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

TORGLIP D

1. Generic Name

Dapagliflozin and Vildagliptin Sustained Release Tablets (5 mg + 100 mg) and (10 mg + 100 mg)

2. Qualitative and quantitative Composition

TORGLIP D 5

Each bilayer tablet contains:

Dapaglifloizin propanediol USP

eq.to Dapagliflozin ……..…5 mg

Vildagliptin I.P……..…...100 mg

(As sustained Release)

Colour: Ferric oxide Red USP-NF

The excipients used are Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Ferric Oxide Red, Croscarmellose Sodium.

TORGLIP D 10

Each bilayer tablet contains:

Dapaglifloizin propanediol USP

eq.to Dapagliflozin……...……10 mg

Vildagliptin I.P…… …..100 mg

(As sustained Release)

Colour: Ferric oxide yellow USP-NF

The excipients used are Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Ferric Oxide Yellow, Croscarmellose Sodium.

3. Dosage form and strength

Dosage form: Bilayered tablets

Strength: Dapagliflozin 5 mg / 10 mg and Vildagliptin 100 mg

4. Clinical particulars

4.1 Therapeutic indication

It Is Indicated For the Treatment of Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin Monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet daily. Each tablet contains a fixed dose of dapagliflozin and Vildagliptin.

Method of administration

TORGLIP D tablets should be given once daily with meals to reduce the gastrointestinal adverse reactions.

4.3 Contraindications

Dapagliflozin and Vildagliptin SR tablets is contraindicated in patients with: hypersensitivity to the active substances or to any of the excipients used in the manufacturing of the finished product, any type of acute metabolic acidosis, diabetic pre-coma, severe renal failure, dehydration, severe infection, shock, cardiac or respiratory failure, acute alcohol intoxication and alcoholism.

4.4 Special warnings and precautions for use

Dapagliflozin

Volume depletion: Before initiating Dapagliflozin, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.

• Ketoacidosis in Patients with Diabetes Mellitus: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue Dapagliflozin, evaluate and treat promptly. Before initiating Dapagliflozin, consider risk factors for ketoacidosis. Patients on Dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

• Urosepsis and Pyelonephritis: Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.

• Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Dapagliflozin.

• Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.

• Genital Mycotic Infections: Monitor and treat if indicated.

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 > 3x 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 3x 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. 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.

4.5 Drugs interactions

No interaction studies have been performed for Dapagliflozin and Vildaglitpin SR tablets. The following statements reflect the information available on the individual active substances.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Dapagliflozin in patients with type 2 diabetes mellitus.

In patients with type 1 diabetes mellitus and a known risk of frequent or severe hypoglycaemia, it may be necessary to reduce the insulin dose at the time of initiating treatment with Dapagliflozin to decrease the risk of hypoglycaemia. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Pharmacokinetic interactions

The metabolism of Dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In in vitro studies, Dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, Dapagliflozin is not expected to alter the metabolic clearance of co administered medicinal products that are metabolised by these enzymes.

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.

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.

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

Pregnancy

There are no data from the use of Dapagliflozin and Vildagliptin SR tablets or Dapagliflozin in pregnant women. 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 this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. 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

The effect of this medicinal product or Dapagliflozin & Vildagliptin on fertility in humans has not been studied.

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), Vildagliptin SR is not recommended.

Hepatic impairment

This medicinal product must not be used in patients with hepatic impairment.

Elderly (≥ 65 years)

This medicinal product should be used with caution as age increases.

Paediatric population

The safety and efficacy of Dapagliflozin and Vildagliptin SR tablets have not yet been established. No data are available.

4.7 Effects on ability to drive and use machines

Dapagliflozin and Vildagliptin SR tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Dapagliflozin and Vildagliptin SR tablets have been demonstrated to be bioequivalent with co administered Dapagliflozin and Vildagliptin. There have been no therapeutic clinical trials conducted with Dapagliflozin and Vildagliptin SR tablets.

Description of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Dapagliflozin

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose).

Vildagliptin

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.

5 Pharmacological properties

5.1 Mechanism of Action

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs.

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action.

Urinary glucose excretion (glucuresis) induced by Dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by Dapagliflozin is also associated with mild diuresis and transient natriuresis.

The effect of vildagliptin layer 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).

5.2 Pharmacodynamic properties

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2diabetes mellitus following the administration of dapagliflozin.

