to moderate, and subjects responded to an initial course of standard treatment and did not result 1n discontinuation from remogliflozin etabonate treatment. These infections were sim1larlyfrequ"ent in males and females.

Urinary tract infections

Urinary tract infections were reported in 2 9% and 4.7% ofsub1ects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg, respectively and 1.5% in subjects who received control arm treatment. All the infections were mild to moderate, and subjects responded to an initial course of standard treatment and did not result in discontinuation from remogliflozin etabonate treatment. These infections were more frequent in females.

Increased creatinine

Increased creatinine was reported in one subject receiving remogliflozin etabonate 250 mg. No adverse event of increased creatinine was reported in subjects receiving remogliffoz1n etabonate 100 mg.

Glomerular filtration rate decreased was reported in 0.3% and 0.8% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg, respectively. The decreases 1n glomerular filtration rate were generally transient during continuous treatment or reversible.

Volume depletion

No event of dehydration or hypovolaemia was reported. Orthostatic hypotension was reported in 0.3% and 0.3% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg. All the events of postural hypotension were mild to moderate.

Metformin

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metform1n.in 2 or 3 daily doses and to increase slowly the doses. The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common ≥1/10; common > 1/100, <1/10; uncommon >1/1,000, <1/100; rare >1/10,000, <1/1,000; very rare <1/10,000. Within each frequency grouping, adverse reactions are presented In order of decreasing seriousness.

Metabolism and nutrition disorders

Very rare

- Lactic acidosis.
- Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended 1f a patient presents with megaloblastic anaemia

Nervous system disorders

Common

- Taste disturbance

Gastrointestinal disorders

Very common

- Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.These undesirable effects occur most frequently during initiation oftherapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or3 daily doses during or after meals. A slow increase oft he dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare

- Skin reactions such as erythema, pruritus, urticarial

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. 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.

4.9 Overdose

Remogliflozin

There is no specific antidote for an overdose of remogliflozin etabonate. Inhibition of SGLT2 is reversible and the half-life of active moiety and metabolite is< 3 hours in diabetic patients. Supportive care (e.g. fluids, electrolyte replacement, and glucose) should be provided as appropriate based on the subject's clinical status. Supratherapeutic doses of 4000 mg remogliflozin etabonate have been administered for upto 3 days to healthy volunteers. Gastro-intestinal complaints (e.g., nausea, vomiting, abdominal pain, diarrhea, flatulence) and dizziness were among the more commonly reported events at this dose and were·reported at a higher incidence than with comparator.

Metformin

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred m 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.

Therapy

In the event of an overdose of Remogliflozin and Metformin, itis reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures as dictated by the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis.

5. Pharmacological properties

5.1 Mechanism of Action

Remogliflozin

Consistent with inhibition of SGLT2, a dose-dependent increase in urine glucose excretion has been observed with a plateau of- 400 mmols/day in healthy subjects (equating to 72 g/day or 288 kcal/day). The maximal filtered glucose excreted in the urine is- 45%. In subjects with T2DM following 2 weeks of dosing, there were statistically significant decreases from baseline in the weighted mean 24-hour plasma glucose concentrations In remogliflozin etabonate twice daily (BID) dosing groups compared to placebo. In the 12 week dose range finding studies in sub1ects with T2DM, remogliflozin etabonate demonstrated a clinically significant lowering of HbA1c (up to 1.07% from baseline versus placebo) and plasma glucose (up to 2.07 mmol/L from baseline versus placebo). The number of reported hypoglycaemic episodes was low. Following 12 weeks of dosing in subjects with T2DM, significant weight loss was observed in the remogliflozin etabonate group compared to placebo (upto 3.51 kg from baseline versus placebo).

Metformin

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 activate 3 mechanisms:

- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- Inmuscle, 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.

5.2 Pharmacodynamic properties

Remogliflozin

Consistent with inhibition of SGLT2, a dose-dependent increase in urine glucose excretion has been observed with a plateau of -400 mmols/day m healthy subjects (equating to 72 g/day or 288 kcal/day). The maximal filtered glucose excreted m the urine is -45%. In subjects with T2DM following 2 weeks of dosing, there were

statistically significant decreases from baseline in the weighted mean 24-hour plasma glucose concentrations In remogliflozin etabonatetw1ce daily (BID) dosing groups compared to placebo. In the 12 week dose range finding studies in sub1ects with T2DM, remogliflozin etabonate demonstrated a clinically significant lowering of HbA1c (up to 1.07% from baseline versus placebo) and plasma glucose (up to 2.07 mmol/L from baseline versus placebo). The number of reported hypoglycaemic episodes was low. Following 12 weeks of dosing in subjects with T2DM, significant weight loss was observed in the remogliflozin etabonate group compared to placebo (upto 3.51 kg from baseline versus placebo).

