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

TORGLIP R

1. Generic Name:

Remogliflozin Etabonate 100 mg and Vildagliptin 50 mg Tablets

2. Qualitative and quantitative composition:

Each film coated tablet contains:
Remogliflozin Etabonate……100 mg
Vildagliptin……..50 mg
Excipients…….q.s.
Colour: Ferric Oxide Yellow U.S.P. NF and Titanium Dioxide I.P.

3. Dosage form and strength:

Dosage form: Film coated tablet
Strength: Remogliflozin Etabonate 100 mg and Vildagliptin 50 mg

4. Clinical particulars:

4.1 Therapeutic indication:

It is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- To improve glycaemic control when Metformin and one of mono-components of fixed dose combination of Remogliflozin Etabonate & Vildagliptin do not provide adequate glycaemic control,
- When already being treated with the free combination of Remogliflozin Etabonate & Vildagliptin

4.2 Posology and method of administration:

Vildagliptin

Posology

Adults

When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than 50 mg vildagliptin once daily.

When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Doses higher than 100 mg are not recommended.

If a dose of Vildagliptin Kappler is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established.

Additional information on special populations

Elderly (≥ 65 years)
No dose adjustments are necessary in elderly patients.
Renal impairment
No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Vildagliptin Kappleris 50 mg once daily *Hepatic impairment*
Vildagliptin Kappler should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN)
Paediatric population
Vildagliptin Kappler is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildagliptin Kappler in children and adolescents (< 18 years) have not been established. No data are available.

Method of administration
Oral use
Vildagliptin Kappler can be administered with or without a meal.

<u>Remogliflozin</u>
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:

Vildagliptin

General

Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment

There is limited experience in patients with ESRD on haemodialysis. Therefore vildagliptin should be used with caution in these patients.

Hepatic impairment

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3 x ULN.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in AST or ALT of 3 x ULN or greater persist, withdrawal of vildagliptin therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin.

Following withdrawal of treatment with vildagliptin and LFT normalisation, treatment with vildagliptin should not be reinitiated.

Cardiac failure

A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.

There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non- clinical toxicology studies (see section 5.3). Although skin lesions were not observed

at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions.

Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Acute pancreatitis

Use of vildagliptin has been associated with a risk of developing acute pancreatitis.

Patients should be informed of the characteristic symptom of acute pancreatitis.

If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia

Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Remogliflozin

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 Drug-Interaction:

Vildagliptin

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Combination with pioglitazone, metformin and glyburide Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACEinhibitors.

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

Remogliflozin

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 coadministration 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.)

Vildagliptin

Pregnancy

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, vildagliptin should not be used during pregnancy.

Breast-feeding

It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for vildagliptin.

Remogliflozin

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 women of childbearing potential should follow appropriate contraceptive measures. 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.

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-adverseeffect 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:

Vildagliptin

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

Remogliflozin

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:

Vildagliptin

Summary of the safety profile

Safety data were obtained from a total of 3,784 patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 weeks duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product. 2,682 patients were treated with 100 mg vildagliptin daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with 50 mg vildagliptin once daily.

The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3 x ULN

(classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for 50 mg vildagliptin once daily, 50 mg vildagliptin twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, nonprogressive in nature and not associated with cholestasis or jaundice.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE Inhibitor).

The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Tabulated list of adverse reactions

Adverse reactions reported in patients who received vildagliptin in double-blind studies as monotherapy and add-on therapies are listed below for each indication by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Combination with metformin

Table: Adverse reactions reported in patients who received 100 mg vildagliptin daily in combination with metformin in double-blind studies (N=208)

Metabolism and nutrition disorders	
Common	Hypoglycaemia.
Nervous system disorders	
Common	Tremor, headache, dizziness.
Uncommon	Fatigue.
Gastrointestinal disorders	
Common	Nausea

Description of selected adverse reactions

In controlled clinical trials with the combination of 100 mg vildagliptin daily + metformin, no withdrawal due to adverse reactions was reported in either the 100 mg vildagliptin daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was common in patients receiving 100 mg vildagliptin daily in combination with metformin (1 %) and uncommon in patients receiving placebo + metformin (0.4 %). No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when 100 mg vildagliptin daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

Clinical trials of up to more than 2 years' duration did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.

