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

ZUCATOR 100

1. Generic Name

Remogliflozin Etabonate Tablets I.P. 100 mg

2. Qualitative and quantitative Composition:

Each film coated tablet contains:

Remogliflozin Etabonate I.P. ….100 mg

Excipients……. q.s.

Colour: Titanium Dioxide U.S.P.

The excipients used are Croscarmellose Sodium, Microcrystalline Cellulose, Povidone, Magnesium Stearate, Hypromellose, Titanium Dioxide and Polyethylene Glycol/Macrogol.

3. Dosage form and strength

Dosage form: Film coated tablets.

Strength: 100 mg

4. Clinical particulars

4.1. Therapeutic indication

Remogliflozin Etabonate is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control.
- Add on therapy with metformin, together with diet and exercise, when these do not provide adequate glycaemic control.

4.2. Posology and method of administration

Posology

The recommended dose is Remogliflozin Etabonate 100 mg twice daily for monotherapy and add-on therapy with metformin. As observed with other SGLT2 inhibitors, when Remogliflozin etabonate is used in addition to insulin or an insulin secretagogue, such as a sulphonylureas, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

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 t1/2 of Remogliflozin etabonate renal impairment also did not affect extent of plasma protein binding. However, Remogliflozin has not been studied in patients with moderate-to-severe renal impairment. Remogliflozin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2). No dosage adjustment is indicated in 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.

Hepatic impairment

The safety, efficacy, and PK of Remogliflozin in patients with hepatic impairment has not been established. Majorly clearance happens through metabolism by CYPs and glucuronidation. Hepatic impairment can impact the PK of Remogliflozin. Remogliflozin is not recommended for use in patients with moderate to severe 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. Due to the limited therapeutic experience in patients 75 years and older, initiation of Remogliflozin therapy is not recommended.

Paediatric population

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

Method of administration

There was no clinically relevant impact of food on the PK of remogliflozin etabonate. Remogliflozin etabonate can be taken orally twice daily with or without food. Tablets are to be swallowed whole.

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.

4.4. Special warnings and precautions for use

Remogliflozin 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 in patients with hepatic impairment has not been established. Remogliflozin is not recommended for use in patients with moderate to severe hepatic impairment.

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, hem concentration, or electrolyte abnormalities. Initiation of Remogliflozin etabonate in patients receiving concomitant diuretics should be undertaken cautiously and where appropriate dose reduction of diuretics considered based upon clinical presentation or laboratory results.

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.

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.

There is no experience in clinical studies with remogliflozin in patients with cardiac failure.

An increase in cases of lower limb amputation (primarily 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.

In patients with diabetes mellitus receiving other SGLT2 inhibitors, reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening 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 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, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.

Caution should be exercised in patients who have potential for complex metabolic abnormalities with intercurrent illnesses and who experience significant volume depletion or significant hypoglycaemia.

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

In a reported study 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 interactions with cytochrome P450 (CYP) inhibitors is low due to the multiple pathways (CYP and non-CYP) of elimination. Following co-administration of remogliflozin etabonate with ketoconazole, a potent CYP3A4 inhibitor, clinically meaningful effect was not observed on the systemic exposure of remogliflozin and its metabolites.

In a Reported 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 remogliflozin 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 RE or bupropion and has no impact on urine glucose excretion.

There is a potential for CYP inducers to alter the pharmacokinetics of remogliflozin and its metabolites.

In a 2-week repeat dose oral toxicity study in rats, incidence of hypoglycaemia 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-week phase 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.

Paediatric population

No interaction studies have been performed in paediatric population.

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

Pregnancy and Lactation

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 of remogliflozin 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).

Fertility

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 in rats and the no-observed-adverse-effect level (NOAEL) were 1200 mg/kg/day (approximately 58 times the maximum recommended human daily dose (MRHDD) of 100 mg twice daily (200 mg/day) on body surface area [mg/m2] basis) and 1000 mg/kg/day (approximately 49 times the MRHDD of 200 mg/day on mg/m2 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 MRHDD of 200 mg/day on mg/m2 basis), respectively. In pre- and post-natal developmental study in rats (200, 600 and 1000 mg/kg/day; oral), no treatment-related 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/m2 basis).

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 is used in combination with a sulphonylureas or insulin.

4.8. Undesirable effects

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, 465 subjects with type 2 diabetes mellitus and having inadequate glycaemic control with metformin treatment with doses ≥1500 mg (≥1000 mg per day in subjects not tolerating higher doses of metformin) were treated with Remogliflozin etabonate in addition to ongoing metformin.

Commonly reported adverse reaction were urinary tract infection (4.9%), pyrexia (2.7%), headache (2.5%), bacteriuria (2.3%), constipation (1.7%), diarrhoea (1.7%), glomerular filtration rate decreased (1.7%), ketonuria (1.7%), cough (1.5%), dyslipidaemia (1.5%), asthenia (1.0%), viral upper respiratory tract infection (1.0%), hypoglycaemia (1.0%),and orthostatic hypotension (1.0%).

