**Summary of Product Characteristics**

**1. Name of the medicinal product**
**DAPAMET 5/500,5/1000,10/500& 10/1000mg**
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg and 10 mg/1000 mg

**2. Qualitative and quantitative composition**
**Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/500 mg**
Each Film Coated Tablet Contains
Dapagliflozin 5 mg
Metformin Hydrochloride USP
500mg (As Extended Release)
**Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg/500 mg**
Each Film Coated Tablet Contains
Dapagliflozin 10 mg
Metformin Hydrochloride USP
500mg (As Extended Release)
**Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/1000 mg**
Each Film Coated Tablet Contains
Dapagliflozin 5 mg
Metformin Hydrochloride USP
1000mg (As Extended Release)
**Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg/1000 mg**
Each Film Coated Tablet Contains
Dapagliflozin 10 mg
Metformin Hydrochloride USP
1000mg (As Extended Release)
Product Contains Lactose.

For full list of excipients, see section 6.1

**3. Pharmaceutical form Film-coated tablet.**
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/500 mg

Light pink coloured, capsule shaped biconvex, film-coated tablets debossed with "MD6" on one side and plain on other side.
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg/500 mg
Brown coloured, Capsule shaped, biconvex, film-coated tablets debossed with "MD7" on one side and plain on other side.
Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/1000 mg

Light pink coloured, oval shaped biconvex, film-coated tablets debossed with "MD5" on one side and plain on other side

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 5 mg/1000 mg

Light pink coloured, oval shaped biconvex, film-coated tablets debossed with "MD5" on one side and plain on other side.

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 10 mg/1000 mg Brown coloured, Oval shaped, biconvex, film-coated tablets debossed with "MD4" on one side and plain on other side.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

**Limitations of Use**

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

### 4.2 Posology and method of administration

This medicinal product should be prescribed by an appropriate healthcare professional. Prior to Initiation of Dapagliflozin and Metformin Hydrochloride Extended Release Tablets

- Assess renal function before initiating Dapagliflozin and Metformin Hydrochloride Extended
- Release Tablets and periodically thereafter
- In patients with volume depletion, correct this condition prior to initiation of Dapagliflozin and Metformin Hydrochloride Extended Release Tablets
- Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is for oral use.
- Take Dapagliflozin and Metformin Hydrochloride Extended Release Tablets once daily in the morning with food. The tablets should be taken whole and never crush, cut, or chew
- Individualize the starting dose of Dapagliflozin and Metformin Hydrochloride Extended
- Release Tablets 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 HCl extended
- release, use two of the 2.5 mg dapagliflozin/1000 mg metformin HCl 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 HCl.
- Patients taking an evening dose of metformin ER should skip their last dose before starting
- Dapagliflozin and Metformin Hydrochloride Extended Release Tablets

**Patients with Renal Impairment**

Dapagliflozin and Metformin Hydrochloride Extended Release Tablet is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2 .

No dose adjustment for Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m2. Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is not recommended in patients with an eGFR below 45 mL/min/1.73 m2.

**Discontinuation for Iodinated Contrast Imaging Procedures**

Discontinue Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets if renal function is stable

**4.3 Contraindications**

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 HCl

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 foruse 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 and Metformin Hydrochloride Extended Release Tablets.

In Dapagliflozin and Metformin Hydrochloride treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl 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 and Metformin Hydrochlorid 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 include

. Before initiating Dapagliflozin and Metformin Hydrochloride Extended Release Tablets, obtain an estimated glomerular filtration rate (eGFR).

. Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2

. Obtain an eGFR at least annually in all patients taking Dapagliflozin and Metformin Hydrochloride Extended Release Tablets. 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 and Metformin Hydrochloride Extended Release Tablets with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function,

result in significant hemodynamic change, Therefore, consider more frequent monitoring of patients.interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs).

