Dapaone-M डापावन् एम
Dapagliflozin and Metformin Hydrochloride
Extended Release Tablets

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

PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.**
- **Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information.**
- **If lactic acidosis is suspected, discontinue the medication and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.**

1. GENERIC NAME
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg and 500 mg
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg and 1000 mg
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg and 500 mg
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg and 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg and 500 mg
Each film coated tablet Contains
Dapagliflozin------5 mg
Metformin Hydrochloride IP------500 mg
(As Extended Release)
Colour : Ferric Oxide Red USP-NF

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg and 1000 mg
Each film coated tablet Contains
Dapagliflozin------5 mg
Metformin Hydrochloride IP------1000 mg
(As Extended Release)
Colour : Ferric Oxide Red USP-NF

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg and 500 mg
Each film coated tablet Contains
Dapagliflozin------10 mg
Metformin Hydrochloride IP------500 mg
(As Extended Release)
Colour : Ferric Oxide Red USP-NF

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg and 1000 mg
Each film coated tablet Contains
Dapagliflozin------10 mg
Metformin Hydrochloride IP------1000 mg
(As Extended Release)
Colour : Ferric Oxide Red USP-NF

3. DOSAGE FORM AND STRENGTH
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets are Available in Formulation as 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, 10 mg/1000 mg.

4. CLINICAL PARTICULARS

4.1. Indications
Dapagliflozin+Metformin tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Dapagliflozin and Metformin is appropriate.

4.2. Posology and Method of Administration

Prior to Initiation of DAPAGLIFLOZIN+METFORMIN
- Assess renal function before initiating Dapagliflozin+Metformin therapy and periodically thereafter.
- In patients with volume depletion, correct this condition prior to initiation of Dapagliflozin+Metformin

Recommended Dosing
- Take Dapagliflozin+Metformin once daily in the morning with food.
- Swallow Dapagliflozin+Metformin tablets whole and never crush, cut, or chew. Occasionally, the inactive ingredients of Dapagliflozin+Metformin will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Individualize the starting dose of Dapagliflozin+Metformin based upon the patient's current regimen.
- To improve glycemic control for patients not already taking Dapagliflozin, the recommended starting dose for Dapagliflozin is 5 mg once daily.
- To reduce the risk of hospitalization for heart failure, the recommended dose for Dapagliflozin is 10 mg once daily.

For patients requiring a dose of 5 mg Dapagliflozin and 2000 mg Metformin extended- release, use two of the 2.5 mg Dapagliflozin/1000 mg Metformin extended-release tablets.

- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg Dapagliflozin and 2000 mg Metformin.
- Patients taking an evening dose of metformin XR should skip their last dose before starting Dapagliflozin+Metformin.

Patients with Renal Impairment
Dapagliflozin+Metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.

No dose adjustment for Dapagliflozin+Metformin is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

Dapagliflozin+Metformin is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2.

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue Dapagliflozin+Metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be

administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Dapagliflozin+Metformin if renal function is stable

4.3. Contraindications

Dapagliflozin+Metformin is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis.
- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to Metformin.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4. Special Warnings and Precautions for Use

Lactic acidosis
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 bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), 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 the 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 Dapagliflozin+Metformin.

In Dapagliflozin+Metformin -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (Metformin is dialyzable, with a 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 Dapagliflozin+Metformin and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function before initiating Dapagliflozin+Metformin, obtain an estimated glomerular filtration rate (eGFR).

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

Obtain an eGFR at least annually in all patients taking Dapagliflozin+Metformin. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of Dapagliflozin+Metformin with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs). Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Dapagliflozin+Metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Dapagliflozin+Metformin if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Dapagliflozin+Metformin should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Dapagliflozin+Metformin.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Dapagliflozin+Metformin.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin- associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Dapagliflozin+Metformin in patients with clinical or laboratory evidence of hepatic disease.

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+Metformin 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. Dapagliflozin+Metformin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin+Metformin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidosis associated with Dapagliflozin+Metformin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin+Metformin 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 many of the postmarketing reports, and particularly 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+Metformin, 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+Metformin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin+Metformin 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+Metformin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin+Metformin 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+Metformin and monitored periodically thereafter. Use of Dapagliflozin+Metformin is not recommended when the eGFR is less than 45 mL/min/1.73 m^2. Dapagliflozin+Metformin is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Dapagliflozin. 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 (e.g., sulfonylurea) are known to cause hypoglycemia. Dapagliflozin+Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Dapagliflozin+Metformin.