Metformin

In 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 attherapeut1c doses 1n controlled, medium-term or long-term clinical studies metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy and safety

A phase III clinical trial was conducted to evaluate efficacy and safety of remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg twice daily as add-on to metformin therapy in subjects with type 2 diabetes mellitus who had inadequate glycaemic control with metformin (with doses ≥ 1500 mg or ≥ 1000 mg per day in subjects not tolerating higher doses of metformin), in a randomized, double blind controlled clinical trial in comparison with dapagliflozin 10 mg once daily. Of the enrolled 906 patients, 347 subjects received remogliflozin etabonate 100 mg and were treated for 24 weeks.

Glycaemic control

Treatment with remogliflozin etabonate 100 mg reduced HbA1c by 0.68% compared to a reduction m HbA1c by 0.59% in the control arm treatment, at24 weeks

Table 3: Analysis of Mean Change in Glycosylated Haemoglobin (HbA1c%) Levels (PP Population): MMRM

Visit	**Statistics**	**Dapagliflozin 10 mg (N=101)**	**Remogliflozin etabonate 100mg (N=163)**
Mean Change From Baseline Week24 (Dav169)	LSM (SE)	-0.59(0.109)	-0.68 (0.083)
	Difference: LSM (SE)		-0.08(0.131)
	90%CI		[-0.30 ,0.13]
	Pvalue[1]		<0.001
	95%CI		[-0.34 0.17]
	Pvalue[2]		0524

Cl= confidence interval·, HbA1 c = glycosylated haemoglobin; LSM =least squares

mean; PP= per protocol: MMRM = mixed model repeated measures; SE= standard error
Difference: LSM (SE) between arms is calculated for remogliflozin etabonate 100 mg vs dapagliflozin 1 O mg (remogliflozin etabonate dapagliflozin).
The 90% Cl and 95% CI for the LSM difference 1n HbA1 c% levels between arms are calculated for remogiflozin etabonate 100 mg minus dapagliflozin 10 mg.
P value[1] is calculated for the 1 sided non inferior test with non inferiority margin 0.35, P value[2] for 2 sided superior test.
P values are calculated for the comparison of treatment arms with treatment as main effect and by considering the baseline HbA1c% value, centre, visit and treatment as covariates.
Exclude rescue medication subjects at each visit.

Fasting plasma glucose
Treatment with remogliflozin etabonate 100 mg reduced fasting plasma glucose by 12.29 mg/dl compared to a reduction in fasting plasma glucose by 16.07 mg/dL in the control arm treatment, at 24 weeks.

Post prandtal plasma glucose
Treatment with remogliflozin etabonate 100 mg reduced postprandial plasma glucose by 24.3 mg/dL compared to a reduction in postprandial plasma glucose by 25.4 mg/dl in the control arm treatment, at 24 weeks Proportion of sub1ects achieving glycem1c control defined as HbA1 c <7% at 24 weeks was 40.7% in the Remogliflozin 100 mg group and 40.4% in control arm treatment. At 24 weeks, a reduction m body weight by around 3 kgs was observed in remogliflozin treatment arms which was comparable to weight reduction observed in control arm. At24 weeks, a small reduction in blood pressure was observed in remogliflozin treatment arms which was comparable to blood pressure reduction observed in control arm.

5.3 Pharmacokinetic properties

Remogliflozin

Absorption

Remogliflozin etabonate was rapidly absorbed and extens·1vely converted to active moiety remogliflozin, and then further to GSK 279782 and GSK 333081. Administration with standard breakfast slightly delayed the T_{max} by approximately 1.0-1.5 hour, however there were no considerable difference in the C_{max} or AUC relative to fasted state. Hence remogliflozin etabonate can be administered with or without food. The steady State mean C_{max} and AUC_{0-100}, of remogliflozin (active moiety) in type 2 diabetic mellitus patients of Indian origin were around 559 ng/ml and 1798 ng.h/mL at 100 mg and 1370 ng/ml and 4610 ng.h/mL at 250 mg, respectively. The single dose mass balance study in humans indicated > 93 % of [^{14}C] remogliflozin etabonate was absorbed. Both remogliflozin etabonate and remogliflozin were P-gp substrates and not P-gp inhibitors. Given remogliflozin etabonate is almost completely absorbed, P-gp inhibitors are not anticipated to impact the PK of remogliflozin etabonate.

Distribution

The plasma protein binding of remogliflozin was around 65%. Either remogliflozin etabonate or remogliflozin were not preferentially distributed to blood cells and there

were no selective association of remogliflozin etabonate or its metabolites with melanin containing tissues.

