For the use of only a Registered medical ractitioner or a Hospital or a Institution.

Rx

Dapagliflozin, Linagliptin & Metformin Hydrochloride (SR) Tablets

DAPAONE®-LM 500

DAPAONE®-LM-LM 1000

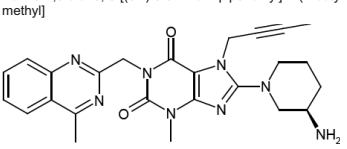
Composition:
Each film coated bilayered tablet contains:

Dapagliflozin Propanediol USP	
eq. to Dapagliflozin	10 mg
Linagliptin	5 mg
Metformin Hydrochloride IP	500 mg
(As sustained release form)	
Excipients	q.s.
Colour : Sunset Yellow	

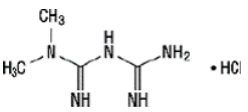
Composition:
Each film coated bilayered tablet contains:

Dapagliflozin Propanediol USP	
eq. to Dapagliflozin	10 mg
Linagliptin	5 mg
Metformin Hydrochloride IP	1000 mg
(As sustained release form)	
Excipients	q.s.
Colour : Quinoline Yellow	

DESCRIPTION:
Linagliptin
ChemicalFormula: C25H28N8O2
MolecularWeight: 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]

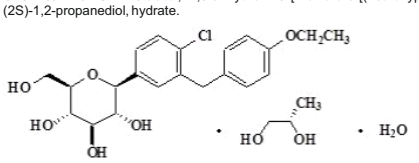


Metformin Hydrochloride
Chemical Formula: C4H11N5.HCl
Molecular Weight:Average:165.63 g/mol
Therapeutic Categories: oral antihyperglycemic agents.
Chemical Name: N, N-dimethylimidodicarbonimidicdiamide hydrochloride



Metformin, is the first-line medication for the treatment of type 2 diabetes, particularly in people
Who are over weight. It is also used in the treatment of polycystic ovary syndrome. It is not associated with weight gain. It is taken by mouth.

Dapagliflozin
ChemicalFormula: 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-2 diabetes mellitus.

DOSAGE AND ADMINISTRATION:
The recommended dose of Tablet should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 & 5 mg linagliptin/1000 mg metformin hydrochloride with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. The recommended starting dose of Dapagliflozin is 5 mg once daily dose can be increased to 10mg 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
Pregnancy Category B
There are no adequate and well controlled studies in pregnant women with Linagliptin, dapagliflozin and Metformin Tablet or its individual components, and some clinical data is available for metformin which indicate that the risk for major malformations was not increased when metformin is taken during the first trimester in pregnancy. In addition, metformin was not associated with increased perinatal complications. Never the less, because these clinical data cannot rule out the possibility of harm, Linagliptin, dapagliflozin and Metformin Tablet should be used during pregnancy only if clearly needed. Linagliptin, dapagliflozin and Metformin Tablet was not teratogenic when administered to Wistar Han rats during the period of organogenesis at doses similar to clinical exposure. At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), the metformin component of the combination was associated with an increased incidence of fetalrib and scapula malformations.

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 rats and1943 times the clinical dose in rabbits, based on exposure. No functional, behavioral, or reproductive toxicity was observed in offspring 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 in to the fetus following oral do sing in pregnant rats and rabbits.

Metformin Hydrochloride
Metformin has been studied for embryo-fetal effects in 2 rat strains and in rabbits. Metformin was not teratogenic in Sprague Dawleyrats up to 600mg/kg or in Wistar Han rats upto 200 mg/kg (2- 3 times the clinical dose based on body surface area or exposure, respectively). At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), an increased incidence of rib and scapula skeletal malformations was observed in the Wistar Han strain. Metformin was not teratogenic in rabbits at doses up to 140 mg/kg (similar to clinical dose based on body surface area).
Metformin administered to female Sprague Dawley rats from gestation day 6 to lactation day 21 up to 600 mg/kg/day (2 times the maximum clinical dose based on body surface area) had no effect on prenatal or postnatal development of offspring.
Metformin crosses the placenta in to the fetus in rats and humans.
Lactation No studies in lactating animals have been conducted with the combined components of Linagliptin, dapagliflozin and Metformin Tablet. In studies performed with the individual components, both linagliptin, and metformin were secreted in the milk of lactating rats. It is not known whether linagliptin, dapagliflozin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because 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; however, metformin is substantially 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%) were75 year sand over.
Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were75 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.
Metformin
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, althoughother reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.
Dapagliflozin
No dapagliflozin dosage change is recommended based on age. A total of 1424 (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 controlintype 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 Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Linagliptin and Metformin Tablet is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2.
If Linagliptin and Metformin 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 Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Linagliptin and Metformin Tablet is not recommended in patients with 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:
• Severerenal impairment (eGFRbelow30mL/min/1.73m2)
• Acuteor chronic metabolic acidosis, including diabetic ketoacidosis. Diabeticketoacidosis should be treated with insulin
•A history of hyper sensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity.
• Hyper sensitivity to dapagliflozin & metformin
• Patients on dialysis