Combination with a sulphonylurea

Table: Adverse reactions reported in patients who received 50 mg vildagliptin in combination with a sulphonylurea in double-blind studies (N=170)

Infections and infestations	
Very rare	Nasopharyngitis.
Metabolism and nutrition disorders	
Common	Hypoglycaemia.
Nervous system disorders	
Common	Tremor, headache, dizziness, asthenia.
Gastrointestinal disorders	
Uncommon	Constipation.

Description of selected adverse reactions

In controlled clinical trials with the combination of 50 mg vildagliptin + a sulphonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6 % in the 50 mg vildagliptin + sulphonylurea vs 0 % in the placebo + sulphonylurea treatment group.

In clinical trials, the incidence of hypoglycaemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2 % versus 0.6 % for placebo + glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when 50 mg vildagliptin daily was added to glimepiride (-0.1 kg and -0.4 kg for vildagliptin and placebo, respectively).

Combination with a thiazolidinedione

Table: Adverse reactions reported in patients who received 100 mg vildagliptin daily in combination with a thiazolidinedione in double-blind studies (N=158)

Metabolism and nutrition disorders	
Common	Weight increase.
Uncommon	Hypoglycaemia.
Nervous system disorders	
Uncommon	Headache, asthenia.
Vascular disorders	
Common	Oedema peripheral

Description of selected adverse reactions

In controlled clinical trials with the combination of 100 mg vildagliptin daily+ a thiazolidinedione, no withdrawal due to adverse reactions was reported in either the 100 mg vildagliptin daily + thiazolidinedione or the placebo + thiazolidinedione treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.6 %) but common in patients receiving placebo + pioglitazone (1.9 %). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the absolute weight increases with placebo, 100 mg vildagliptin daily were 1.4 and 2.7 kg, respectively.

The incidence of peripheral oedema when 100 mg vildagliptin daily was added to a maximum dose of background pioglitazone (45 mg once daily) was 7.0 %, compared to 2.5 % for background pioglitazone alone.

Monotherapy

Table: Adverse reactions reported in patients who received 100 mg vildagliptin daily as monotherapy in double-blind studies (N=1,855)

Infections and infestations	
Very rare	Upper respiratory tract infection, nasopharyngitis
Metabolism and nutrition disorders	
Uncommon	Hypoglycaemia.
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Oedema peripheral.
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia.

Description of selected adverse reactions

In addition, in controlled monotherapy trials with vildagliptin the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3 %) than for placebo (0.6 %) or comparators (0.5 %).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4 % (7 of 1,855) of patients treated with 100 mg vildagliptin daily compared to 0.2 % (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In clinical trials, weight did not change from baseline when 100 mg vildagliptin daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with metformin and a sulphonylurea

Table: Adverse reactions reported in patients who received 50 mg vildagliptin twice daily in combination with metformin and a sulphonylurea (N=157)

Metabolism and nutrition disorders	
Common	Hypoglycaemia.
Nervous system disorders	
Common	Dizziness, tremor.
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
General disorders and administration site conditions	
Common	Asthenia.

Description of selected adverse reactions

There were no withdrawals due to adverse reactions reported in the vildagliptin + metformin + glimepiride treatment group versus 0.6 % in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycaemia was common in both treatment groups (5.1 % for the vildagliptin + metformin + glimepiride group versus 1.9 % for the placebo + metformin + glimepiride group).

One severe hypoglycaemic event was reported in the vildagliptin group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

Combination with insulin

Table: Adverse reactions reported in patients who received 100 mg vildagliptin daily in combination with insulin (with or without metformin) in double-blind studies (N=371)

Metabolism and nutrition disorders	
Common	Decreased blood glucose.
Nervous system disorders	
Common	Headache, chills.
Gastrointestinal disorders	
Common	Nausea, gastro-oesophageal reflux disease.
Uncommon	Diarrhoea, flatulence.