Metabolism

Remogliflozin etabonate is extensively metabolized, leading to loss of ethyl hydrogen carbonate, N-dealkylation, O-dealkylalion, oxidation, loss of glucose and glucuronidation. In vitro studies have demonstrated that CYP3A4 is the primary enzyme involved in the metabolism of remogliflozin in human hepatic microsomes with minor contribution from CYP2C19 A clinical study with ketoconazole (a potentCYP3A4 inhibitor) resulted in a 1 8-fold increase 1n remogliflozin exposure, suggesting that risk of drug interactions with CYP inhibitors is low due to the multiple pathways of elimination.

Elimination

The mean plasma elimination half-life of remogli1lozln and GSK 279782 were around 1.5 to 1.9 hours and 2 3 to 3.8 hours in healthy volunteers after a single dose of remogliflozin etabonate at 100mg or 250 mg. In the same study the mean plasma halflife of prodrug was mostly around 0.4 hours to 0.7 hours. In radiolabelled AME study, approximately 93% was excreted in urine ofwh1ch about11 % of the dose was recovered as remogliflozin in urine; the majority of drug-related material is eliminated via the urine as inactive glucuronide metabolites.

Metformin

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 1s 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 (Vd) ranged between 63-2761.

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 65hours. 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 plasma.
Characteristics in specific groups of patients

Renal impairment

The available data in sub1ects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Remogliflozin

Remogliflozin etabonate has been evaluated in repeat dose oral (gavage) toxicity studies of duration up to 13 weeks in mice, 26 weeks in rats and 52 weeks in drugs. The NOAELs established in 13-, 26- and 52-week oral tox1c1ty studies 1n mice, rats and dogs were 2000, 1200 and 650 mg/kg/day, respectively. The systemic exposure achieved at these NOAEL doses provided several fold margins to that of AUC_{0-24} achieved at the MRHDD of 100 mg BID (200 mg/day) in type 2 diabetic patients in phase III clinical trial. The NOAEL (650 mg/kg/day) dose in 52-week oral toxicity study in dog provides ~1154 to 1341-fold (remogliflozin etabonate) and ~35 to 45-fold (remogliflozin) safety margin compared to their systemic exposure achieved at 200 mg/day in type 2 diabetes patients. Additionally in a 13-week combination toxicology studies in rats, remogliflozin etabonate and metformin HCI were co-administered to rats once daily by oral gavage for 90 consecutive days. The NOAEL for remogliflozin etabonate/metformin HCI combination was 300/200 mg/kg/day. Both remogliflozin etabonate (prodrug) and remogliflozin (active entity) were non-genotoxic in various in vitro and in vivo assays In 2-year oral gavage carcinogenicity studies in mice and rats, remogliflozin etabonate was found non-carcinogenic upto 600 mg/kg/day which provides approximately 13- and 19-fold margin on AUC basis, respectively compared to human systemic exposure of remogliflozin at 200 mg/day in type 2 diabetes patients (-15- and -30-fold, respectively of MRHDD of 200 mg/day on mg/m^2 basis).

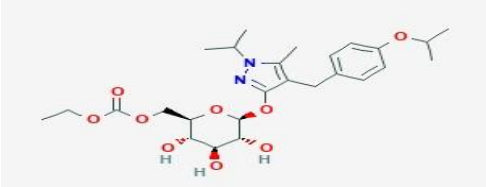
Metformin

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

7. Description

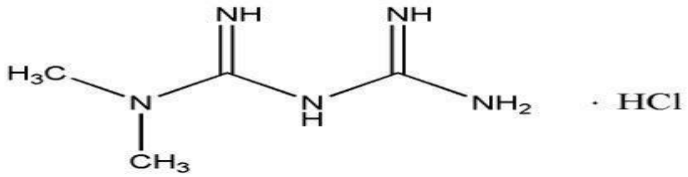
Remogliflozin Etabonate

Remogliflozin Etabonate is ethyl [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate. Its molecular formula is $C_{26}H_{38}N_2O_9$ and molecular weight is 522.6 g/mol. The chemical structure is:



Metformin Hydrochloride

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



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

ZUCATOR M 500

Remogliflozin Etabonate and Metformin Hydrochloride Tablets are White to off white coloured, capsule shaped, biconvex, film coated tablets with break line on one side and plain on other side. The excipients used are Microcrystalline Cellulose, Ferric oxide yellow, Croscarmellose sodium, Povidone K30, Magnesium Stearate, Hypromellose, Polyethylene Glycol/Macrogol and Titanium Dioxide.

ZUCATOR M 1000

Remogliflozin Etabonate and Metformin Hydrochloride Tablets are White to off white coloured, capsule shaped, biconvex, film coated tablets with plain on both sides. The excipients used are Microcrystalline Cellulose, Ferric oxide yellow, Croscarmellose sodium, Povidone K30, Magnesium Stearate, Hypromellose, Polyethylene Glycol/Macrogol and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ZUCATOR M is available in Alu-Alu blister strip of 10 tablets.