WARNINGS AND PRECAUTIONS:
Lactic Acidosis
Metformin
There have been post marketing cases of metformin - associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmi as have occurred with severe acidosis Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase risk of lactic acidosis, especially in patients at risk.
If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Linagliptin and Metformin Tablet. In Linagliptin and Metformin Tablet -treated patients with adiagnos is or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.
Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Linagliptin and Metformin Tablet and report these symptoms to their healthcare provider.
Pancreatitis
There have been post marketing reports of acute pancreatitis, including fatal pancreatitis, inpatients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Linagliptin and Metformin Tablet and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Linagliptin and Metformin Tablet.

Use with Medications Known to Cause Hypoglycemia
Linagliptin
Insulin secret agogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secret agogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with place bo in a clinical trial. The use of linagliptin incombination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia. Therefore, a lower dose of the insulin secret agogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin and Metformin Tablet.
Metformin
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs..

Hypersensitivity Reactions
There have been post marketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of Linagliptin and Metformin Tablet). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Linagliptin and Metformin Tablet, assess for other potential causes for the event, and institute alternative treatment for diabetes.
Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use cautioninapatient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Linagliptin and Metformin tablet. Vitamin B12 Levels
In controlled, 29-week clinical trials of metformin, a decrease to sub normal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to inte rference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1year) of the clinical trials. This risk maybe more relevant to patients receiving long-termtreatment with metformin, and adverse hematologic and neurologic reactions have been reported post marketing. The decrease in vitamin B12 levels appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised inpatients on Linagliptin and Metformin Tablet and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurement at 2- to 3-year intervals may be useful.
Severe and Disabling Arthralgia
There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to on set of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
Bullous Pemphigoid
Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immun osuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Linagliptin and Metformin Tablet. If bullous pemphigoid is suspected, Linagliptin and Metformin Tablet should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.
Macro vascular Out comes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with linagliptin or metformin or any other anti diabetic 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 60 ml/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 keto acidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 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 Dapaglifloz in increases the risk of genitalmy cotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

ADVERSE REACTIONS:
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.
Linagliptin / Metformin
The safety of concomitantly administered linagliptin (daily dose5 mg) and metformin (mean daily dose of approximately1800 mg) has been valuated in 2816 patients with type 2 diabetes mellitus treated for ≥12 weeks in clinical trials.
Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse events which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than inpatients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%).
In a 24-week factorial design study, adverse events reported in ≥5% of patients receiving linagliptin + metformin and were more common than in patients given placebo are shown in Table-
Adverse Reactions Reported in ≥5% of Patients Treated with Linagliptin + Metformin and Greater than with Placebo in a 24-week Factorial-Design Study

	Placebon=72	**Linagliptin Monotherapy n=142**	**Metformin Monotherapy n=291**	**Combinationof LinagliptinwithMetformin n=286**
	n (%)	n (%)	n (%)	n (%)
Nasopharyngitis	1(1.4)	8(5.6)	8(2.7)	18(6.3)
Diarrhea	2(2.8)	5(3.5)	11 (3.8)	18(6.3)

Other adverse reactions reported in clinical studies withtreatment oflinagliptin+ metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperreactivity), cough, decreased appetite, nausea, vomiting, pruritus, and pancreatitis.