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. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Dapagliflozin+Metformin 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+Metformin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Vitamin B_{12} Concentrations
In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2- to 3-year intervals in patients on Dapagliflozin+Metformin and manage any abnormalities.

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.

4.5. Drug Interactions

Positive Urine Glucose Test

Dapagliflozin
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

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

Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Dapagliflozin+Metformin may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients**.**

Drugs that Reduce Metformin Clearance
Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin+Metformin.

Drugs Affecting Glycemic Control

Metformin
Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Dapagliflozin+Metformin, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Dapagliflozin+Metformin, observe the patient closely for hypoglycemia.

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

Pregnancy
There are no data from the use of medication or Dapagliflozin in pregnant women. Studies in rats treated with Dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Breast-feeding
It is unknown whether this medicinal product or Dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded. This medicinal product should not be used while breast-feeding.

Fertility
The effect of this medicinal product or Dapagliflozin on fertility in humans has not been studied. In male and female rats, Dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity.

Elderly
No Dapagliflozin+Metformin dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Paediatric population
Safety and effectiveness of Dapagliflozin+Metformin in pediatric patients under 18 years of age have not been established.

Renal impairment
Dapagliflozin

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.

Dapagliflozin was evaluated in two glycemic control studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2, and an eGFR of 30 to less than 60 mL/min/1.73 m^2). The safety profile of Dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m2 was similar to the general population of patients with type 2 diabetes. Although patients in the Dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation. Patients with renal impairment using Dapagliflozin for glycemic

4.7.Effects on Ability to Drive and Use Machines
Dapagliflozin+metformin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8.Undesirable Effects
Table 1 shows common adverse reactions associated with the use of Dapagliflozin and metformin. These adverse reactions were not present at baseline, occurred more commonly on Dapagliflozin and metformin than on placebo, and occurred in at least 2% of patients treated with either Dapagliflozin 5 mg or Dapagliflozin 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin

Adverse Reaction	**Dapagliflozin 5 mg and Metformin**	**Dapagliflozin 10 mg and Metformin**
Female genital mycotic infections*	9.4	9.3
Nasopharyngitis	6.3	5.2
Urinary tract infections†	6.1	5.5
Diarrhea	5.9	4.2
Headache	5.4	3.3
Male genital mycotic infections‡	4.3	3.6
Influenza	4.1	2.6
Nausea	3.9	2.6
Back pain	3.4	2.5
Dizziness	3.2	1.8
Cough	3.2	1.4
Constipation	2.9	1.9
Dyslipidemia	2.7	1.5
Pharyngitis	2.7	1.5

Increased urination§	2.4	2.6
Discomfort with urination	2.2	1.6

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial.

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.

‡ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, and balanoposthitis.

§ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

Metformin
In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Additional adverse reactions have been identified. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dapagliflozin
- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

Metformin
- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

Description of selected adverse reactions

Volume Depletion
Dapagliflozin causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension)

Hypoglycemia
Severe events of hypoglycemia were reported in patients treated with Dapagliflozin 10 mg.

Genital Mycotic Infections
Genital mycotic infections were more frequent with Dapagliflozin treatment. Infections were more frequently reported in females than in males. The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection.

Hypersensitivity Reactions
Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with Dapagliflozin treatment. If hypersensitivity reactions occur, discontinue use of Dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis
Events of diabetic ketoacidosis (DKA) patients in the Dapagliflozin-treated group. The events were evenly distributed over the study period.

Laboratory Tests
Increases in Serum Creatinine and Decreases in eGFR

Dapagliflozin
Initiation of Dapagliflozin causes an increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, the serum creatinine and 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

Dapagliflozin
Increases from baseline in mean hematocrit values were observed in Dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed.

Increase in Low-Density Lipoprotein Cholesterol Dapagliflozin

Dapagliflozin

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in Dapagliflozin-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and Dapagliflozin 10 mg groups, respectively. In the DECLARE study, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in Dapagliflozin 10 mg-treated and the placebo groups, respectively.

