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

ENCELIN DM/ TORGLIP DM

BOX WARNING

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of a rare but serious infection of the genitals and area around the genitals have been reported with Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotising fasciitis of the perineum, is also referred to as Fournier's gangrene.

Lactic acidosis

Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmias. The onset of metformin associated lactic acidosis is often subtle and accompanied by non-specific symptoms such as malaise, myalgias, respiratory distress, somnolence and abdominal pain. Metformin associated lactic acidosis was characterised by elevated blood lactate levels (>5 mmol/litre), anion gap acidosis (without evidence of ketonuria or ketonemia), an increase in lactate/pyruvate ratio, and metformin in plasma levels generally >5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g. carbonic anhydrase inhibitors like topiramate), age 65 years or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g. acute congestive heart failure), excessive alcohol intake and hepatic impairment. If lactic acidosis is suspected, discontinue Dapagliflozin and metformin hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. **Generic Name**

   Vildagliptin (As sustained release), Dapagliflozin and Metformin Hydrochloride (As sustained release) Tablets (100 mg+10 mg+ 500 mg) and (100 mg+10 mg+ 1000 mg)

2. **Qualitative and quantitative composition**

   ENCELIN DM / TORGLIP DM 100/10/500

   Each uncoated bilayered tablet contains

   Metformin Hydrochloride I.P. ……500 mg

   (As sustained release)

   Dapagliflozin Propanediol USP

   equivalent to Dapagliflozin……...10 mg

   Vildagliptin I.P.

   (As sustained release) …….100 mg

   Excipients …….……...q.s.

   Colour: Ferric oxide Yellow USP –NF.

   The excipients used are Hydroxypropylmethyl Cellulose 200M (HPMC K 200M), Povidone K 30, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicon dioxide, Magnesium Stearate,

Calcium Stearate, Hypromellose, Polyethylene Glycol, Lactose monohydrate, Pregelatinized Starch, Ferric Oxide Yellow, Dicalcium phosphate anhydrous, carbomer (Biopal 974P).

ENCELIN DM / TORGLIP DM 100/10/1000

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Metformin Hydrochloride I.P. ……..…...1000 mg

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Excipients ……..…...…q.s.

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3. Dosage form and strength

Dosage form: Uncoated bilayered tablet

Strength: Dapagliflozin 10 mg, Vildagliptin (As Sustained Release) 100 mg and Metformin Hydrochloride (As Sustained Release) 500 mg Tablets

Dapagliflozin 10 mg, Vildagliptin (As Sustained Release) 100 mg and Metformin Hydrochloride (As Sustained Release) 1000 mg Tablets

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of patients with type 2 diabetes mellitus.

4.2. Posology and method of administration

Posology

The recommended dose is one tablet daily. Each bilayer uncoated tablet contains a fixed dose of Dapagliflozin Vildagliptin and Metformin Hydrochloride.

Method of administration

It should be given orally once daily.

4.3. Contraindications

Dapagliflozin

- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema.
- Patients who are being treated for glycemic control without established CVD or multiple CV

risk factors with severe renal impairment.

- Patients on dialysis.

Vildagliptin

- Contraindicated in patients with type 1 diabetes, diabetic ketoacidocis.

Metformin

Metformin are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m2).

Known hypersensitivity to metformin hydrochloride.

Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Diabetic ketoacidosis should be treated with insulin.

4.4. Special warnings and precautions for use

Dapagliflozin

Volume depletion: Before initiating, 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 medication, evaluate and treat promptly. Before initiating, 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 drug.

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.

Artralgia

Post marketing report shown DPP-4 inhibitors like viladgliptin induced Arthralgia.

Metformin Hydrochloride

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

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

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

Renal impairment—The post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney

4.5. Drugs interactions

No interaction studies have been performed for Dapagliflozin and Vildaglitpin SR and Metformin SR tablets.

The following statements reflect the information available on the individual active substances.

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.

No interaction studies have been performed for Dapagliflozin and Vildaglitpin SR and Metformin SR tablets.

The following statements reflect the information available on the individual active substances.

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 ACE-inhibitors.

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 sympathomimetic.

Dapagliflozin

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Carbonic Anhydrase Inhibitors

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

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin and Metformin Hydrochloride Extended Release Tablet.

Metformin

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

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

Patients with 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) on haemodialysis, It is not recommended.