Description of selected adverse reactions

In controlled clinical trials using 50 mg vildagliptin twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals due to adverse reactions was 0.3 % in the vildagliptin treatment group and there were no withdrawals in the placebo group.

The incidence of hypoglycaemia was similar in both treatment groups (14.0 % in the vildagliptin group vs 16.4 % in the placebo group). Two patients reported severe hypoglycaemic events in the vildagliptin group, and 6 patients in the placebo group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

Post-marketing experience

Table: Post-marketing adverse reactions

Gastrointestinal disorders	
Not known	Pancreatitis.
Hepatobiliary disorders	
Not known	Hepatitis (reversible upon discontinuation of the medicinal product), abnormal liver function tests (reversible upon discontinuation of the medicinal product).
Musculoskeletal and connective tissue disorders	
Not known	Myalgia.
Skin and subcutaneous tissue disorders	
Not known	Urticaria, exfoliative and bullous skin lesions, including bullous pemphigoid.

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, 465 subjects with type 2 diabetes mellitus and havin inadequate glycaemic control with metformin treatment with dose ≥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)

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.

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
Infections and infestations	Bacteriuria, Urinary tract infection Viral upper respiratory tract infection	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-glutamyltransferase 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
Renal and urinary disorders	Ketonuria	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

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 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.

4.9 Overdose:

Vildagliptin

Information regarding overdose with vildagliptin is limited.

Symptoms

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management

In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

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 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:

Vildagliptin

Mechanism of action

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

Remogliflozin

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:

Vildagliptin

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors,
ATC code: A10BH02

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor.

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucosedependent insulin secretion. Treatment with 50-100 mg vildagliptin daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test.

In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.
By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.
The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.
The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Clinical efficacy and safety
More than 15,000 patients with type 2 diabetes participated in double-blind placeboor active-controlled clinical trials of up to more than 2 years' treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received 50 mg vildagliptin once daily or 100 mg daily. More than 1,900 patients receiving 50 mg vildagliptin once daily or 100 mg daily were ≥ 65 years. In these trials, vildagliptin was administered as monotherapy in drug- naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.
Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA1c from baseline at studyendpoint.
In clinical trials, the magnitude of HbA1c reductions with vildagliptin was greater in patients with higher baseline HbA1c.
In a 52-week double-blind controlled trial, vildagliptin (50 mg twice daily) reduced baseline HbA1c by -1 % compared to -1.6 % for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.
In a 24-week double-blind controlled trial, vildagliptin (50 mg twice daily) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20 % with vildagliptin and -1.48 % with rosiglitazone in patients with mean baseline HbA1c of 8.7 %. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1 % vs. 4.1 % respectively).
In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day). After two years, mean reduction in HbA1c was - 0.5% for vildagliptin and -0.6 % for gliclazide, from a mean baseline HBA1c of 8.6 %. Statistical non-inferiority was not achieved.
Vildagliptin was associated with fewer hypoglycaemic events (0.7 %) than gliclazide (1.7 %).
In a 24-week trial, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2,020 mg). Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0 % with pioglitazone added to metformin. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.
In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1,894 mg). After 1 year mean reductions in HbA1c were -0.4 % with vildagliptin added to metformin and -0.5 % with glimepiride added to metformin, from a mean baseline HbA1c of 7.3

%. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7 %) than in the glimepiride group (16.2 %). At study endpoint (2 years), the HbA1c was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.
In a 52-week trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1,928 mg/day). After 1 year, mean reductions in HbA1c were -0.81 %with vildagliptin added to metformin (mean baseline HbA1c 8.4 %) and -0.85 % with gliclazide added to metformin (mean baseline HbA1c 8.5 %); statistical non-inferiority was achieved (95 % CI -0.11-- 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.
In a 24-week trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1,000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1,000 mg twice daily reduced HbA1c by -1.82 %, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61 %, metformin 1,000 mg twice daily by -1.36 % and vildagliptin 50 mg twice daily by -1.09 % from a mean baseline HbA1c of 8.6 %. The decrease in HbA1c observed in patients with a baseline ≥ 10.0 % was greater.
A 24-week, multi-centre, randomised, double-blind, placebo-controlled trial was conducted to evaluate the treatment effect of 50 mg vildagliptin once daily compared to placebo in 515 patients with type 2 diabetes and moderate renal impairment (N=294) or severe renal impairment (N=221). 68.8 % and 80.5 % of the patients with moderate and severe renal impairment respectively were treated with insulin (mean daily dose of 56 units and 51.6 units respectively) at baseline. In patients with moderate renal impairment vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.53 %) from a mean baseline of 7.9 %. In patients with severe renal impairment, vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.56 %) from a mean baseline of 7.7 %.
A 24-week randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥ 1,500 mg daily) and glimepiride (≥ 4 mg daily).
Vildagliptin in combination with metformin and glimepiride significantly decreased HbA1c compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA1c of 8.8 % was -0.76 %.
A 24-week randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA1c 8.8 % was -0.72 %. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c was -0.63 % and -0.84 %, respectively. The incidence of hypoglycaemia in the overall population was 8.4 % and 7.2 % in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).
In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA1c when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5 % vs. 0.2 %). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9 % vs. 29.6 %).
A 52-week multi-centre, randomised, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (NYHA functional class I-III) to evaluate the effect of

vildagliptin 50 mg twice daily (N=128) compared to placebo (N=126) on left-ventricular ejection fraction (LVEF).
Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were balanced overall. There were more cardiac events in vildagliptin treated patients with NYHA class III heart failure compared to placebo. However, there were imbalances in baseline cardiovascular risk favouring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA1c compared with placebo (difference of 0.6 %) from a mean baseline of 7.8 % at week 16. In the subgroup with NYHA class III, the decrease in HbA1c compared to placebo was lower (difference 0.3 %) but this conclusion is limited by the small number of patients (n=44). The incidence of hypoglycaemia in the overall population was 4.7 % and 5.6 % in the vildagliptin and placebo groups, respectively.

Cardiovascular risk
A meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and IV monotherapy and combination therapy clinical studies of up to more than 2 years duration (mean exposure 50 weeks for vildagliptin and 49 weeks for comparators) was performed and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute myocardial infarction, stroke or cardiovascular death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95 % CI 0.61-1.11)]. A MACE occurred in 83 out of 9,599 (0.86 %) vildagliptin-treated patients and in 85 out of 7,102 (1.20 %) comparatortreated patients. Assessment of each individual MACE component showed no increased risk (similar M-H RR). Confirmed heart failure (HF) events defined as HF requiring hospitalisation or new onset of HF were reported in 41 (0.43 %) vildagliptin-treated patients and 32 (0.45 %) comparator-treated patients with M-H RR 1.08 (95 % CI 0.68-1.70).

Table: Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy IT population)

Monotherapy placebo controlled studies	**Mean baseline HbA1c (%)**	**Mean change from baseline in HbA1c (%) at week 24**	**Placebo-corrected mean change in HbA1c (%) at week 24 (95 % CI)**
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)
Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
* $p < 0.05$ for comparison versus placebo			
Add-on / Combination studies			
Vildagliptin 50 mg twice daily + metformin	8.4	-0.9	-1.1* (-1.4, -0.8)

Monotherapy placebo controlled studies	Mean baseline HbA1c (%)	Mean change from baseline in HbA1c (%) at week 24	Placebo-corrected mean change in HbA1c (%) at week 24 (95 % CI)
(N=143)			
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	8.5	-0.6* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + metformin + glimepiride (N=152)	8.8	-1.0	-0.8* (-1.0, -0.5)
* $p < 0.05$ for comparison versus placebo + comparator			

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus.

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 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 addon 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)	-0.58 (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:

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased Cmax (19 %).

However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85 %.