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 frequency 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: Summary of Frequency Categories of TEAEs for Remogliflozin etabonate (Safety Population)

System organ class	**Common**	**Uncommon**
Blood and lymphatic system disorders		Anaemia Eosinophilia Iron deficiency anaemia, Microcytic anaemia, Thrombocytopenia Thrombocytosis
Ear and labyrinth disorders		Vertigo
Eye disorders		Eye pain Lacrimation increased
Gastrointestinal disorders	Constipation Diarrhoea	Abdominal discomfort Abdominal pain Abdominal pain upper Gastritis Gastrooesophageal reflux disease Hyperchlorhydria Stomatitis Vomiting
General disorders and administration site conditions	Asthenia Pyrexia	Fatigue Pain
Hepatobiliary disorders		Hyperbilirubinaemia

System organ class	Common	Uncommon
Infections and infestations	Bacteriuria, Urinary tract infection Viral upper respiratory tract infection	Gastroenteritis Genital infection fungal Herpes zoster Lower respiratory tract infection Periodontitis Pharyngitis Pulpitis dental Pyuria Upper respiratory tract infection Vaginal infection Viral infection Vulvovaginal candidiasis Vulvovaginitis
Investigations	Glomerular filtration rate decreased.	Blood bicarbonate abnormal Blood cholesterol increased. Blood creatinine increased. Blood lactic acid increased. Blood pressure increased. Blood triglycerides increased. Electrocardiogram QT prolonged Gamma-glutamyl transferase increased. Hepatic enzyme increased. Low density lipoprotein increased. Weight decreased
Metabolism and nutrition disorders	Dyslipidaemia Hypoglycaemia	Decreased appetite. Diabetic ketoacidosis Hypercholesterolemia Hypertriglyceridaemia Hypocalcaemia Lactic acidosis Polydipsia
Musculoskeletal and connective tissue disorders		Arthralgia Back pain Costochondritis Musculoskeletal pain Myalgia Pain in extremity
Nervous system disorders	Headache	Dizziness Hypoaesthesia
Psychiatric disorders		Anxiety Insomnia

System organ class	Common	Uncommon
Renal and urinary disorders	Ketonuria	Dysuria Pollakiuria Polyuria
Reproductive system and breast disorders		Balanoposthitis Pruritus genital Vulvovaginal pruritus
Respiratory, thoracic and mediastinal disorders	Cough	Oropharyngeal pain Rhinitis allergic
Skin and subcutaneous tissue disorders		Rash Skin lesion Urticaria
Vascular disorders	Orthostatic hypotension	Hypertension

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 Remo groups, 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 a TEAE, the subject is counted once for that event.

Description of selected adverse reactions

Hypoglycemia

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, balanitis and related genital infections

Vulvovaginitis, balanitis and related genital infections were reported in 1.8% and 1.2% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg, respectively and 2.7% 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 similarly frequent in males and females.

Urinary tract infections

Urinary tract infections were reported in 3.1% and 6.6% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg, respectively and 2.1% 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 remogliflozin etabonate 100 mg. Glomerular filtration rate decreased was reported in 0.4% and 2.9% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg, respectively. The decreases in 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 1.3% and 0.8% of subjects who received remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg. All the events of postural hypotension were mild to moderate.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

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 up to 3 days to healthy volunteers. Gastro-intestinal complaints (e.g., nausea, vomiting, abdominal pain, diarrhoea, flatulence) and dizziness were among the more commonly reported events at this dose and were reported at a higher incidence than with comparator.

5. Pharmacological properties

5.1. Mechanism of Action

As an active ingredient, Zucator contains Remogliflozin etabonate (RE). It is the prodrug of remogliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), enabling urinary glucose excretion to reduce hyperglycemia for the treatment of type 2 diabetes.

5.2. Pharmacodynamic properties

Consistent with inhibition of SGLT2, a dose-dependent increase in urine glucose excretion has been observed with a plateau of ~400 mmol/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 subjects 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 hypoglycemic 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 (up to 3.51 kg from baseline versus placebo).

Clinical efficacy and safety

In a reported study 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 glycemic 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 612 subjects, 224 subjects received remogliflozin etabonate 100 mg and 241 subjects received remogliflozin etabonate 250 mg and were treated for 24 weeks.

Glycaemic control

Treatment with remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg reduced HbA1c by 0.72% and 0.77%, respectively compared to a reduction in HbA1c by 0.58% in the control arm treatment, at 24 weeks.