Linagliptin
Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% vs 6.1%), diarrhea (3.3% vs 3.0%), and cough (2.1% vs 1.4%).
Rates for other adverse reactions for linagliptin 5 mg vs placebo when linagliptin was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when linagliptin was used as add-on to sulfonylurea; hyperlipidemia(2.7%vs0.8%)and weight increased(2.3%vs0.8%)when linagliptin was usedas add-on to pioglitazone; and constipation (2.1% vs 1%) when linagliptin was used as add-on to basal insulin therapy.
Other adverse reactions reportedin clinical studies with treatment of linagliptin mono therapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program,

pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (place boand active comparator, sulfonylurea). Three additional cases of pan creat it is were reported following the last administered dose of linagliptin.
Metformin
The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., mega loblastic anemia)

Hypoglycemia
Linagliptin/Metformin
In a 24-week factorial design study, hypoglycemia was reported in 4 (1.4%) of 286 subjects treated with linagliptin + metformin, 6 (2.1%) of 291 subjects treated with metformin, and 1 (1.4%) of 72 subjects treated with placebo. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 (22.9%) of 792 patients reported hypoglycemia compared with 39 (14.8%) of 263 patients administered placebo in combination with metformin and sulfonylurea. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.
Linagliptin In the study of patients receiving linagliptin as add-on therapy to a stable dose of insulin for up to 52 weeks (n=1261), no significant difference in the incidence of investigator reported hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self- measured blood glucose ≤70 mg/dL, was noted between the linagliptin-(31.4%) and placebo- (32.9%) treated groups.

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

DRUG INTERACTIONS:
Drug Interactions with Metformin
Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Linagliptin and Metformin Tablet may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
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 Linagliptin and Metformin Tablet.

Drug Interactions with Linagliptin
Inducers of P-glycoprote in and CYP3A4 Enzymes
Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As Linagliptin and Metformin Tablet is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

Insulin Secret agogues or Insulin
Co-administration of Linagliptin and Metformin Tablet with an insulin secret agogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secret agogue or insulin to reduce the risk of hypoglycemia.

Drugs Affecting Glycemic Control
Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockingdrugs, and isoniazid. When such drugs are administered to a patient receiving Linagliptin and Metformin Tablet, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Linagliptin and Metformin Tablet, the patient should be observed closely for hypoglycemia.
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.
Interferencewith1,5-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:
In the event of an overdose with Linagliptin and Metformin Tablet, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastro intestinal tract, employ clinical monitoring, and institutes upportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom Linagliptin and Metformin Tablet over dosage is suspected.
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.

Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin over dosage is suspected.
Dapagliflozin- There were no reports of overdose during the clinical development program for dapagliflozin. In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures, as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied

CLINICAL PHARMACOLOGY:
Mechanism of Action Linagliptin
Linagliptin is an inhibitor of DPP-4, an enzyme 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 in cretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both in cretin hormones are involved in the physiological regulation of glucose homeostasis. In cretin 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 ofnormaland elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin hydrochloride
Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and post prandial plasma glucose.Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucoseuptake andutilization. Metformin does not produce hypoglycemiaine it her patients with type 2 diabetes or in healthy subjects, except in unusual circumstances, and does not cause hyper insulinemia. with metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics
Linagliptin
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 oraldose 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.

Pharmacokinetics
Absorption
Linagliptin The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, 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. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple dose soflinagliptin5 mg, isapproximately12hours. After once-dailydosing, 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. Plasma AUC oflinagliptin 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.
Metformin Hydrochloride The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration(Cmax), a 25% lower are a under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of the time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered under fasting conditions. The clinical relevance of these decreases is unknown.

Distribution
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% to 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.
Metformin Hydrochloride The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours andaregenerally<1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.
Metabolism
Linagliptin 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.
Metformin Intravenous single-dose studies in normal subjects demonstrate that metformin is excrete dun changed in the urine and does not under go hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.
Excretion
Linagliptin 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.
Metformin Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.
Dapagliflozin Mechanism of Action
Sodium-glucose cotransporter 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 thereby 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 afterload of the heart and down regulation of sympathetic activity.
Pharma codynamics
General- Dapaglifloz in doses 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 discont in uation 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 meaning ful 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 metabolismis a minor clearance pathway in humans. Dapagliflozin is extensive lymetabolized, primarilytoyield 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 radio activity is excreted in urine and feces, respectively. In urine, less than 2% ofthe 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 approximately12.9 hours following a single oral dose of dapagliflozin 10 mg.
Hepatic Insufficiency
Inpatients with mild and moderate hepatic impairment (Child-PughclassesAand 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 upto 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 pharmacokinetic analysis, gender does not have a clinically meaning ful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

INCOMPATIBILITIES:
No incompatibility study have been found

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

SHELF LIFE: 24Months

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

Manufactured by:
Mascot Health Series Pvt. Ltd.
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