Distribution

The plasma protein binding of vildagliptin is low (9.3 %) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vss) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69 % of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57 % of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4 % of dose). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic

clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [14C] vildagliptin, approximately 85 % of the dose was excreted into the urine and 15 % of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23 % of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Linearity/non-linearity

The Cmax for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in specific groups of patients

Gender

No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Elderly

In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32 %, with an 18 % increase in peak plasma concentration as compared to young

healthy subjects (18-40 years). These changes are, however, not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic impairment

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in patients with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20 % and 8 %, respectively), while the exposure to vildagliptin for patients with severe impairment was increased by 22 %. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30 %, which is not considered to be clinically relevant. There was no correlation between the severity of the hepatic disease and changes in the exposure to vildagliptin.

Renal impairment

A multiple-dose, open-label trial was conducted to evaluate the pharmacokinetics of the lower therapeutic dose of vildagliptin (50 mg once daily) in patients with varying degrees of chronic renal impairment defined by creatinine clearance (mild: 50 to < 80 ml/min, moderate: 30 to < 50 ml/min and severe: < 30 ml/min) compared to normal healthy control subjects.

Vildagliptin AUC increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151 and BQS867 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment.

LAY151 concentrations were approximately 2-3-fold higher than in patients with severe renal impairment.

Vildagliptin was removed by haemodialysis to a limited extent (3 % over a 3-4 hour haemodialysis session starting 4 hours post dose).

Ethnic group

Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

Remogliflozin

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:

Vildagliptin

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on Cmax).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at $\geq$ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity

study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59 fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose).

Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

Remogliflozin

6.1 Animal Toxicology or Pharmacology

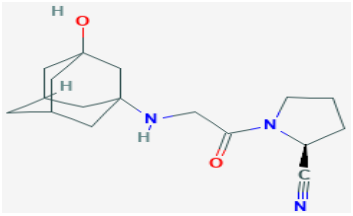
Remogliflozin etabonate has been evaluated in repeat dose oral (gavage) toxicity studies of duration up to 13 weeks in mice, 26 weeks in rats and 52 weeks in dogs. The NOAELs established in 13-, 26- and 52-week oral toxicity studies in mice, rats and dogs were 2000, 1200 and 650 mg/kg/day, respectively. 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 coadministered 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 nongenotoxic 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:

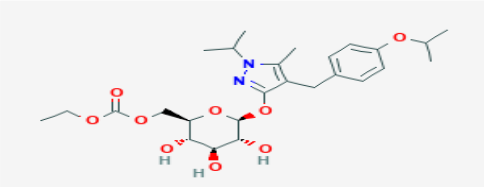
Vildagliptin

Vildagliptin is (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile. The empirical formula is $C_{17}H_{25}N_3O_2$ and its molecular weight is 303.4 g/mol. The chemical structure is:



Remogliflozin Etabonate

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 and Vildagliptin Tablets are white to off-white, capsule shaped, biconvex, film coated tablet with break line on one side and plain on other side.

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:

TORGLIP R are packed in Blister pack of 10 tablets.

8.4 Storage and handing instructions:

- Store below 30°C. Protect from light and moisture.
- Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

TORGLIP R
Remogliflozin Etabonate 100 mg and Vildagliptin 50 mg Tablets

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

- Keep this leaflet. You may need to read it again.
- If you have any 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. See section 9.4.

What is in this leaflet?

9.1 What TORGLIP R is and what it is used for

The name of your medicine is **TORGLIP R** which is combination of Remogliflozin Etabonate and Vildagliptin. It is indicated in adults aged 18 years and older with type 2 diabetes mellitus: to improve glycaemic control when Metformin and one of mono-components of fixed dose combination of Remogliflozin Etabonate & Vildagliptin do not provide adequate glycaemic control and When already being treated with the free combination of Remogliflozin Etabonate & Vildagliptin

9.2 What you need to know before you take TORGLIP R

Do not take TORGLIP R Tablets

- if you ae allergic to TORGLIP R or any of the other ingredients of this medicine
- If you think you may be allergic to TORGLIP R or any of the other ingredients TORGLIP R Tablets do not take this medicine and talk to your doctor.

