LINAUR™-D

tablets

1. Generic Name: Linagliptin and Dapagliflozin Tablets

2. Qualitative and Quantitative composition:

Each film coated tablet contains:

Linagliptin ..... 5 mg

Dapagliflozin Propanediol USP

equivalent to Dapagliflozin ..... 10 mg

Colour: Ferric Oxide USP-NF (Yellow)

3. Dosage form and strength:

Dosage form: Film coated tablets is available in oral dosage form.

Strength: Available in Linagliptin 5 mg & Dapagliflozin 10 mg.

4. Clinical particulars

4.1. Therapeutic indication

In patients with type-2 Diabetes Mellitus inadequately controlled on Metformin

4.2. Posology and method of administration

The recommended dose is 1 tablet once daily or as directed by the Physician.

Method of administration: For oral use.

4.3. Contraindication

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use:

General

Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia

Linagliptin alone showed a comparable incidence of hypoglycemia to placebo. In clinical trials of linagliptin as part of combination therapy with medicinal products not known to cause hypoglycemia (metformin), rates of hypoglycemia reported with linagliptin were similar to rates in patients taking placebo. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycemia was increased over that of placebo. Sulphonylureas and insulin are known to cause hypoglycemia. Therefore, caution is advised

when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of sulphonylurea or insulin may be considered.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Linagliptin should be discontinued; if acute pancreatitis is confirmed, Linagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Linagliptin should be discontinued.

Dapagliflozin

General

Dapagliflozin should not be used in patients with type 1 diabetes mellitus.

Renal impairment

Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment. In one study in patients with type 2 diabetes mellitus with moderate renal impairment (GFR < 60 mL/min), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

4.5. Drug interactions:

Linagliptin

In vitro assessment of interactions

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4 but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein

substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and in vivo interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of interactions

Effects of other medicinal products on linagliptin

Clinical data described below suggests that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Rifampicin: multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, resulted in a 39.6% and 43.8% decreased linagliptin steady- state AUC and Cmax, respectively, and about 30% decreased DPP-4 inhibition at trough. Thus, full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administered longterm. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied.

Ritonavir: co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of Pglycoprotein and CYP3A4, increased the AUC and Cmax of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4- 5-fold after coadministration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors.

Metformin:

co-administration of multiple three times daily doses of 850 mg metformin with 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin in healthy volunteers.

Sulphonylureas:

the steady-state pharmacokinetics of 5 mg linagliptin was not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide).

Dapagliflozin

Pharmacodynamic interactions

Diuretics

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

Insulin and insulin secretagogues

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

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9). In in vitro studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected. Following coadministration of dapagliflozin with Mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

Dapagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after dapagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium. In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

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

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

4.6 Use in special population

Linagliptin

Pregnancy The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy.

Breast-feeding Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility No studies on the effect on human fertility have been conducted for linagliptin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Dapagliflozin

Pregnancy There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding 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 7 milk, as well as pharmacologically mediated effects in nursing. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7. Effects on ability to drive and use machine.

Linagliptin has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia especially when combined with sulphonylurea and/or insulin. Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8. Undesirable effects:

Linagliptin

<u>Summary of the safety profile</u>

In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to linagliptin 5 mg (63.4% versus 59.1%). Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (4.3% versus 3.4%). The

most frequently reported adverse reaction was "hypoglycaemia" observed under the triple combination, linagliptin plus metformin plus sulphonylurea 14.8% versus 7.6% in placebo. In the placebo-controlled studies 4.9% of patients experienced "hypoglycaemia" as an adverse reaction under linagliptin. Of these, 4.0% were mild and 0.9% were moderate and 0.1% were classified as severe in intensity. Pancreatitis was reported more often in patients randomized to linagliptin (7 events in 6,580 patients receiving linagliptin versus 2 events in 4,383 patients receiving placebo).

Tabulated list of adverse reactions

Due to the impact of the background therapy on adverse reactions (e.g. on hypoglycaemias), adverse reactions were analysed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to metformin plus sulphonylurea, and add-on to insulin).

The placebo-controlled studies included studies where linagliptin was given as monotherapy with short-term duration of up to 4 weeks

monotherapy with ≥ 12-week duration

add-on to metformin T4/EU/SPC/13

add-on to metformin + sulphonylurea

add on to metformin and empagliflozin

add-on to insulin with or without metformin

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received 5 mg linagliptin in double-blind studies as monotherapy or as add-on therapy are presented in the table below.