**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 and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride 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 and Metformin Hydrochloride Extended Release Tablets

**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 and Metformin Hydrochloride Extended Release Tablets.

**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 and Metformin

Hydrochloride Extended Release Tablets. 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 m2), elderly

patients, or patients on loop diuretics. Before initiating Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 and. Metformin Hydrochloride Extended Release Tablet is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with Dapagliflozin And Metformin Hydrochloride Extended Release Tablets 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 And Metformin Hydrochloride Extended Release Tablets may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets , 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 and Metformin Hydrochloride Extended Release Tablets for at least 3 days prior to surgery Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 Metformin Hydrochloride Extended Release Tablet and monitored periodically thereafter.Use of Dapagliflozin and Metformin Hydrochloride Extended Release Tablet is not recommended when the eGFR is less than 45 mL/min/1.73 $m^2$. Dapagliflozin and Metformin Hydrochloride Extended Release Tablet 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 and Metformin Hydrochloride Extended Release Tablet 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 and Metformin Hydrochloride Extended Release Tablet**.**

**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 and Metformin Hydrochloride Extended Release Tablet presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along 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 and Metformin Hydrochloride Extended Release Tablet, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

**Vitamin B12 Concentrations.**

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2- to 3-year intervals in patients on Dapagliflozin and Metformin Hydrochloride Extended Release Tablet 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 Interaction with other medicinal products and other forms ofinteraction 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 and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets

**Drugs Affecting Glycemic Control**

Metformin HCl

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 and Metformin Hydrochloride Extended Release Tablets, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Dapagliflozin and Metformin Hydrochloride Extended Release Tablets, observe the patient closely for hypoglycemia

## 4.6 Fertility, pregnancy and lactation

**Pregnancy Pregnancy**

Risk Summary

Based on animal data showing adverse renal effects, Dapagliflozin and Metformin Hydrochloride Extended Release Tablets is not recommended during the second and third trimesters of pregnancy.

Limited data with Dapagliflozin and Metformin Hydrochloride Extended Release Tablets or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a

clear association with metformin and major birth defect or miscarriage risk. 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Clinical Considerations**

*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**

Risk Summary

There is no information regarding the presence of Dapagliflozin and Metformin Hydrochloride Extended Release Tablets or dapagliflozin in human milk the effects on the breastfed infant, or the effects on milk production.

Risk Summary

There is no information regarding the presence of Dapagliflozin and Metformin Hydrochloride Extended Release Tablets or dapagliflozin in human milk the effects on the breastfed infant, or the effects on milk production.

Limited published studies report that metformin is present in human milk . However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Dapagliflozin is present in the milk of lactating rats . However, due to species specific differences in lactation physiology, the

clinical relevance of these data are not clear. 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 and Metformin Hydrochloride Extended Release Tablets is not recommended while breastfeeding.

**Females and Males of Reproductive Potential**

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some an ovulatory woman.

## 4.7 Effects on ability to drive and use machines

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Lactic Acidosis
Hypotension
Ketoacidosis
Acute Kidney Injury
Urosepsis and Pyelonephritis
Use with Medications Known to Cause Hypoglycemia
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) Vitamin B12 Concentrations
Genital Mycotic Infections

**Clinical Trials Experience**

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 clinical practice. *Dapagliflozin and Metformin HCl*

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate- or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combina-tion with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metfor-min, 2 initial combination with metformin studies, and 2 studies of patients with CVD and type 2 diabeteswho received their usual treatment [with metformin as background therapy]). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) the population was male; 88% White, 6% Asian, and 3% Black

or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

The overall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treated with dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformin group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinua-tion and reported in at least 3 patients treated with dapagliflozin 10 mg and metformin were renal impairment (0.7%), increased blood creatinine (0.2%), decreased renal creatinine clearance (0.2%), and urinary tract infection (0.2%).

Table 1 shows common adverse reactions associated with the use of Dapagliflozin and Met-formin. 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** | **% of Patients** | | |
|---|---|---|---|
| | **Pool of 8 Placebo-Controlled Studies** | | |
| | **Placebo and Metformin** | **Dapagliflozin 5 mg and Metformin** | **Dapagliflozin 10 mg and Metformin** |
| | **N=1185** | **N=410** | **N=983** |
| Female genital mycotic infections* | 1.5 | 9.4 | 9.3 |
| Nasopharyngitis | 5.9 | 6.3 | 5.2 |
| Urinary tract infections† | 3.6 | 6.1 | 5.5 |
| Diarrhea | 5.6 | 5.9 | 4.2 |
| Headache | 2.8 | 5.4 | 3.3 |
| Male genital mycotic infections‡ | 0 | 4.3 | 3.6 |
| Influenza | 2.4 | 4.1 | 2.6 |
| Nausea | 2.0 | 3.9 | 2.6 |
| Back pain | 3.2 | 3.4 | 2.5 |
| Dizziness | 2.2 | 3.2 | 1.8 |
| Cough | 1.9 | 3.2 | 1.4 |
| Constipation | 1.6 | 2.9 | 1.9 |