Patients with Hepatic Impairment

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 2.5 x ULN.

Pregnant Women

There are no data from the use of drug 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, drug should not be used during pregnancy.

Lactating Women

It is unknown whether 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. It should not be used during breast-feeding.

Paediatric Patients

The safety and efficacy of drug has not yet been established. No data are available.

Geriatric Patients

In Patients ≥ 65 years, It should be used with caution as age increases.

Fertility

The effect of this medicinal product on fertility in humans has not been studied.

4.7. Effects on ability to drive and use machines

It has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

It has been demonstrated to be bioequivalent with co-administered Dapagliflozin and Vildagliptin.

Dapagliflozin

In the reported clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin. The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo. In the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus (DECLARE study), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin. The most frequently reported adverse reactions across the clinical studies were genital infections.

Table 1: Adverse reactions in placebo-controlled clinical studiesa and postmarketing experience

System organ class	**Very common**	**Common***	**Uncommon** *	**Rare**	**Very rare**
Infections and infestations		Vulvovaginitis, balanitis and related genital	Fungal infection**		Necrotising fasciitis of the

		infections[*,b,c] Urinary tract infection[*,b,d]			perineum (Fournier's gangrene)[b,i]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletionb,e Thirst[**]	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation[**] Dry mouth[**]		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**]		
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment[**,b] Blood urea increased[**] Weight decreased[**]		

a) The table shows up to 24-week (short-term) data regardless of glycaemic rescue. b) See corresponding subsection below for additional information. c) Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess. d) Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis. e) Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension. f) Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased. g) Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus –0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects. h) Mean percent

change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%. i) See below this section for details j) Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively. k) Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate. *Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo. **Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Vulvovaginitis, balanitis and related genital infections

In the reported 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection. In the DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin. In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus. For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia. 11 In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively). In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at weeks 24 and 104. At weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin. In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea. In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%)

patients treated with placebo.

Volume depletion

In the reported 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo. In the DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m 2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

In the reported DECLARE study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred 12 evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population.

Urinary tract infections

In the reported 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection. In the DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73 m2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73 m2 (18.5% dapagliflozin 10 mg versus 9.3% placebo). Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment. In the DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m2), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Vildagliptin

The safety and tolerability of vildagliptin (50 mg qd, 50 mg bid and 100 mg qd) have been assessed by pooling data from more than 11,000 patients from 36 Phase II and III reported studies (including

3 open label studies) ranging in duration from 12 to more than 104 weeks. The studies used in this pooled analysis have assessed vildagliptin as monotherapy, add-on therapy to other oral anti-diabetic agents (metformin, TZD, SU and insulin) and as an initial combination therapy with metformin or pioglitazone. Patients not receiving vildagliptin (all comparators group) were taking only placebo or metformin, TZD, SU, acarbose or insulin. For the calculation of frequency of adverse drug reactions for the individual indications, safety data from a subset of pivotal controlled trials of at least 12 week's duration was considered. Safety data were obtained from 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) who received vildagliptin as monotherapy or in combination with another agent.

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 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.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration, the incidence of ALT or AST elevations >= 3x 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 vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Tabulated summary of adverse drug reactions from clinical trials

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 MedDRA system organ class and absolute frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Monotherapy

The overall incidence of withdrawal from monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies, hypoglycemia was uncommon, reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with vildagliptin 50 mg twice 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.

Vildagliptin is weight neutral when administered as monotherapy.

Table 2: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1373) as monotherapy in double-blind studies

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Uncommon	Edema peripheral

Long term clinical trials of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with metformin

In reportedclinical trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo + metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with metformin.

Table 3: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with metformin in double-blind studies

Nervous system disorders	
Common	Tremor, dizziness, headache

Long-term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.

When vildagliptin was studied as an initial combination therapy with metformin, no additional safety signal or unforeseen risk was observed.

Combination with a sulfonylurea

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

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

At the recommended dose of 50 mg, vildagliptin is weight neutral when administered in combination with glimepiride.

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg once daily in combination with a sulfonylurea in double-blind studies (n=170)

Nervous system disorders	
Common	Tremor, headache, dizziness
General disorders and administration site conditions	
Common	Asthenia

Combination with a thiazolidinedione

In reported clinical trials with the combination of vildagliptin and a thiazolidinedione, 0.7% of patients withdrew for adverse reactions in the vildagliptin 50 mg once daily + pioglitazone group, and there were no withdrawals due to adverse reactions reported in either the vildagliptin 50 mg twice daily + pioglitazone or the placebo + pioglitazone treatment groups.