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

Visit	**Statistics**	**Dapagliflozin 10mg (N=101)**	**Remogliflozin etabonate 100mg (N=163)**	**Remogliflozin etabonate 250mg (N=166)**
Mean Change From Baseline - Week 24 (Day 169)	LSM (SE)	-0.58 (0.116)	-0.72 (0.093)	-0.77 (0.090)
	Difference: LSM (SE)		-0.14 (0.144)	-0.19 (0.143)
	90% CI	90% CI	[-0.38, 0.10]	[-0.42, 0.05]
	P value[1]	*P* value[1]	<0.001	<0.001
	95% CI	95% CI	[-0.42, 0.14]	[-0.47, 0.09]
	P value[2]	*P* value[2]	0.332	0.190

CI = confidence interval; HbA1c = 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 or remogliflozin etabonate 250 mg vs dapagliflozin 10 mg (remogliflozin etabonate - dapagliflozin).

The 90% CI and 95% CI for the LSM difference in HbA1c% levels between arms are calculated for remogliflozin etabonate 100 mg or remogliflozin etabonate 250 mg minus dapagliflozin 10 mg.

P value1 is calculated for the 1-sided non-inferior test with non-inferiority margin 0.35, P value2 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.

Fasting plasma glucose

Treatment with remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg reduced fasting plasma glucose by 17.86 mg/dL and 20.94 mg/dL, respectively compared to a reduction in fasting plasma glucose by 20.23 mg/dL in the control arm treatment, at 24 weeks.

Post prandial plasma glucose

Treatment with remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg reduced post prandial plasma glucose by 39.2 mg/dL and 41.5 mg/dL, respectively compared to a reduction in post prandial plasma glucose by 32.4 mg/dL in the control arm treatment, at 24 weeks.

Proportion of subjects achieving glycemic control defined as HbA1c <7% at 24 weeks was 36.4% in the Remogliflozin 100 mg group and 37.1% in the Remogliflozin 250 mg group and 30.3% in control arm treatment.

At 24 weeks, a reduction in body weight by around 3 kgs was observed in remogliflozin treatment arms which was comparable to weight reduction observed in control arm.

At 24 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

Absorption

Remogliflozin etabonate was rapidly absorbed and extensively converted to active moiety remogliflozin, and then further to GSK 279782 and GSK 333081. Administration with standard breakfast slightly delayed the Tmax by approximately 1.0-1.5 hour, however there were no considerable difference in the Cmax or AUC relative to fasted state. Hence remogliflozin etabonate can be administered with or without food. The steady state mean Cmax and AUC0-tau 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 [14C] 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-dealkylation, 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 potent CYP3A4 inhibitor) resulted in a 1.8-fold increase in 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 remogliflozin 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 half-life of prodrug was

mostly around 0.4 hours to 0.7 hours. In radiolabelled AME study, approximately 93% was excreted in urine of which about 11% of the dose was recovered as remogliflozin in urine; the majority of drug-related material is eliminated via the urine as inactive glucuronide metabolites.

6. Nonclinical properties

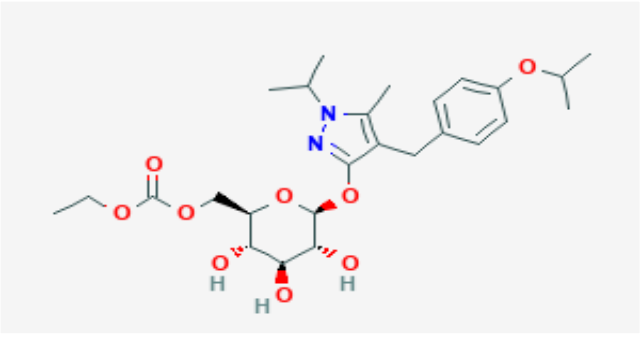
6.1. Animal Toxicology or Pharmacology

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 dogs. The NOAELs established in 13-, 26- and 52-week oral toxicity studies in 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 AUC0-achieved at the MRHDD of 100 mg BID (200 mg/day) in type 2 diabetes patients in phase III clinical trial. The NOAEL (650 mg/kg/day) in 52-week dog study 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 HCl were co-administered to rats once daily by oral gavage for 90 consecutive days. The NOAEL for remogliflozin etabonate/metformin HCl 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 up to 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/m2 basis).

7. Description

Remogliflozin Etabonate is ethyl [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1-propan-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:



Remogliflozin Etabonate Tablets are white, round, biconvex, film coated tablets with breakline on one side and another side plain surface. The excipients used are Croscarmellose Sodium, Microcrystalline Cellulose, Povidone, Magnesium Stearate, Hypromellose, Titanium Dioxide and Polyethylene Glycol/Macrogol.

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 is available in pack of 10 Tablets.

8.4. Storage and handing instructions

Store in a dry place, at a temperature between 15°C to 30°C.

Keep out of reach of children

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Glenmark Pharmaceuticals Ltd.,

Samlik Marchak, Industrial Growth Centre,

Near Ranipool, District: Gangtok,

Sikkim – 737135.

11. Details of permission or licence number with date

Mfg Lic No. M/602/2012 issued on 11 06 2024

12. Date of revision

Feb 2026

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/Zucator 100 mg/Feb 2026/04/PI