| | | | |
|---|---|---|---|
| Dyslipidemia | 1.4 | 2.7 | 1.5 |
| Pharyngitis | 1.1 | 2.7 | 1.5 |
| Increased urination§ | 1.4 | 2.4 | 2.6 |
| Discomfort with urination | 1.1 | 2.2 | 1.6 |

* Genital mycotic infections include the following adverse reactions, listed in order of frequencyreported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).

† 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 frequencyreported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, and balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

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

*Metformin HCl*

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nau-sea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the pa-tients treated with metformin extended-release.

**Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg for Glycemic Control**

*Dapagliflozin*

The data in Table 2 are derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies dapagliflozin was used as monotherapy, and in 8 studies dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with met-formin.

These data reflect exposure of 2338 patients to dapagliflozin with a mean exposure dura-tion of 21 weeks. Patients received placebo (N=1393), dapagliflozin 5 mg (N=1145), or dapagliflozin 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a

mean HbA1c of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of pa- tients (mean eGFR 86 mL/min/1.73 $m^2$).

Table 2 shows common adverse reactions associated with the use of dapagliflozin. These ad- verse reactions were not present at baseline, occurred more commonly on dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

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

| **Adverse Reaction** | **% of Patients** | | |
|---|---|---|---|
| | **Pool of 12 Placebo-Controlled Studies** | | |
| | **Placebo N=1393** | **Dapagliflozin 5 mg N=1145** | **Dapagliflozin 10 mg N=1193** |
| Female genital mycotic infections* | 1.5 | 8.4 | 6.9 |
| Nasopharyngitis | 6.2 | 6.6 | 6.3 |
| Urinary tract infections† | 3.7 | 5.7 | 4.3 |
| Back pain | 3.2 | 3.1 | 4.2 |
| Increased urination‡ | 1.7 | 2.9 | 3.8 |
| Male genital mycotic infections§ | 0.3 | 2.8 | 2.7 |
| Nausea | 2.4 | 2.8 | 2.5 |
| Influenza | 2.3 | 2.7 | 2.3 |
| Dyslipidemia | 1.5 | 2.1 | 2.5 |
| Constipation | 1.5 | 2.2 | 1.9 |
| Discomfort with urination | 0.7 | 1.6 | 2.1 |
| Pain in extremity | 1.4 | 2.0 | 1.7 |

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, dapagliflozin 5 mg=581, dapagliflozin 10 mg=598).

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

‡ Increased urination includes the following adverse reactions, listed in

order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ 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 male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

**Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg for Glycemic Control**

Dapagliflozin 10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 pl cebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 $m^2$).

**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) for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3

**Table 3: Adverse Reactions of Volume Depletion* in Clinical Studies with Dapagliflozin**

| | **Pool of 12 Placebo Controlled** | | | **Pool of 13 Placebo** | | **DECLARE Study** | |
|---|---|---|---|---|---|---|---|
| | **Placebo** | **Dapagliflozin 5 mg** | **Dapagliflozin 10 mg** | **Placebo** | **Dapagliflzin 1 mg** | **Placebo** | **Dapagliflozin 10 mg** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Overall population N (%)** | N=1393 5 (0.4%) | N=1145 7 (0.6%) | N=1193 9 (0.8%) | N=2295 17 (0.7%) | N=2360 27 (1.1%) | N=8569 207 (2.4%) | N=8574 213 (2.5%) |
| **Patient Subgroup n (%)** | | | | | | | |
| Patients on Loop diuretics | =55 1 (1.8%) | n=40 0 | n=31 3 (9.7%) | 267 4 (1.5%) | 236 6 (2.5%) | =934 57 (6.1%) | =866 57 (6.6%) |
| Patients with moderate renal impairment with eGFR 30 and <60 mL/min | 107 2 (1.9%) | 107 1 (0.9%) | n=89 1 (1.1%) | 268 4 (1.5%) | 265 5 (1.9%) | =658 30 (4.6%) | =604 35 (5.8%) |
| Patients 65 years of age | n=276 1 (0.4%) n | n=216 1 (0.5%) n | n=204 3 (1.5%) n | n=711 6 (0.8%) n | n=665 11 (1.7%) n | n=39 50 121 (3.1%) n | n=3948 117 (3.0%) |