In clinical trials, no hypoglycemia events were reported in patients receiving vildagliptin 50 mg once daily + pioglitazone 45 mg, hypoglycemia was uncommon in patients receiving vildagliptin 50 mg twice daily + pioglitazone 45 mg (0.6%) but common in patients receiving placebo + pioglitazone 45 mg (1.9%). No severe hypoglycemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the change in body weight compared to placebo was +0.1 kg and +1.3 kg for vildagliptin 50 mg daily and vildagliptin 50 mg twice daily, respectively.

The incidence of peripheral edema when vildagliptin was added to a maximum dose of background pioglitazone (45 mg once daily) was 8.2% as 50 mg once daily and 7.0%, as 50 mg twice daily compared to 2.5% for background pioglitazone alone. The incidence of edema when vildagliptin was added to pioglitazone as dual initial therapy in drug naïve patients was, however, less than for pioglitazone alone (50 mg once daily 3.5%, 50 mg twice daily 6.1% vs. pioglitazone 30 mg 9.3%).

Table 5: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n= 146) or 50 mg twice daily (n=158) in combination with a thiazolidinedione in double-blind studies

Investigations	
Common	Weight increase
General disorders and administration site conditions	
Common	Edema peripheral

Combination with insulin

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

The incidence of hypoglycemia was similar in both treatment groups (14.0% in the vildagliptin group versus 16.4 % in the placebo group). Two patients reported severe hypoglycemic events in

the vildagliptin group, and 6 patients - in the placebo group.

At the end of the study, the 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).

Table 6: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with insulin (with or without metformin (n=371))

Nervous system disorders	
Common	Headache
Gastrointestinal disorders	
Common	Nausea, gastroesophageal reflux disease
Uncommon	Diarrhea, flatulence
General disorders and administration site conditions	
Common	Chills
Investigations	
Common	Blood glucose decreased

Combination with metformin and SU

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

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride vs. 1.9% for the placebo + metformin + glimepiride). One severe hypoglycemic event was reported in the vildagliptin group.

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

Table 7: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and SU (n=157)

Nervous system disorders	
Common	Dizziness, tremor
General disorders and administration site condition	
Common	Asthenia
Metabolism and nutritional disorders	
Common	Hypoglycemia
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis

Adverse drug reactions from spontaneous reports and literature cases - Post-marketing Experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with vildagliptin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known.

- Hepatitis reversible upon drug discontinuation
- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid.
- Pancreatitis.
- Arthralgia, sometimes severe.

Adverse events observed more than 2% in the clinical trial conducted with Vysov-D were: headache (2.2%), nasopharyngitis (2.7%), urinary tract infections (2.2%), hypoglycaemia (4.4%).

Metformin

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

General

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

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

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

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

Renal impairment—The post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the

severity of renal impairment because metformin is substantially excreted by the kidney.

If you experience any side-effects, talk to your doctor.

Reporting of suspected 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: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

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.

Metformin

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

5. Pharmacological properties

5.1. Mechanism of Action

Dapagliflozin

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycaemic 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 hypoglycaemia. 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.

Vildagliptin

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).

Metformin HCL

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2. Pharmacodynamic poperties

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

Absorption

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Vildagliptin

In a fasting state, vildagliptin is rapidly absorbed following oral administration. Peak plasma concentrations are observed at 1.7 hours following administration. Plasma concentrations of vildagliptin increase in an approximately dose-proportional manner.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Vildagliptin

The mean volume of distribution of vildagliptin at steady-state after intravenous administration is 71 L, suggesting extravascular distribution.

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. 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 is the predominant drug-related component in human plasma.

Vildagliptin

About 69% of orally administered vildagliptin is eliminated via metabolism not mediated by cytochrome P450 enzymes. Based on the findings of a rat study, DPP-4 contributes partially to the hydrolysis of vildagliptin. Vildagliptin is metabolized to pharmacologically inactive cyano (57%) and amide (4%) hydrolysis products in the kidney. LAY 151 (M20.7) is a major inactive metabolite and a carboxylic acid that is formed via hydrolysis of the cyano moiety: it accounts for 57% of the

dose. Other circulating metabolites reported are an N-glucuronide (M20.2), an N-amide hydrolysis product (M15.3), two oxidation products, M21.6 and M20.9.

