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

LINAXA D (GLUCRETA L)

1. Generic Name

Dapagliflozin 10 mg and Linagliptin 5 mgTablet

2. Qualitative and quantitative composition

Each film coated tablet contains;

Dapagliflozin Propanediol USP

eq. to Dapagliflozin …….10 mg

Linagliptin…….5 mg

Excipients……..q.s.

Colours: Ferric oxide Red NF & Titanium dioxide I.P.

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: Linagliptin 5 mg and Dapagliflozin 10 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 film coated tablet contains a fixed dose of Linagliptin and Dapagliflozin.

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.

Linagliptin

No dose adjustment is recommended for patients with renal impairment and hepatic impairment.

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.

Linagliptin

Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues are known to cause hypoglycemia. The use of Linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin.

Macrovascular outcome

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Linagliptin tablets or any other antidiabetic drug.

4.5 Drug interaction

No interaction studies have been performed for Dapagliflozin and Linagliptin tablets.

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

Linagliptin

Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure suggesting that the efficacy of Linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with P-gp or CYP 3A4 inducer.

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT). No dose adjustment of Linagliptin is recommended based on results of the described pharmacokinetic studies.

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.

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

Patients with Renal impairment

Results of study, supported by results of population pharmacokinetic analyses, indicate that no dose adjustment is recommended in patients with renal impairment.

Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC0-24 and approximately 23% lower Cmax compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition. No dose adjustment of linagliptin is necessary in patients with hepatic impairment.

Gender

No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population

pharmacokinetic analysis.

Geriatric

No dose adjustment is recommended based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population

pharmacokinetic analysis.

Pediatric

Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed.

Race

No dose adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic

data, including subjects of White, Hispanic, Black, and Asian racial groups.

Pregnant Women

There are no data from the use of drug in pregnant women. There are no adequate data from the use of linaliptin in pregnant women.

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 linagliptin is excreted in human milk. It should not be used during breast-feeding.

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

Dapagliflozin

In the 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 infections*,b,c Urinary tract infection*,b,d	Fungal infection**		Necrotising fasciitis of the 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		Rashj			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[**]		

The table shows up to 24-week (short-term) data regardless of glycaemic rescue. bSee corresponding subsection below for additional information. cVulvovaginitis, 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. dUrinary 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. eVolume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension. fPolyuria includes the preferred terms: pollakiuria, polyuria, urine output increased. gMean 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. hMean 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%. iSee below this section for details jAdverse 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. kReported 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 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.

<u>Hypoglycaemia</u>

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 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 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 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.

Linagliptin

Following 52 weeks treatment in a controlled study comparing linagliptin with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% patients treated with linagliptin (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were arthralgia (5.7% vs 3.5%), back pain (6.4% vs 5.2%), and headache (5.7% vs 4.2%).

Other adverse reactions reported in clinical studies with treatment of linagliptin were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity), and myalgia. In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with linagliptin compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin

Hypoglycemia

In the placebo-controlled studies, 195 (7.6%) of the total 2566 patients treated with linagliptin 5 mg reported hypoglycemia compared to 49 patients (4.1%) of 1183 placebo treated patients. The incidence of hypoglycemia was similar to placebo when linagliptin was administered as monotherapy or in combination with metformin, or with pioglitazone. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 of 791 (22.9%) of patients reported hypoglycaemia compared with 39 of 263 (14.8%) of patients administered placebo in combination with metformin and a sulfonylurea.

Laboratory Tests

Changes in laboratory findings were similar in patients treated with linagliptin 5 mg compared to patients treated with placebo. Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7 % in the linagliptin group).

No clinically meaningful changes in vital signs were observed in patients treated with linagliptin.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
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).

Linagliptin

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of linagliptin (equivalent to 120 times the recommended daily dose) there were no dose related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

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.

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

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.

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100 mg dose.

At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5 mg dose.

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.

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant.

Linagliptin may be administered with or without food.

Distribution

Dapagliflozin

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

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75%-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment

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.

Linagliptin

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway.

Small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-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.

Linagliptin

Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

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.

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

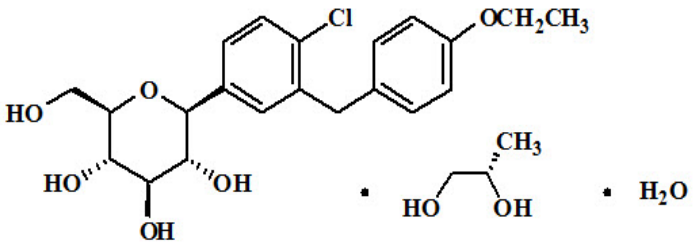
Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an in vivo micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

7. Description

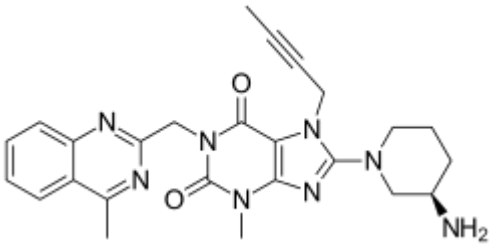
Dapagliflozin Propanediol:

Dapagliflozin Propanediol monohydrate: D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1); It has an empirical formula of C21H25ClO6•C3H8O2•H2O and a molecular weight of 502.98 gm/mole.
Structural formula of Dapagliflozin is:



Linagliptin

Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2- quinazolinyl)methyl]- The empirical formula is C25H28N8O2 and the molecular weight is 472.54 g/mol. The structural formula is:



LINAXA D (GLUCRETA L):

Dapagliflozin and Linagliptin tablets are reddish brown colored, round, biconvex, film coated tablets, plain on both sides. The excipients used are Mannitol, pregelatinised Starch, Sodium Starch Glycolate, Colloidal Sillicon Dioxide, Calcium Stearate, Instacoat aqua Brown.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not available

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

LINAXA D (GLUCRETA L) 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

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,

Dist.:Valsad, Gujarat State, INDIA

11. Details of permission or licence number with date

Mfg. Licence No: G/25/2011 Issued on: 06.07.2023

12. Date of revision

JUN 2024

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LINAXA D (GLUCRETA L) 5 mg + 10 mg/Jun-2024/02/PI