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

Table No: 1 Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add on therapies in clinical trial and from post-marketing experience

System organ class Adverse reaction	Frequency of adverse reaction
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia [1]	very common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Pancreatitis	rare#
Constipation [2]	uncommon
Skin and subcutaneous tissue disorders	
Angioedema*	rare
Urticaria*	rare
Rash*	uncommon
Bullous pemphigoid	rare#
Investigations	
Amylase increased	uncommon
Lipase increased**	common

Lipase increased**common Based on post-marketing experience.

** Based on lipase elevations >3xULN observed in clinical trials

Based on Linagliptin cardiovascular and renal safety study (CARMELINA), see also below

1 Adverse reaction observed in combination with metformin plus sulphonylurea

2 Adverse reaction observed in combination with insulin.

Dapagliflozin

Summary of the safety profile

Type 2 diabetes mellitus

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, 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.

Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a

median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1.73 m2. In the dapagliflozin cardiovascular outcome study in patients with heart failure with left ventricular ejection fraction > 40% (DELIVER), 3,126 patients were treated with dapagliflozin 10 mg and 3,127 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 25 mL/min/1.73 m2. The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2, and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2. The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Table No 2. 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,j]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,j,k]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash[i]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria*[f]			
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 mgversus ‑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 section 4.4.

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.

4.9. Overdose

Linagliptin

Symptoms

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were generally well tolerated. There is no experience with doses above 600 mg in humans.

Therapy

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures if required.

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). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

5. Pharmacological properties

5.1. Mechanism of action

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.

Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant

reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodeling and diastolic function and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD studies. Other effects include an increase in hematocrit and reduction in body weight. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin. SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

5.2. Pharmacodynamic properties

Linagliptin

Pharmacodynamics 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.

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years. This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations. Urinary uric acid excretion was also increased transiently (for 3-7
days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations range from -48.3 to -18.3 micromoles/L (-0.87 to -0.33 mg/dL).

5.3. Pharmacokinetic properties

Linagliptin

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (Tmax); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (Cmax) was 8.9 nmol/L. Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and Cmax and AUC increased by a factor of 1.3 at steady state compared with the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced Cmax by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution

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 concentrationdependent, 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

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion

Following administration of an oral [14C]-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.

Dapagliflozin

Absorption

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

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.

Biotransformation

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3- O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme presents in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg -dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

6. Nonclinical properties

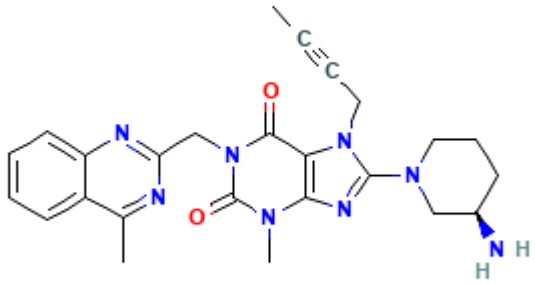
6.1 Animal Toxicology or Pharmacology: Not required.

7. Description

This product (tablet) contains Linagliptin and Dapagliflozin as active ingredients and it is indicated for the treatment in the patients with type-2 Diabetes Mellitus inadequately controlled on Metformin. Linagliptin is 8-[(3*R*)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]purine-2,6-dione and

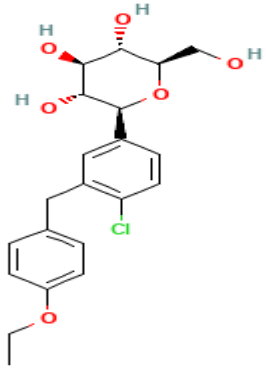
Molecular Formula - $C_{25}H_{28}N_8O_2$

Molecular Weight - 472.5 g/mol and structural formula is-



Dapagliflozin is a (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol .Molecular Formula - $C_{21}H_{25}ClO_6$

Molecular Weight- 408.9 g/mol



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life: 24 months

8.3 Packaging Information

10 Tablets pack in Alu-Alu packing

8.4 Storage and handling instructions

Store at a temperature not exceeding 30◦C. Keep all medicines out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, pharmacist or nurse.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

9.1 Adverse reactions: Refer part 4.8.

9.2 Drug Interactions: Refer part 4.5.

9.3 Dosage: Refer part 4.2.

9.4 Storage: Refer part 8.4.

9.5 Risk factors: Refer part 4.4.

9.6 Self-monitoring information: NA

9.7 Information on when to contact a health care provider or seek emergency help.

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications: Refer part 4.3.

10. Details of manufacturer:

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,

Ranipur, Haridwar-249 403, Uttarakhand.

11. Details of permission or license number with date: 31/UA/2013

12. Date of revision: March 2024