1.NAME OF THE MEDICINAL PRODUCT

Dapagliflozinand Metformin Hydrochloride Extended Release tablets

DAPZIN5 M

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Eachfilm coated tablet contains:

Dapagliflozin ..... …….5 mg

MetforminHydrochloride USP ..... 500 mg

Excipientwith known effect: Each film-coated tablet contains 25.285 mg of lactose anhydrous. Forthe full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Filmcoated tablets

Orangecolored oval shaped, beveled edge, biconvex, film coated tablets de bossed with "DM 1" on one faceand plain on other face with an approximate dimension of 16.65 mm in length, 8.15 mm in width & 7.20mm in thickness.

4.CLINICAL PARTICULARS

4.1Therapeutic indications:

Dapagliflozinand Metformin HCl Extended Release tablets is indicated as an adjunct to diet and exercises to improve glycaemic control in adults with type 2 diabetes mellitus.

Dapagliflozinis indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetesmellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

Limitationsof Use

Dapagliflozinand Metformin HCl Extended Release tablets is not recommended for patients with type 1 diabetesmellitus or diabetic ketoacidosis.

4.2Posology and method of administration

Prior to I nitiation of Dapagliflozin and M etform in HCl Ex tended Release tablets

Assessrenal function before initiating Dapagliflozin and Metformin HCl Extended Release therapy and periodicallythereafter.

- Inpatients with volume depletion, correct this condition prior to initiation of Dapagliflozin and MetforminHCl Extended Release tablets.

Recomm ended Dosage

- TakeDapagliflozin and Metformin HCl Extended Release tablets once daily in the morning with food.
- SwallowDapagliflozin and Metformin HCl Extended Release tablets whole and never crush, cut, or chew.Occasionally, the inactive ingredients of Dapagliflozin and Metformin HCl Extended Release tabletswill be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Individualizethe starting dose of Dapagliflozin and Metformin HCl Extended Release tablets based uponthe patient's current regimen.
- Toimprove glycaemic control for patients not already taking dapagliflozin, the recommended starting dosefor dapagliflozin is 5 mg once daily.
- Toreduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mgonce daily.
- Forpatients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl Extended Release, usetwo of the 2.5 mg dapagliflozin/1000 mg metformin HCl Extended Release tablets.
- Dosingmay be adjusted based on effectiveness and tolerability while not exceeding the maximum recommendeddaily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.
- Patientstaking an evening dose of metformin XR should skip their last dose before starting Dapagliflozinand Metformin HCl Extended Release tablets.

Patients w ith Renal I m pairm ent

Dapagliflozinand Metformin Extended Release tablets is contraindicated in patients with an estimated glomerularfiltration rate (eGFR) below 60 mL/min/1.73 m2

Nodose adjustment for Dapagliflozin and Metformin HCl Extended-release is needed in patients with an eGFRgreater than or equal to 45 mL/min/1.73 m2.

Dapagliflozinand Metformin HCl Extended-release is not recommended in patients with an eGFR below 45mL/min/1.73 m2.

Discontinuationfor I odinated Contrast I m aging P rocedures

DiscontinueDapagliflozin and Metformin Extended Release tablets at the time of, or prior to, an iodinated contrastimaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in

patientswho will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imagingprocedure; restart Dapagliflozin and Metformin Extended Release tablets if renal function is stable.

4.3Contraindications:

Dapagliflozinand Metformin Extended Release tablets are contraindicated in patients with:

- Moderateto severe renal impairment (eGFR below 60 mL/min/1.73 m 2), end stage renal disease or patientson dialysis
- Historyof a serious hypersensitivity reaction to Dapagliflozin or hypersensitivity to Metformin hydrochloride
- Acuteor chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
- Diabeticketoacidosis should be treated with insulin.

4.4Special warning and precautions for use

LacticAcidosis

Therehave been post-marketing cases of Metformin-associated lactic acidosis, including fatal cases. Thesecases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias,abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotensionand resistant bradyarrhythmia have occurred with severe acidosis.