Vildagliptin

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin sustained release tablets 100 mg 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.

5.3 Pharmacokinetic properties

Dapagliflozin

Absorption:

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Geometric mean steady-state Dapagliflozin Cmax and AUCτ values following once daily 10 mg doses of Dapagliflozin were 158 ng/mL and 628 ng.h/mL, respectively. Maximum Dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increased proportionally to the increment in Dapagliflozin dose. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of Dapagliflozin in healthy subjects. Administration with a high-fat meal decreased Dapagliflozin Cmax by up to 50% and prolonged Tmax by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution:

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Metabolism:

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life (t1/2) for Dapagliflozin was 12.9 hours following a single oral dose of Dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]- Dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 h]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of Dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Excretion:

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged Dapagliflozin. After administration of 50 mg [14C]-Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

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 metabolised 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.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Dapagliflozin:

In vivo primary pharmacodynamic studies with Dapagliflozin were carried out in single-dose, dose ranging studies in non-diabetic and diabetic rats or mice in order to evaluate the potency, SGLT2-specificity and duration of action in stimulating urinary glucose excretion, and to describe the secondary consequences of urinary glucose excretion, such as changes in urine volume or blood or plasma glucose effects. Subsequently a multiple-dose study was carried out to evaluate the ability of Dapagliflozin to have sustained effects on urinary glucose excretion, urine volume, and fasting plasma glucose in diabetic rats over a two-week dosing period.

Dapagliflozin increased renal glucose excretion in (healthy, non-diabetic) experimental animals. This was accompanied, by osmotic diuresis as measured by increased urine flow. An oral glucose tolerance test was also performed showing that Dapagliflozin was able to significantly reduce glucose area under the curve (AUC), compared to vehicle treatment. A study in knock-out mice

lacking the gene for SGLT2 revealed that SGLT2 is indeed the main target for Dapagliflozin at least at lower doses. This study also demonstrated the reversibility of Dapagliflozin's action towards SGLT2.

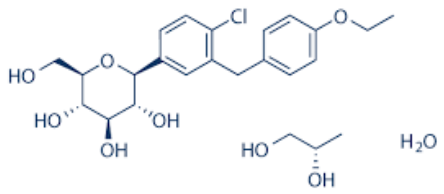
Vildagliptin is a selective and potent inhibitor of DPP-4. The IC50 value for inhibition of human DPP-4 is about 3 nM and similar activity was observed with the rat enzyme, demonstrating the lack of species selectivity. Vildagliptin showed some activity at the related enzymes DPP-8 and DPP-9 (Ki values of 506 nM and 65 nM respectively). Although these values are 253 and 32 times higher than the Ki for DPP-4, activity at Cmax in humans (2.3 μM) is likely. No assays exist allowing evaluation of DPP-8/DPP-9 inhibition in vivo. The possibility of activity at one or both of these targets is considered a safety concern in relation to the occurrence of skin lesions in monkeys. No, or minimal, inhibition was seen with other related enzymes.

In vivo pharmacodynamic studies were performed in rats and monkeys. These studies demonstrated the in vivo inhibition of DPP-4 and increased plasma levels of GLP-1. Studies in diabetic rats and in insulin-resistant monkeys demonstrated a glucose-lowering effect of Vildagliptin. Chronic effects of Vildagliptin were studied in pre-diabetic and insulin-treated diabetic monkeys. Beneficial effects were observed on HbA1c, fasting insulin, fibrinogen and PAI-1.

7 Description

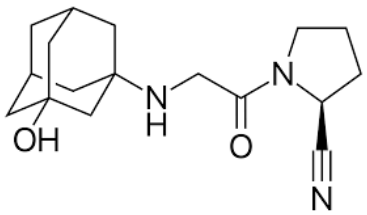
Dapagliflozin Propanediol

Dapagliflozin Propanediol monohydrate is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-Chloro-3-[(4-Ethoxyphenyl)Methyl]Phenyl]-6-(Hydroxymethyl)Oxane-3,4,5-Triol;(2*S*)-Propane-1,2-Diol;Hydrate. The empirical formula is $C_{24}H_{35}ClO_9$ and its molecular weight is 503.0 g/mol. The chemical structure is:



Vildagliptin

Vildagliptin is (S)-1-[2-(3-hydroxyadamant-1-ylamino)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:



Torglip D 5

Dapagliflozin and Vildagliptin Sustained Release Tablets (5 mg+ 100 mg) are white to off white/pink colored, round, biconvex, uncoated bilayer tablets, plain on both sides. The excipients

used are Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Hydroxypropylmethyl Cellulose, Ferric Oxide Red, Croscarmellose Sodium.

