For the use of a registered medical practitioner only

Rx

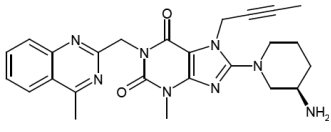
Dapagliflozin & Linagliptin Tablets

DAPAONE®-L

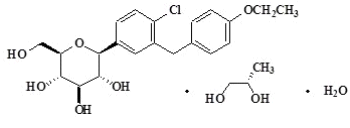
Composition:
Each film coated tablet contains:

Dapagliflozin Propanediol USP	
eq. to Dapagliflozin	10 mg
Linagliptin	5 mg
Excipients	q.s.
Colour: Quinoline Yellow	

DESCRIPTION:
Linagliptin
Chemical Formula: C25H28N8O2
Molecular Weight: 472.54g/mol
Therapeutic Categories: anorally-active inhibitor of the dipeptidylpeptidase-4 (DPP-4) enzyme.
Chemical Name: 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]



Dapagliflozin
Chemical Formula: C21H25ClO6•C3H8O2•H2O
Molecular Weight: 502.98g/mol
Therapeutic Categories: sodium-glucoseco-transporter2(SGLT2)inhibitor.
Chemical Name: D-glucitol,1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-,(1S)-, compounded with (2S)-1,2-propanediol, hydrate.



INDICATION:
Inpatients with Type-2diabetesmellitus

DOSAGE AND ADMINISTRATION:
The recommended dose of Tablet should be individualized on the basis of both effectiveness and to lerability, while not exceeding the maximum recommended dose of 2.5 & 5 mg linagliptin. The recommended starting dose of dapagliflozin is 5 mg once daily dose can be increased to 10 mg orally once daily for additional glycemic control. To reduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mg once daily.
Route of Administration: To be taken orally

USE IN SPECIAL POPULATION:
Pregnancy
The safety of this Tablet in pregnant women has not been established. There are no adequate and well-controlled studies data from the use of combination of Linagliptin + Dapagliflozin in pregnant women. Tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Linagliptin
Linagliptin was not teratogenic when administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times the clinical dose in ratsand1943 times the clinical dose in rabbits, based on exposure. No functional, behavioral, or reproductive toxicity was observed in off spring of female Wistar Han rats when administered linagliptin from gestation day 6 to lactation day 21 at a dose 49 times the maximum recommended human dose, based on exposure.
Linagliptin crosses the placenta into the fetus following or aldosing in pregnant rats and rabbits.

Lactation
No studies in lactating animals have been conducted with the combined components of Linagliptin and Dapagliflozin Tablet. In studies performed with the individual components, linagliptin & dapagliflozin were secreted in the milk of lactating rats. It is not known whether linagliptin & dapagliflozin is excreted in human milk. Be cause the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of Tablet in pediatric patients under 18 years of age have not been established.

Geriatric Use
Linagliptin is minimally excreted by the kidney.
Linagliptin
There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin;1085(27%) patients were 65 years and over, while131(3%) were 75years and over.
Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No over all differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Dapagliflozin
No dapagliflozin dosage change is recommended based on age. Atotalof1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of dapagliflozin in improving glycemic controlin type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension

Renal impairment
Linagliptin is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2.
If Linagliptin Tablet is discontinued due to evidence of renal impairment, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg. No dose adjustment of linagliptin is recommended in patients with renal impairment.
Dapagliflozin- Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) or ESRD.

Hepatic impairment
Dapagliflozin- No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

CONTRA-INDICATION:

•History of a serious hypersensitivity reaction to Linagliptin + Dapagliflozin, such as urticaria, anaphylactic reactions or angioedema

•Severe renal impairment (eGFRbelow30mL/min/1.73m2)
•Patientson dialysis

WARNINGS AND PRECAUTIONS:
Linagliptin
Use with Medications Known to Cause Hypoglycemia
Insulin secretagogues and insulin 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. The use of linagliptin in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin.

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

Dapagliflozin
Hypotension
Dapagliflozin causes intra vascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR less than 60ml/min/1.73 m2), elderly patients, or patients on loop diuretics. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.
Ketoacidosis
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. This tablet is not indicated for the treatment of patients with type 1 diabetes mellitus.
Genital Mycotic Infections
Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