Metformin-associatedlactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter),anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvateratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactateincreasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients atrisk.

Ifmetformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptlyin a hospital setting, along with immediate discontinuation of Dapagliflozin and Metformin ExtendedRelease tablets.

InDapagliflozin and Metformin Extended Release tablets -treated patients with a diagnosis or strong suspicionoflacticacidosis,promptHemodialysisisrecommendedtocorrectheacidosisandremove accumulatedmetformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute undergood hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educatepatients and their families about the symptoms of lactic acidosis and if these symptoms occur instructthem to discontinue Dapagliflozin and Metformin Extended Release tablets and report these symptomsto their healthcare provider.

Foreach of the known and possible risk factors for Metformin-associated lactic acidosis, recommendationsto reduce the risk of and manage Metformin-associated lactic acidosis are provided below:

RenalImpairment: The post marketing metformin-associated lactic acidosis cases primarily occurred in patientswith significant renal impairment. The risk of metformin accumulation and metformin-associated lacticacidosis increases with the severity of renal impairment because metformin is substantially excreted bythe kidney. Clinical recommendations based upon the patient's renal function include.

- Beforeinitiating Dapagliflozin and Metformin Extended Release tablets, obtain an estimated glomerularfiltration rate (eGFR).
- Dapagliflozinand Metformin Extended Release tablets is contraindicated in patients with an eGFR less than60 mL/minute/1.73 m2
- Obtainan eGFR at least annually in all patients taking Dapagliflozin and Metformin Extended Release tablets.In patients at increased risk for the development of renal impairment (e.g., the elderly), renal functionshould be assessed more frequently.

Hypotension

Dapagliflozincauses 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), elderlypatients, or patients on loop diuretics.

Beforeinitiating Dapagliflozin and Metformin Extended Release tablets in patients with one or more of thesecharacteristics, volume status should be assessed and corrected. Monitor for signs and symptoms ofhypotension after initiating therapy.

Ketoacidosis

Reportsof ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identifiedin post marketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium-glucoseco transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis

havebeen reported in patients taking dapagliflozin. Dapagliflozin and Metformin Extended Release tablets arenot indicated for the treatment of patients with type 1 diabetes mellitus.

Patientstreated with Dapagliflozin and Metformin Extended Release tablets who present with signs and symptomsconsistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of bloodglucose levels as ketoacidosis associated with Dapagliflozin and Metformin Extended Release tabletsmay be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozinand Metformin Extended Release tablets should be discontinued, the patient should be evaluatedand prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid andcarbohydrate replacement.

Inmany of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosiswas not immediately recognized, and the institution of treatment was delayed because the presentingblood glucose levels were below those typically expected for diabetic ketoacidosis (often less than250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolicacidosis 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, acutefebrileIlness,reducedcaloricintake,surgery,pancreaticdisorderssuggestinginsulindeficiency (e.g.,type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Beforeinitiating Dapagliflozin and Metformin Extended Release tablets, consider factors in the patient historythat may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restrictionand alcohol abuse.

Forpatients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin and MetforminExtended Release tablets for at least 3 days prior to surgery.

Considermonitoringforketoacidosisandtemporarilydiscontinuing Dapagliflozinand Metformin Extended Releasetablets in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting dueto acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Dapagliflozinand Metformin Extended Release tablets.

Educatepatients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozinand Metformin Extended Release tablets and seek medical attention immediately if signs andsymptomsoccur.

AcuteK idney I njury and I m pairm ent in Renal Function

Dapagliflozincauses intravascular volume contraction, and can cause renal impairment. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receivingdapagliflozin: some reports involved patients younger than 65 years of age.
Beforeinitiating Dapagliflozin and Metformin Extended Release tablets, consider factors that may predisposepatients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heartfailure, and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarilydiscontinuing Dapagliflozin and Metformin Extended Release tablets in any setting of reduced oralintake (such as acute illness or fasting) or fluid losses (gastrointestinal illness or excessive heat exposure);monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinueDapagliflozin and Metformin Extended Release tablets promptly and institute treatment.
Renalfunction should be evaluated prior to initiation of Dapagliflozin and Metformin HCl Extended Releasetablets and monitored periodically thereafter. Use of Dapagliflozin and Metformin HCl Extended Releasetablets is not recommended when the eGFR is less than 45 mL/min/1.73 m2. Dapagliflozin and MetforminHCl Extended Release tablets is contraindicated in patients with an eGFR below 30 mL/min/1.73m2.