Torglip D 10

Dapagliflozin and Vildagliptin Sustained Release Tablets (10 mg + 100 mg) are white to off white/yellow colored, round, biconvex, uncoated bilayer tablets, plain on both sides. The excipients used are Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Hydroxypropylmethyl Cellulose, Ferric Oxide Yellow, Croscarmellose Sodium.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

TORGLIP D 5/10 is available in pack of 10 tablets.

8.4 Storage and handing instructions

Store below 30° C

Keep out of reach of children.

9 Patient Counselling Information

Package leaflet: Information for the user

TORGLIP D

Dapagliflozin and Vildagliptin Sustained Release 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.

What is in this leaflet

9.1 What TORGLIP D is and what it is used for

TORGLIP D contain Vildagliptin (As sustained release) and Dapagliflozin Tablets It Is Indicated For the Treatment of patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin Monotherapy.

9.2 What you need to know before you take TORGLIP D

Do not take TORGLIP D

TORGLIP D tablets is contraindicated in patients with: hypersensitivity to the active substances or to any of the excipients used in the manufacturing of the finished product, any type of acute metabolic acidosis, diabetic pre-coma, severe renal failure, dehydration, severe infection, shock, cardiac or respiratory failure, acute alcohol intoxication and alcoholism.

Warnings and precautions

Dapagliflozin

Volume depletion: Before initiating Dapagliflozin, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.

• Ketoacidosis in Patients with Diabetes Mellitus: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue Dapagliflozin, evaluate and treat promptly. Before initiating Dapagliflozin, consider risk factors for ketoacidosis. Patients on Dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

• Urosepsis and Pyelonephritis: Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.

• Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Dapagliflozin.

• Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.

• Genital Mycotic Infections: Monitor and treat if indicated.

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 > 3x 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 3x 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. 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.

Pregnancy, breast-feeding and fertility

Pregnancy

There are no data from the use of Dapagliflozin and Vildagliptin SR tablets or Dapagliflozin in pregnant women. 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 this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. 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

The effect of this medicinal product or Dapagliflozin & Vildagliptin on fertility in humans has not been studied.

9.3 How to take TORGLIP D

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will determine what dose is appropriate for you.

TORGLIP D tablets should be given once daily with meals to reduce the gastrointestinal adverse reactions.

If you forget to take TORGLIP D

It is important to take your TORGLIP D tablet regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose.

9.4 Possible side effects

TORGLIP D tablets have been demonstrated to be bioequivalent with co administered Dapagliflozin and Vildagliptin. There have been no therapeutic clinical trials conducted with Dapagliflozin and Vildagliptin SR tablets.

Description of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store TORGLIP D

Store below 30° C

9.6 Contents of the pack and other information

TORGLIP D 5

Torglip D 5 consists of Dapaglifloizin propanediol USP and Vildagliptin IP As active ingredients of 5 mg and 100 mg Repectively.

Dapagliflozin and Vildagliptin Sustained Release Tablets are white to off white/pink colored, round, biconvex, uncoated bilayer tablets, plain on both sides. The excipients used are

Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Ferric Oxide Red, Croscarmellose Sodium.

Torglip D 10

Torglip D 10 consists of Dapaglifloizin propanediol USP and Vildagliptin IP As active ingredients of 10 mg and 100 mg Repectively.

Dapagliflozin and Vildagliptin Sustained Release Tablets are white to off white/yellow colored, round, biconvex, uncoated bilayer tablets, plain on both sides. The excipients used are Microcrystalline Cellulose, Hydroxypropylmethyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Lactose monohydrate, Ferric Oxide Yellow, Croscarmellose Sodium.

TORGLIP D 5/10 is available in pack of 10 tablets.

10 Details of manufacturer

Exemed Pharmaceuticals

Plot no. 133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi-396 195,

Dist.: Valsad, INDIA

11 Details of permission or licence number with date

Mfg Licence No: G/25/2011 Issued on 12.04.2022

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORGLIP D (5 mg + 100 mg) (10 mg + 100 mg)/Jul-2024/02/PI