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

**Hypoglycemia**

The frequency of hypoglycemia by study *[see Clinical Studies (14.1)]* is shown in Table 4. Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin. Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Clinical Studies

| | **Placebo** | **Dapagliflozin 5 mg** | **Dapagliflozin 10 mg** |
|---|---|---|---|
| **Add-on to Metformin (24 weeks)** | **N=137** | **N=137** | **N=135** |
| Severe [n (%)] | 0 | 0 | 0 |
| Glucose < 54 mg/dL [n (%)] | 0 | 0 | 0 |
| **Add-on to DPP4 inhibitor (with or without Metformin) (24 weeks)** | **N=226** | **–** | **N=225** |
| Severe [n (%)] | 0 | – | 1 (0.4) |
| Glucose < 54 mg/dL [n (%)] | 1 (0.4) | – | 1 (0.4) |
| **Add-on to Insulin with or without other OADs‡ (24 weeks)** | **N=197** | **N=212** | **N=196** |
| Severe [n (%)] | 1 (0.5) | 2 (0.9) | 2 (1.0) |
| Glucose < 54 mg/dL [n (%)] | 43 | 55 | 45 |

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose < 54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with dapagliflozin 10 mg and 83 (1.0%) out of 8569 patients treated with placebo.

**Genital Mycotic Infections**

Genital mycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of pa- tients treated with dapagliflozin 10 mg. Infections were more frequently reported in females than in males (see Table 2). 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 during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively). In the DE- CLARE study, serious genital mycotic infections were reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Genital mycotic infec- tions that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo.

**Hypersensitivity Reactions**

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment. Across the clinical program, serious anaphylactic reactions and se-vere cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapagliflozin-treated patients. If hypersensitivity reactions oc-cur, discontinue use of dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

**Ketoacidosis**

In the DECLARE study, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and

in 12 out of 8569 patients in the placebo 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 pa- tients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 $m^2$)

***Increase in Hematocrit***

*Dapagliflozin*

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit val-ues were observed in dapagliflozin-treated patients starting at W*eek 1* and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients.

***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 HCl*

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previ-ously normal serum vitamin B12 levels was observed in approximately 7% of patients.

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

## 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 HCl**

Overdose of metformin HCl 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 over dosage is suspected

## 5. Pharmacological properties

Mechanism of Action

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodiumglucose cotransporter 2 (SGLT2) inhibitor, and metformin HCl, 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 HCl*

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

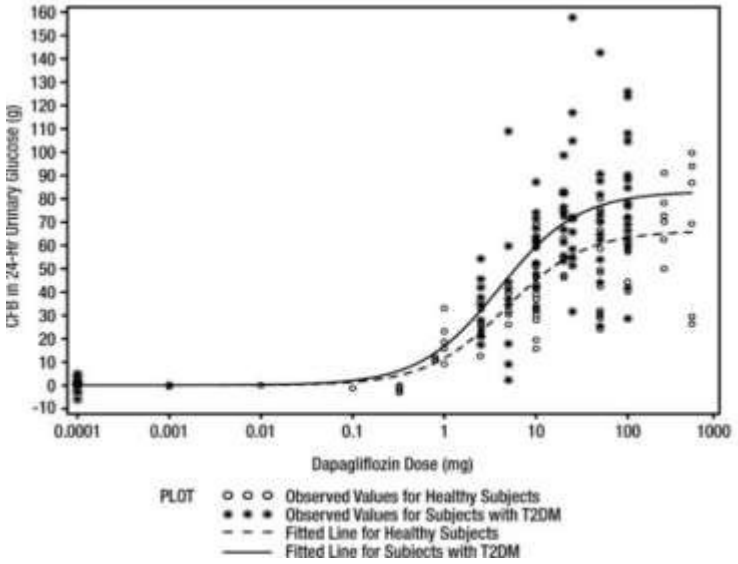
## 5.1 Pharmacodynamic properties General

### Dapagliflozin

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 (see Figure1). 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. 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.

**Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)**



**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.

## 5.2 Pharmacokinetic properties

*Dapagliflozin and Metformin Hydrochloride Extended Release Tablets.*

The administration of Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 and Metformin Hydrochloride Extended Release Tablets 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 fastedstate. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

*Metformin HCl*

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 HCl*

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 HCl*

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excretedunchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion dapagliflozin dose and is the predominant drug- related component in human plasma.

*Metformin HCl*

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 Hcl*

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 maybe a compartment of distribution.

**Specific 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

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 HCl*

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 HCl*

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 and Metformin Hydrochloride Extended Release Tablets 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 HCl*

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19,females=16). 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 HCl*

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 and Metformin Hydrochloride Extended Release Tablets have not been performed, although such studies have been conducted with the individual Dapagliflozin and Metformin components.

unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

***Effects of Other Drugs on Metformin***

Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

| **Coadministered Drug (Dose Regimen)*** | **Metformin (Dose Regimen)*** | **Metformin Change† in AUC‡** |
|---|---|---|
| **No dosing adjustments required for the following:** | | |
| Glyburide (5 mg) | 850 mg | § ↓9% |
| Furosemide (40 mg) | 850 mg | § ↑15% |
| Nifedipine (10 mg) | 850 mg | ↑9% |
| Propranolol (40 mg) | 850 mg | ↓10% |
| Ibuprofen (400 mg) | 850 mg | § ↑5% |
| Drugs eliminated by renal tubular secretion may increase the accumulation of metformin[see Drug Interactions (7.4)]. | | |
| Cimetidine (400 mg) | 850 mg | ↑40% |

All metformin and coadministered drugs were given as single doses.
† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate theexposure increase and decrease, respectively.
‡AUC = AUC(INF).
§Ratio of arithmetic means.

**Effects of Metformin on Other Drugs**

**Effect of Metformin on Coadministered Drug Systemic Exposure**

| Coadministered Drug (Dose Regimen)* | Metformin (Dose Regimen)* | Coadministered Drug Change† in AUC‡ |
|---|---|---|
| No dosing adjustments required for the following: | | |
| Glyburide (5 mg) | 850 mg | ↓22%§ |
| Furosemide (40 mg) | 850 mg | ↓12%§ |
| Nifedipine (10 mg) | 850 mg | ↑10%¶ |
| Propranolol (40 mg) | 850 mg | ↑1%¶ |
| Ibuprofen (400 mg) | 850 mg | ↓3%# |
| Cimetidine (400 mg) | 850 mg | ↓5%¶ |

All metformin and coadministered drugs were given as single doses.
† Percent change (with/without coadministered drug and no change = 0%);
↑ and ↓ indicate the exposure increase and decrease, respectively.
‡AUC = AUC(INF) unless otherwise noted.
§Ratio of arithmetic means, p-value of difference <0.05.
¶AUC(0-24 hr) reported.
#Ratio of arithmetic means.

**Effects of Other Drugs on Dapagliflozin**
**Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure**

| **Coadministered Drug (Dose Regimen)*** | **Dapagliflozin (Dose Regimen*)** | Dapagliflozin **Change† in AUC‡** |
|---|---|---|
| No dosing adjustments required for the following: | | |
| Oral Antidiabetic Agents | | |
| Metformin (1000 mg) | 20 mg | ↓1% |
| Pioglitazone (45 mg) | 50 mg | 0% |
| Sitagliptin (100 mg) | 20 mg | ↑8% |
| Glimepiride (4 mg) | 20 mg | ↓1% |
| Voglibose (0.2 mg three times | 10 mg | ↑1% |

**Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure**

| **Coadministered Drug (Dose Regimen)*** | **Dapagliflozin (Dose Regimen*)** | Dapagliflozin **Change† in AUC‡** |
|---|---|---|
| No dosing adjustments required for the following: | | |
| daily) | | |
| Other Medications | | |
| Hydrochlorothiazide (25 mg) | 50 mg | ↑7% |
| Bumetanide (1 mg) | 10 mg once daily for 7 days | ↑5% |
| Valsartan (320 mg) | 20 mg | ↑2% |
| Simvastatin (40 mg) | 20 mg | ↓1% |
| Anti-infective Agent | | |
| Rifampin (600 mg once daily for 6 days) | 10 mg | ↓22% |
| Nonsteroidal Anti-inflammatory Agent | | |

| | | |
|---|---|---|
| Mefenamic Acid (loading dose of 500 mg<br>followed by 14 doses of 250 mg every 6 | 10 mg | ↑51% |

Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%);
↑ and ↓ indicate the exposure increase and decrease, respectively.
‡AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

**Effects of Dapagliflozin on Other Drugs**

**Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

| **Coadministered Drug (Dose Regimen)*** | **Dapagliflozin (Dose Regimen*)** | **Coadministered Drug** |
|---|---|---|
| | | **Chan † in AU ‡** |
| No dosing adjustments required for the following: | | |
| Oral Antidiabetic Agents | | |
| Metformin (1000 mg) | 20 mg | 0% |
| Pioglitazone (45 mg) | 50 mg | 0% |
| Sitagliptin (100 mg) | 20 mg | ↑1% |

**Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

| **Coadministered Drug (Dose Regimen)*** | **Dapagliflozin (Dose Regimen *** | **Coadministered Drug** |
|---|---|---|
| | | **Chan † in AU ‡** |
| Glimepiride (4 mg) | 20 mg | ↑13% |
| Other Medications | | |
| Hydrochlorothiazide (25 mg) | 50 mg | ↓1% |
| Bumetanide (1 mg) | 10 mg once daily for 7 days | ↑13% |
| Valsartan (320 mg) | 20 mg | ↑5% |
| Simvastatin (40 mg) | 20 mg | ↑19% |
| Digoxin (0.25 mg) | 20 mg loading dose then 10 mg once daily for 7 days | 0% |
| Warfarin (25 mg) S-warfarin R-warfarin | 20 mg loading dose then 10 mg once daily for 7 days | ↑3%<br>↑6% |

Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡ AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multipledoses.

### 5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets No animal studies have been conducted with Dapagliflozin and Metformin Hydrochloride Extended Release Tablets 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 HCl*

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.

## 6.Pharmaceutical particulars

### 6.1 List of excipients

Sodium Carboxy Methyl Cellulose, Isopropyl Alcohol, Hypromellose, Microcrystalline Cellulose (PH 102), Magnesium Stearate, Sodium Lauryl Sulfate, Crospovidone, Lactose Monohydrate, Silicon Dioxide, Iron Oxide Sicovit Red 30 E 172 and Purifed Water

**Coating Material**

**For 5mg/500 mg and 5 mg/1000 mg**

**Opadry II Purple 85F500030(**Polyvinyl alcohol-part. Hydrolysed, Titanium dioxide, Macrogol, Talc, Iron oxide red, Ferrosoferric oxide)

**Opadry II White 85F18422** (Polyvinyl alcohol-part. Hydrolysed, Titanium dioxide, Macrogol, Talc)

**For 10 mg/500 mg and 10 mg/1000 mg**

**Opadry II Purple 85F500030** (Polyvinyl alcohol-part. Hydrolysed, Titanium dioxide, Macrogol, Talc, Iron oxide red, Ferrosoferric oxide)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 Months.

### 6.4 Special precautions for storage

Do not store above 30°C. Keep out of the sight and reach of children.

### 6.5 Nature and contents of container

10's PVC/Aclar-Alu blister pack and HDPE container.

Commercial supply will be based on market

requirements

**6.6 Special precautions for disposal**

Not Applicable.

**7. Marketing Authorisation Holder MSN Laboratories Private Limited, MSN HOUSE",**

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**Manufacture By**

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**8. MARKETING AUTHORISATION NUMBER(S)**

H2025/CTD11762/22766

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

July 2023.

**10. DATE OF REVISION OF THE TEXT**

18th August 2026