Warnings and precautions

- Talk to your doctor, pharmacist or nurse before taking TORGLIP R Tablets
- if you have type 1 diabetes (i.e. your body does not produce insulin) or if you hav a condition called diabetic ketoacidosis.
- if you are taking an anti-diabetic medicine known as a sulphonylurea (your doctor may want to reduce your dose of the sulphonylurea when you take it together with TORGLIP R Tablets in order to avoid low blood glucose [hypoglycaemia]).
- if you have moderate or severe kidney disease (you will need to take a lower dose of TORGLIP R Tablets
- if you are on dialysis.
- if you have liver disease.
- if you suffer from heart failure.
- if you have or have had a disease of the pancreas.
- If you have previously taken TORGLIP R but had to stop taking it because of liver disease, you should not take this medicine.
- Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking TORGLIP R Tablets. Should these occur, you should promptly consult your doctor.
- A test to determine your liver function will be performed before the start of TORGLIP R
- Tablets treatment, at three month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible.

Children and adolescents

The use of TORGLIP R Tablets in children and adolescents up to 18 years of age is not recommended.

- Remogliflozin should not be initiated in patients with moderate to severe renal 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.
- 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.
- 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.
- There is no experience in clinical studies with remogliflozin in patients with cardiac failure.
- 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.
- 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.
- Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during treatment with remogliflozin etabonate.

Other medicines and TORGLIP R Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may wish to alter your dose of TORGLIP R Tablets if you are taking other medicines such as:

- thiazides or other diuretics (also called water tablets)
- corticosteroids (generally used to treat inflammation)
- thyroid medicines
- certain medicines affecting the nervous system.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You should not use TORGLIP R Tablets during pregnancy.
- It is not known if TORGLIP R Tablets passes into breast milk. You should not use TORGLIP R Tablets if you are breast-feeding or plan to breast-feed.
- 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.
- 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

Driving and using machines

If you feel dizzy while taking TORGLIP R Tablets, do not drive or use machines.

TORGLIP R Tablets contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

9.3 How to take TORGLIP R

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

How much to take and when

The amount of TORGLIP R Tablets people have to take varies depending on their condition. Your doctor will tell you exactly how many tablets of TORGLIP R Tablets to take. The maximum daily dose is 100 mg.

The usual dose of TORGLIP R Tablets is either:

- 50 mg daily taken as one dose in the morning if you are taking TORGLIP R Tablets with another medicine called a sulphonylurea.
- 100 mg daily taken as 50 mg in the morning and 50 mg in the evening if you are taking TORGLIP R Tablets alone, with another medicine called metformin or a glitazone, with a combination of metformin and a sulphonylurea, or with insulin.
- 50 mg daily in the morning if you have moderate or severe kidney disease or if you are on Dialysis

How to take TORGLIP R Tablets

- Swallow the tablets whole with some water.

How long to take TORGLIP R Tablets

- Take TORGLIP R Tablets every day for as long as your doctor tells you. You may have to take this treatment over a long period of time.
- Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you take more TORGLIP R Tablets than you should

- If you take too many TORGLIP R Tablets, or if someone else has taken your medicine, talk to your doctor straight away. Medical attention may be needed. If you need to see a doctor or go to the hospital, take the pack with you.

If you forget to take TORGLIP R Tablets

- If you forget to take a dose of this medicine, take it as soon as you remember. Then take your next dose at the usual time. If it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking TORGLIP R Tablets

- Do not stop taking TORGLIP R Tablets unless your doctor tells you to. If you have questions about how long to take this medicine, talk to your doctor**.**

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some symptoms need immediate medical attention:

You should stop taking TORGLIP R Tablets and see your doctor immediately if you experience the following side effects:

- Angioedema (rare: may affect up to 1 in 1,000 people): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulties breathing, sudden onset rash or hives, which may indicate a reaction called “angioedema”.

- Liver disease (hepatitis) (rare): Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis).
- Inflammation of the pancreas (pancreatitis) (frequency not known): Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to your back, as well as nausea and vomiting.