8.4 Storage and handing instructions

Store in a dry place, at a temperature between 15°C to 30°C Keep all medicines 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.
- 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. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1 What ZUCATOR M is and what it is used for
9.2 What you need to know before you use ZUCATOR M
9.3 How to use ZUCATOR M
9.4 Possible side effects
9.5 How to store ZUCATOR M
9.6 Contents of the pack and other information

9.1 What ZUCATOR M is and what it is used for

The active ingredient in ZUCATOR M is Remogliflozin Etabonate and Metformin Hydrochloride.

ZUCATOR M is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

•in patients insufficiently controlled on their maximally tolerated dose of metformin alone.

•in patients already being treated with the combination of remogliflozin and metformin as separate tablets

9.2 What you need to know before you use ZUCATOR M

Do not take ZUCATOR M if you have:

- Hypersensitivity to the active substance 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).
- 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 impairment, acute alcohol intoxication, alcoholism.

Pregnancy, breast feeding and fertility

No clinical studies with remogliflozin etabonate have been conducted in pregnant or lactating women and it is not known if remogliflozin etabonate or remogliflozin (active moiety) is secreted in human breast milk. Remogliflozin etabonate is not recommended during pregnancy and breastfeeding.

The effect of Remogliflozin etabonate and Metformin on fertility in humans has not been studied.

Driving and using machines

Currently, there is no information available to assess any possible effect of remogliflozin on the ability to drive or use machinery. Patients should be alerted to the risk of hypoglycaemia when remogliflozin issued in combination with a sulphonylurea or insulin.

9.3 How to use ZUCATOR M

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

ZUCATOR M should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet. It a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken on the same lime. In that case, the missed dose should be skipped. No sex or age related effect was identified in glucose lowering effect of remogliflozin etabonate.

If you take more ZUCATOR M than you should

Go to the nearest casualty department or contact your doctor immediately. Take the tablet carton with you.

If you forget to take ZUCATOR M

If you miss a dose, take one as soon as you can. If you have missed several doses, tell your doctor. Do not take a double dose to make up for a forgotten dose.

If you stop taking ZUCATOR M

Do not stop taking the tablets or reduce the dose without telling your doctor first. If you suddenly stop taking the tablets you may feel sick (nausea), have a headache or feel generally unwell. 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, this medicine can cause side effects, although not everybody gets them.

The side effects are usually mild and improve without you having to stop taking this medicine.

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 or3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability**.**

Common:

- Urinary tract infection
- Taste disturbance

Uncommon

- Anaemia
- Vertigo
- Abdominal pain
- Constipation
- Diarrhoea
- Gastritis
- Asthma
- Fatigue
- Pyrexia
- Bacteriura,
- Genital infection fungal
- Vulvovaginal candidiasis
- Vulvovaginitis
- Blood bicarbonate abnormal
- Blood creatinine increased
- Blood/acne acid increased
- Glomerular filtration rale decreased
- Weight decreased
- Diabeticketoacidosis
- Dyslipidaemia
- Hypercholesterolaemia
- Hyperlactacidaemia
- Hypertriglyceridaemia
- Hypoglycaemia
- Lactic acidosis
- Polydipsia
- Pain in extremity
- Dizziness
- Headache
- Dysuria
- Ketonuria
- Pollakiuria
- Polyuria
- Renal failure

- Pruritus genital
- Vaginal discharge
- Vulvovaginal pruritus
- Hyperhidrosis
- Intertrigo
- Urticaria
- Orthostatic hypotension

Very rare:
- Lactic acidosis
- Decrease of vitamin B 12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended 1f a patient presents with megaloblastic anaemia.
- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation
- Skin reactions such as erythema pruritus, urticaria

Reporting of side effects
If you get any side effects, talk to your doctor. 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.

9.5 How to store ZUCATOR M
Store in a dry place, at a temperature between 15°C to 30°C. Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

What ZUCATOR M contains:
- The active substance is Remogliflozin Etabonate and Metformin Hydrochloride.

- The excipients used are Microcrystalline Cellulose, Ferric oxide yellow, Croscarmellose sodium, Povidone K30, Magnesium Stearate, Hypromellose, Polyethylene Glycol/Macrogol and Titanium Dioxide.

What are the contents of the pack
ZUCATOR M is available in Alu-Alu blister strip of 10 tablets.

10. Details of manufacturer Manufactured in India by:
Glenmark Pharmaceuticals Ltd.
B/2, Mahalaxmi Chambers, 22,
Bhulabhai Desai Road, Mumbai 400 026.
At : Plot No. 21-22, Pharmacity, Selaqui
Distt. Dehradun – 248 011, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No. 1/UA/LL/2018

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Under licence from Glenmark Pharmaceuticals Ltd.

IN/ZUCATOR M 500, 1000/JAN 20/02/PI