ADVERSE REACTIONS:
Linagliptin
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety evaluation of Linagliptin 5 mg once daily in patients with type 2 diabetes is based on 14 placebo-controlled trials, 1 active-controlled study, and one study in patients with severe renal impairment. In the14 placebo-controlledstudies, a total of 3625 patients were randomized and treated with Linagliptin 5 mg daily and 2176 with placebo. The mean exposure in patients treated with Linagliptin across studies was 29.6 weeks. The maximum follow-up was 78 weeks. linagliptin 5 mg once daily was studied as mono therapy in three place bo-controlledtrialsof 18 and 24 weeks' duration and in five additional placebo-controlled studies lasting ≤ 18 weeks. The use of linagliptin in combination with other anti hyperglycemic agents was studied in six placebo-controlledtrials: two with metformin (12 and 24 weeks' treatment duration); one with a sulfonylurea (18 weeks' treatment duration); one with metformin and sulfonylurea (24 weeks' treatment duration); one with pioglitazone (24 weeks' treatment duration); and one with insulin (primary endpoint at 24 weeks).
In a pooled data set of 14 placebo-controlled clinical trials, adverse reactions that occurred in ≥2% of patients receiving linagliptin (n=3625) and more commonly than in patients given placebo (n= 2176), are shown in Table 1. The overall incidence of adverse events with TRADJENTA were similar to placebo.

Adverse Reactions Reported in ≥2% of Patients Treated with Linagliptin and Greater than Placebo in Placebo-Controlled Clinical Studies of Linagliptin Monotherapy or Combination Therapy

	Number(%) of Patients	
	Linagliptin 5 mg n=3625	Placebo n=2176
Nasopharyngitis	254(7.0)	132(6.1)
Diarrhea	119(3.3)	65(3.0)
Cough	76(2.1)	30(1.4)

Rates for other adverse reactions for linagliptin 5 mg versus placebo when linagliptin was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4%vs0%) when linagliptin was used as add-onto sulfonylurea; hyperlipidemia (2.7%vs0.8%) and weight increased (2.3%vs0.8%) when linagliptin was use das add-on to pioglitazone; and constipation (2.1% vs 1%) when linagliptin was used add-on to basal insulin therapy.
Following 104 weeks' treatment in a controlled study comparing linagliptin with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% of patients treated with linagliptin (n = 776) and more frequently than in patients treated with a sulfonylurea (n=775) were backpain (9.1%vs8.4%), arthralgia (8.1%vs6.1%), upper respiratory tract infection (8.0%vs7.6%), headache (6.4%vs5.2%), cough (6.1%vs4.9%) and pain in extremity (5.3%vs3.9%).

Dapagliflozin
Volume Depletion
Ketoacidosisin Patients with Diabetes Mellitus Urosepsis and Pyelonephritis
Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Genital MycoticInfections

DRUG INTERACTIONS:
Linagliptin
Inducers of P-glycoproteinandCYP3A4Enzymes
Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may bereduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

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 with1, 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.

OVER DOSAGE:
Linagliptin
In the event of an overdose with linagliptin, contact the Poison Control Center. 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. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.
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.
Dapagliflozin-There were no reports of overdose during the clinical development program for dapagliflozin. In the event of an over dose, contact the Poison Control Center. It is a lsoreasonable to employ supportive measures, as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied

CLINICAL PHARMACOLOGY:
Linagliptin Mechanism of Action
Linagliptin is an inhibitor of DPP-4, anenzyme that degrades the in cretin 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

levelthroughout 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.

Pharmacodynamics
Linagliptin binds to DPP-4 in a reversible manner and 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.
Pharma cokinetics Absorption
The absolute bio availability 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 linagliptin5 mg to healthy subjects is approximately 1110L, 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
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 eliminatedvia the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 ml/min.

Dapagliflozin Mechanism of Action
Sodium-glucosecotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and there by increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre-and after load of the heart and down regulation of sympathetic activity.

Pharmacodynamics
General-Dapagliflozindoses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.
Cardiac Electrophysiology-Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

Pharmacokinetics Absorption
Oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax 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 Cmax by up to 50% and prolongs Tmax 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.

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

Metabolism
The metabolism of dapagliflozin is primarily mediated by UGT1A9;CYP-mediated metabolism is a minor clearance path way in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-Oglucuronide accounted for 61% of a 50 mg dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination
Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of 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 ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Hepatic In sufficiency
In patients with mild and moderate hepatic impairment (Child-Pughclasses A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-PughclassC), mean Cmax and AUC of dapagliflozin were up to 40%and 67% higher, respectively, as compared to healthy matched controls.
Effects of Age, Gender, Race and Body Weight on Pharma cokinetics
Based on a population pharma cokinetic analysis, gender does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

INCOMPATIBILITIES:
No incompatibility study have been found

PACKAGING INFORMATION:
10x10 tablets packed in an Alu-Alu blister.

SHELF LIFE:
Refer as on carton

STORAGE AND HANDLING INSTRUCTIONS:
Store protected from light & moisture, at a temperature not exceeding 30°C.

Manufactured by:
Mascot Health Series Pvt. Ltd.
Plot No. 79,80, Sec-6A, IIE, Sidcul,
Haridwar-249403

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MSN Laboratories Private Limited.
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