Vitamin B12 Concentrations

Metformin
A decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.

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

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.

Metformin
Overdose of Metformin has occurred, including ingestion of amounts >50 grams. 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 overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action
Dapagliflozin+Metformin combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Dapagliflozin, a sodium- glucose cotransporter 2 (SGLT2) inhibitor, and Metformin, a biguanide.

Dapagliflozin
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.

Metformin
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

5.2 Pharmacokinetic Properties

Dapagliflozin+Metformin
The administration of Dapagliflozin+Metformin in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both Dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of Dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as Dapagliflozin+Metformin combination tablets.

Absorption

Dapagliflozin
Following 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.

Metformin
Following a single oral dose of metformin extended-release, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on Cmax and Tmax of metformin.

Distribution

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

Metformin
Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate- release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin
The metabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O- glucuronide accounted for 61% of a 50 mg [14C]-Dapagliflozin dose and is the predominant drug- related component in human plasma.

Metformin
Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin
Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-Dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for Dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.

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.

Pharmacokinetic/pharmacodynamic relationship(s)

Special populations

Renal Impairment
Dapagliflozin
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.

Metformin
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.

Hepatic Impairment

Dapagliflozin
In patients with mild and moderate hepatic impairment (Child-Pugh classes 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-Pugh class C), mean Cmax and AUC of Dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Metformin
No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Geriatric

Dapagliflozin
Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Metformin
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric
Pharmacokinetics of Dapagliflozin+Metformin in the pediatric population has not been studied.

Gender

Dapagliflozin
Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Metformin
Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender.

Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

Dapagliflozin
Based on a population pharmacokinetic analysis, race (White, Black, or Asian) does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Metformin
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body Weight

Dapagliflozin
Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Drug Interactions
Specific pharmacokinetic drug interaction studies with DAPAGLIFLOZIN+METFORMIN have not been performed, although such studies have been conducted with the individual Dapagliflozin and metformin components.

6. NONCLINICAL PROPERTIES

Dapagliflozin+Metformin
No animal studies have been conducted with Dapagliflozin+Metformin to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with Dapagliflozin and metformin individually.

Dapagliflozin
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.

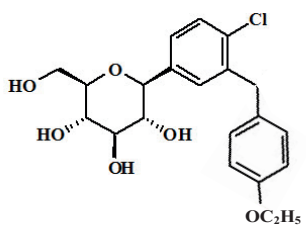
Metformin
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

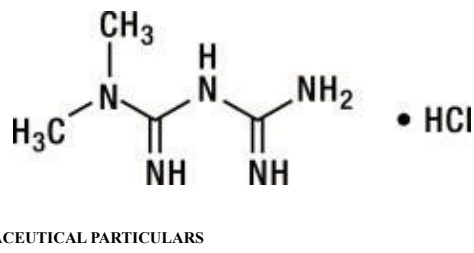
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human dose based on body surface area comparisons.

7. DESCRIPTION
Dapagliflozin+Metformin extended release tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: Dapagliflozin and metformin hydrochloride.

Dapagliflozin
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:



Metformin hydrochloride
Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 2.8-11.5. The pH of a 1% aqueous solution of metformin hydrochloride is 6-7. The structural formula is:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
None

8.2 Packing Information
10's Blister.

8.3 Storage and Handling Instructions
Store below 30°C.

9. PATIENT COUNSELING INFORMATION
Advise the patient to read package insert.

10. DETAILS OF MANUFACTURER & LICENCE NUMBER WITH STRENGTH

Strength: 5 mg and 500 mg
Manufactured by: **MSN Laboratories Private Limited,**
Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, India.
Mfg. Lic. No.: 38/MD/AP/2007/F/CC

Strength: 5 mg and 1000 mg, 10 mg and 500 mg, 10 mg and 1000 mg
Manufactured by: **MSN Laboratories Private Limited,**
Formulation Division, Unit-II, Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal), Rangareddy (District) - 509 228,
Telangana, India.
Mfg. Lic. No.: 5/MN/TS/2014/F/G

Packed at: **MSN Laboratories Private Limited,**
Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, India.
Mfg. Lic. No.: 38/MD/AP/2007/F/CC

11. DATE OF REVISION
February 2021

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