Dapagliflozin Tablets 5/10 mg
DAPAONE

To be sold by retail on the prescription of a Registered Medical Practitioner only.

PRESCRIBING INFORMATION

1. GENERIC NAME
Dapagliflozin Tablets 5 mg
Dapagliflozin Tablets 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dapagliflozin Tablets 5 mg
Each Film Coated Tablet Contains
Dapagliflozin ….. 5 mg
Colours: Ferric Oxide Yellow USP-NF &
Titanium Dioxide IP

Dapagliflozin Tablets 10 mg
Each Film Coated Tablet Contains
Dapagliflozin ….. 10 mg
Colours: Ferric Oxide Yellow USP-NF &
Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
Dapagliflozin is available as film coated tablets 5 mg and 10 mg.

4. CLINICAL PARTICULARS

4.1. Indications
Dapagliflozin is indicated in adults aged 18 years and older with Type-II diabetic mellitus to improve glycemic control

Dapagliflozin is indicated as mono-therapy when diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Limitations of Use
Dapagliflozin is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

4.2. Posology and Method of Administration
Prior to Initiation of Dapagliflozin
Assess renal function prior to initiation of Dapagliflozin therapy and periodically thereafter. In patients with volume depletion, correct this condition prior to initiation of Dapagliflozin.

Recommended Dosage
To improve glycemic control, the recommended starting dose of Dapagliflozin is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

To reduce the risk of hospitalization for heart failure, the recommended dose of Dapagliflozin is 10 mg once daily.

Patients with Renal Impairment
No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

Use of Dapagliflozin is not recommended when the eGFR is less than 45 mL/min/1.73 m^2.

Dapagliflozin is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

4.3. Contraindications
- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema.
- Severe renal impairment, (eGFR less than 30 mL/min/1.73 m^2) end-stage renal disease (ESRD), or patients on dialysis.

4.4. Special Warnings and Precautions for Use
Hypotension
Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Dapagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), 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
Fatal cases of ketoacidosis have been reported in patients taking Dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with Dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Dapagliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Dapagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury
Dapagliflozin causes intravascular volume contraction and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving Dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of Dapagliflozin. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating Dapagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing Dapagliflozin in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue Dapagliflozin promptly and institute treatment.

Renal function should be evaluated prior to initiation of Dapagliflozin and monitored periodically thereafter. Use of Dapagliflozin is not recommended when the eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis
Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or insulin secretagogues. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Dapagliflozin.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Both males and females have been equally affected. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Dapagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

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.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

4.5. Drug Interactions

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

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

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).

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 coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on Dapagliflozin
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 drugmetabolising 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 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.

4.6. Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

Pregnancy
Dapagliflozin is not recommended during the second and third trimesters of pregnancy.

Limited data with Dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown *[Reference FARXIGA US FDA label. Dated: Jan-2020]*.

Disease-associated maternal and/or embryofetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity

Lactation
There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin is not recommended while breastfeeding.

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation *[Reference FARXIGA US FDA label. Dated: Jan-2020]*.

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

Geriatric Use
No dosage change is recommended based on age. 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 Dapagliflozin had adverse reactions of hypotension.

Renal Impairment
Use of Dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD. Patients with renal impairment using Dapagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. Patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, receiving Dapagliflozin experienced bone fractures.

Hepatic Impairment
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.

4.7. Effects on Ability to Drive and Use Machines
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
The following important adverse reactions of Dapagliflozin:
- Hypotension
- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: 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), and not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections Urinary tract infection	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion Thirst	Diabetic ketoacidosis	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation Dry mouth		

Skin and subcutaneous tissue disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria Polyuria	Nocturia		
Reproductive system and breast disorders			Vulvovaginal pruritus Pruritus genital		
Investigations		Haematocrit increased Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[b]	Blood creatinine increased during initial treatment Blood urea increased Weight decreased		

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.

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.

Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia and hypotension.

Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of Dapagliflozin causes an increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline at Week 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2).

Increase in Hematocrit

Increases from baseline in mean hematocrit values were observed in Dapagliflozin -treated patients.

Increase in Low-Density Lipoprotein Cholesterol

Changes from baseline in mean lipid values were reported in Dapagliflozin -treated patients.

Decrease in Serum Bicarbonate

Concomitant therapy of Dapagliflozin with exenatide extended-release resulted in serum bicarbonate value of less than or equal to 13 mEq/L.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

In the event of overdose employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 downregulation of sympathetic activity.

5.2 Pharmacodynamic Properties

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of Dapagliflozin. Dapagliflozin 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 at Week 12. 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 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects *[Reference FARXIGA US FDA label. Dated: Jan-2020]*.

5.3 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. 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 pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [^{14}C]-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 [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.

Specific Populations

Renal Impairment

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic Impairment

In case of mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively.

Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

Pediatric

Pharmacokinetics in the pediatric population has not been studied.

Drug Interactions

In Vitro Assessment of Drug Interactions

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effects of Other Drugs on Dapagliflozin

No dose adjustments are recommended for dapagliflozin.

Effects of Dapagliflozin on Other Drugs

Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 **µg**/mL. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively *[Reference FARXIGA US FDA label. Dated: Jan-2020]*.

7. DESCRIPTION

Dapagliflozin belongs to the chemical class of Sodium-glucose co-transporter 2 (SGLT2) inhibitors. It is available as film-coated tablets containing 5 mg and 10 mg. Dapagliflozin is described chemically as (1S)-1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl] -D-glucitol. The molecular formula is $C_{21}H_{25}ClO_6$ and the molecular weight is 408.88. The structural formula is:

Dapagliflozin is available as off-white amorphous powder. Dapagliflozin is soluble in methanol and is insoluble in cyclohexane, water, pH 1.2 solution (hydrochloric acid buffer), pH 3 (solution acid phthalate buffer), pH 4.5 solution (acetate buffer), phosphate buffer (pH 6.8, 7.2, 8.0), 0.1N Hcl.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

10's Alu-Alu blister pack

8.3 Storage and Handling Instructions

Store below 30°C.

9. PATIENT COUNSELING INFORMATION

Advise the patient to read package insert.

Hypotension

Inform patients that symptomatic hypotension may occur with Dapagliflozin and advise them to contact their healthcare provider if they experience such symptoms. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of Dapagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness and labored breathing) occur, instruct patients to discontinue Dapagliflozin and seek medical attention immediately.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of Dapagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue Dapagliflozin use in those settings.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's Gangrene) have occurred with Dapagliflozin. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice.

Genital Mycotic Infections in Males (e.g., Balanitis)

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with Dapagliflozin. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

Pregnancy

Advise pregnant patients of the potential risk to a fetus with treatment with Dapagliflozin. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant.

Lactation

Advise patients that use of Dapagliflozin is not recommended while breastfeeding.

Laboratory Tests

Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine.

Missed Dose

If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of Dapagliflozin at the same time.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulations Division, Unit-06, Sy. No.
(Parts of), 745,811-813,824 & 825,
Burgul Village, Farooqnagar Mandal,
Ranga Reddy District, Pincode 509202,
Telangana State, India.

630018-00

11. DETAILS OF MANUFACTURING LICENCE NUMBER

Mfg. Lic. No.: TS/RR/2024-116346

12. DATE OF REVISION

May 2024.