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Vildagliptin

Vildagliptin is eliminated via metabolism. Following oral administration, approximately 85% of the radiolabelled vildagliptin dose was excreted in urine and about 15% of the dose was recovered in feces. Of the recovered dose in urine, about 23% accounted for the unchanged parent compound.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Clinical Studies

An open label, randomized, balanced, two treatment, two sequence, two period, cross-over, single-dose oral relative bioavailability study was conducted to compare and assess the rate and extent of absorption of the given FDC of Dapagliflozin 10mg + Vildagliptin Sustained Release 100mg + Metformin 1000 mg Sustained Release Tablets (T) (test product – T) versus individual reference formulations of Dapagliflozin 10 mg + Vildagliptin Sustained Release 100 mg (R1) and Metformin 1000 mg Sustained Release Tablets (R2) in healthy, adult, human male subjects under fed condition. The study showed that this FDC formulation of Dapagliflozin 10mg + Vildagliptin Sustained Release 100mg + Metformin 1000 mg Sustained Release Tablets (T) when compared to the individual reference formulations of Dapagliflozin 10 mg + Vildagliptin Sustained Release 100 mg (R1) and Metformin 1000 mg Sustained Release Tablets (R2) met the relative bioavailability criteria as the statistical outcome of 90% Confidence Intervals for Ln-transformed pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence limits of 80.00 to 125.00%. Hence, as per this study it is concluded that this FDC Dapagliflozin 10 mg + Vildagliptin Sustained Release 100 mg + Metformin 1000 mg Sustained Release Tablets (T) is bioequivalent to the individual components of reference formulations when administered as a single oral dose in

healthy, adult, human male subjects under fasting condition. Also, the FDC of Dapagliflozin 10mg + Vildagliptin Sustained Release 100 mg + Metformin 1000 mg Sustained Release Tablets (T) was found to be safe and well tolerated in participated subjects.

Mean pharmacokinetic parameters of Dapagliflozin 10 mg (Test versus Reference product), Vildagliptin Sustained Release 100 mg (Test versus Reference product) Metformin 1000 mg Sustained Release Tablets (Test versus Reference product) after single oral dose in healthy, adult, human male subjects under fasting condition are given below

Dapagliflozin 10 mg	C_{max} (ng/mL) (Mean ± SD)	AUC_{0-t} (ng*hr/mL) (Mean ± SD)	$AUC_{0-\infty}$ (ng*hr/mL) (Mean ± SD)	Mean $T_{1/2}$ (h)	Mean T_{max} (h)
Test	90.6380 ±25.5678	515.6897 ±121.6452	550.2650 ±125.1185	6.3088 ±2.2398	6.3771 ±2.3357
Reference	94.6397 ±19.8231	520.7500 ±117.7235	559.5022 ±123.5883	6.5508 ±2.5351	1.9104 ±1.0915

Vildagliptin 100 mg	Cmax (ng/mL) (Mean ± SD)	AUC0-t (ng*hr/mL) (Mean ± SD)	AUC0-∞ (ng*hr/mL) (Mean ± SD)	Mean T1/2 (h)	Mean Tmax (h)
Test	187.1294 ±70.6771	1856.4256 ±477.7055	1939.4417 ±425.3002	4.5442 ± 2.7806	6.1250 ±2.4771
Reference	182.3000 ±57.8265	1957.9678 ±515.9103	2023.0734 ±521.0366	4.1342 ± 2.7792	5.9167 ± 2.0938

Metformin 1000 mg	Cmax (ng/mL) (Mean ± SD)	AUC0-t (ng*hr/mL) (Mean ± SD)	AUC0-∞ (ng*hr/mL) (Mean ± SD)	Mean T1/2 (h)	Mean Tmax (h)
Test	1468.1258 ± 468.7324	16152.5488 ±5529.1815	16426.7703 ±5544.0508	4.2446 ± 0.9699	5.7083 ± 2.1209
Reference	1536.4143 ± 497.0626	15231.4818 ± 4870.9549	15545.3784 ± 4891.2545	4.1796 ± 0.6322	5.4375 ±1.6831

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

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.