Other side effects

Some patients have had the following side effects while taking Vildagliptin 50 mg Tablets and metformin:

- Common (may affect up to 1 in 10 people): Trembling, headache, dizziness, nausea, low blood Glucose
- Uncommon (may affect up to 1 in 100 people): Tiredness

Some patients have had the following side effects while taking Vildagliptin 50 mg Tablets and a sulphonylurea:

- Common: Trembling, headache, dizziness, weakness, low blood glucose
- Uncommon: Constipation
- Very rare (may affect up to 1 in 10,000 people):
- Sore throat, runny nose
- Some patients have had the following side effects

While taking Vildagliptin 50 mg Tablets and a glitazone:

- Common: Weight increase, swollen hands, ankle or feet (oedema)
- Uncommon: Headache, weakness, low blood glucose

Some patients have had the following side effects while taking Vildagliptin 50 mg Tablets alone:

- Common: Dizziness
- Uncommon: Headache, constipation, swollen hands, ankle or feet (oedema), joint pain, low
- blood glucose
- Very rare: Sore throat, runny nose, fever

Some patients have had the following side effects while taking Vildagliptin 50 mg Tablets, metformin and a sulphonylurea:

- Common: Dizziness, tremor, weakness, low blood glucose, excessive sweating

Some patients have had the following side effects while taking Vildagliptin 50 mg Tablets and insulin (with or without metformin):

- Common: Headache, chills, nausea (feeling sick), low blood glucose, heartburn
- Uncommon: Diarrhoea, flatulence

Since this product has been marketed, the following side effects have also been reported:

- Frequency not known (cannot be estimated from the available data): Itchy rash, inflammation of the pancreas, localised peeling of skin or blisters, muscle pain.

Common: (≥ 1/100 to < 1/10)

- Constipation
- Diarrhoea
- Asthenia
- Pyrexia
- Bacteriuria,
- Urinary tract infection
- Viral upper respiratory tract Infection
- Glomerular filtration rate decreased
- Dyslipidaemia

- Hypoglycaemia
- Headache
- Ketonuria
- Cough
- Orthostatic hypotension

Uncommon (≥ 1/1,000 to < 1/100)

- Anaemia
- Eosinophilia
- Iron deficiency anaemia,
- Microcytic anaemia,
- Thrombocytopenia
- Thrombocytosis
- Vertigo
- Eye pain
- Lacrimation increased Abdominal discomfort
- Abdominal pain
- Abdominal pain upper
- Gastritis
- Gastrooesophageal reflux
- disease
- Hyperchlorhydria
- Stomatitis
- Vomiting
- Fatigue
- Pain
- Hyperbilirubinaemia
- 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
- Blood bicarbonate abnormal
- Blood cholesterol increased
- Blood creatinine increased
- Blood lactic acid increased
- Blood pressure increased
- Blood triglycerides increased

- Electrocardiogram QT
- prolonged
- Gamma-glutamyltransferase
- increased
- Hepatic enzyme increased
- Low density lipoprotein
- increased
- Weight decreased
- Decreased appetite
- Diabetic ketoacidosis
- Hypercholesterolemia
- Hypertriglyceridaemia
- Hypocalcaemia
- Lactic acidosis
- Polydipsia
- Arthralgia Back pain
- Costochondritis
- Musculoskeletal pain
- Myalgia Pain in extremity
- Dizziness
- Hypoaesthesia
- Anxiety
- Insomnia

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.

9.5 How to store TORGLIP R

- Store below 30°C. Protect from light and moisture.
- Keep out of reach of children.

9.6 Contents of the pack and other information

What TORGLIP R contains

- The active substance is Remogliflozin Etabonate and Vildagliptin**.**
- **Colours:** Ferric Oxide Yellow U.S.P.-NF and Titanium Dioxide I.P.
- **TORGLIP R** are packed in Blister pack of 10 tablets.

10. Details of manufacturer

Manufactured By:

Glenmark Pharmaceuticals Ltd.

Samlik Marchak, Industrial Growth Centre, East Sikkim, Sikkim-737135

11. Details of permission or licence number with date

Mfg Lic No M/602/2012 issued on 01.12.2020

12. Date of revision

NA

MARKETED BY