Metformin

Major target organs of metformin were heart and liver, as evidenced by heart hypertrophy with immune cell infiltration/inflammation and liver hypertrophy with concomitant hepatic injury and elevated LFT biomarkers, starting at approximately 10-times the expected clinical AUC exposures.

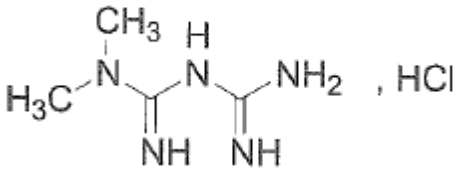
Metformin clinical toxicity hallmarks include lactic acidosis and gastrointestinal side effects (e.g., diarrhea, bloating, discomfort).

A notable new toxicity issue was identified in the nonclinical program suggesting potential metformin-induced teratogenicity. Metformin is not listed as teratogenic at approximate clinical exposures (body surface area estimates) on current labels.

7. Description

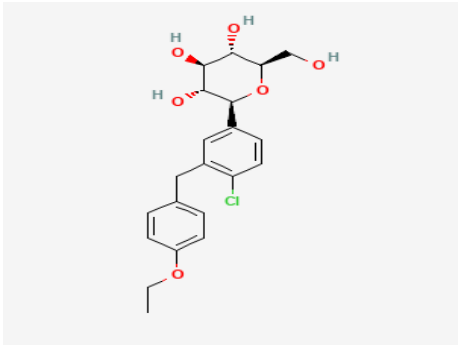
Metformin Hydrochloride

Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula is $C_4H_{11}N_5$, HCl and its molecular weight is 165.6 g/mol. The chemical structure of Metformin Hydrochloride is:



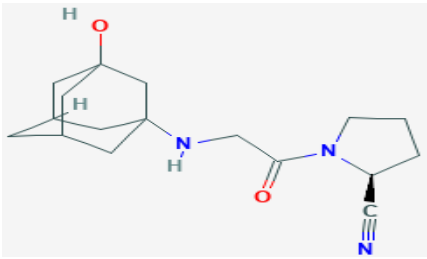
Dapagliflozin Propanediol:

Dapagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3 [(4ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol. The empirical formula is $C_{21}H_{25}ClO_6$ and molecular weight is 408.9 g/mol. The chemical structure is :



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:



ENCELIN DM / TORGLIP DM 100/10/500

Vildagliptin, Dapagliflozin & Metformin Hydrochloride Sustained Release Tablets are white to off white/ yellow colored, capsule shape, biconvex, uncoated bilayer tablets, plain on both sides.

The excipients used are Hydroxypropylmethyl Cellulose 200M (HPMC K 200M), Povidone K 30, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicon dioxide, Magnesium Stearate, Calcium Stearate, Hypromellose, Polyethylene Glycol, Lactose monohydrate, Pregelatinized Starch, Ferric Oxide Yellow, Dicalcium phosphate anhydrous, carbomer (Biopal 974P).

ENCELIN DM / TORGLIP DM 100/10/1000

Vildagliptin, Dapagliflozin & Metformin Hydrochloride Sustained Release Tablets are white to off white/ yellow colored, oval shape, biconvex, uncoated tablets, plain on both sides.

The excipients used are Hydroxypropylmethyl Cellulose 200M (HPMC K 200M), Povidone K 30, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicon dioxide, Magnesium Stearate, Calcium Stearate, Hypromellose, Polyethylene Glycol, Lactose monohydrate, Pregelatinized

Starch, Ferric Oxide Yellow, Dicalcium phosphate anhydrous, carbomer (Biopal 974P).

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

ENCELIN DM AND TORGLIP DM is available in pack of 10 tablets.

8.4. Storage and handing instructions

Store below 30º C

Keep out of reach of children.

9. Patient Counselling Information

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

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

10. Details of manufacturer

Exemed Pharmaceuticals

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

Selvas Road, Vapi-396 195,

Gujarat, INDIA.

11. Details of permission or licence number with date

100/10/1000mg: Lic.No. G/25/2011 issued on 23.11.2022

100/10/500mg: Lic.No. G/25/2011 issued on 24.11.2022

12. Date of revision

JUN 2024

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ENCELIN DM & TORGLIP DM (100 mg +10 mg+ 500/1000 mg) /JUN-24/02/PI