Urosepsisand P yelonephritis
Therehave been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritisrequiring hospitalization in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatmentwith SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs andsymptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia w ith Concom itant Use w ith I nsulin and I nsulin Secretagogues
Insulinand insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Dapagliflozin andMetformin HCl Extended-release may increase the risk of hypoglycemia when combined with insulin and/oran insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be requiredto minimize the risk of hypoglycemia when used in combination with Dapagliflozin and MetforminHCl Extended Release tablets.

NecrotizingFasciitis of the P erineum (Fournier’s Gangrene)
Reportsof necrotizing fasciitis of the perineum (Fournier’s Gangrene), a rare but serious and life-threateningnecrotizing infection requiring urgent surgical intervention, have been identified in

postmarketingsurveillance 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.
Patientstreated with Dapagliflozin and Metformin HCl Extended Release tablets presenting with pain or tenderness,erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessedfor necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibioticsand, if necessary, surgical debridement. Discontinue Dapagliflozin and Metformin HCl Extended Releasetablets, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemiccontrol.

Vitamin B 12 Concentrations
Incontrolled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normalserum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients.This decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complexis, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuationof metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitaminB12 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 inpatients on Dapagliflozin and Metformin HCl Extended Release tablets and manage any abnormalities

GenitalM ycotic I nfections
Dapagliflozinincreases the risk of genital mycotic infections. Patients with a history of genital mycotic infectionswere morelikelyto developgenitalmycoticinfections.Monitorandtreatappropriately.

Thismedicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, theLapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5Interaction with other medicinal products and other forms of interactions:
Positive Urine Glucose Test
Dapagliflozin

Monitoringglycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitorsas SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.Use alternative methods to monitor glycemic control.

Interference w ith 1, 5-anhydroglucitol (1, 5-AG) Assay

Dapagliflozin

Monitoringglycemic control with 1, 5-AG assay is not recommended as measurements of 1, 5-AG are unreliablein assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitorglycemic control.

CarbonicAnhydrase I nhibitors

Topiramateor other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequentlycauses a decrease in serum bicarbonate and induce non-anion gap, hyperchloraemic metabolic acidosis.Concomitant use of these drugs with Dapagliflozin and Metformin Extended Release tablets may increasethe risk for lactic acidosis. Consider more frequent monitoring of these patients.

Drugsthat Reduce M etform in Clearance

Concomitantuse of drugs that interfere with common renal tubular transport systems involved in the renalelimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin

extrusion[MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemicexposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risksof concomitant use.

Alcohol

Alcoholis known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessivealcohol intake while receiving Dapagliflozin and Metformin Extended Release tablets.

DrugsAffecting Glycaem ic Control

MetforminHC

Certaindrugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These medicationsinclude 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 MetforminHCl Extended Release tablets, observe the patient closely for loss of blood glucose control. Whensuch drugs are withdrawn from a patient receiving Dapagliflozin and Metformin HCl Extended Releasetablets, observe the patient closely for hypoglycemia.

4.6Fertility, pregnancy and lactation

Pregnancy

Basedon animal data showing adverse renal effects, Dapagliflozin and Metformin HCl Extended Release tabletsis not recommended during the second and third trimesters of pregnancy.

Limiteddata with Dapagliflozin and Metformin HCl Extended Release tablets or dapagliflozin in pregnant womenare not sufficient to determine drug-associated risk for major birth defects or miscarriage.

Publishedstudies with metformin use during pregnancy have not reported a clear association with metforminand major birth defect or miscarriage risk. There are risks to the mother and fetus associated withpoorly controlled diabetes in pregnancy

ClinicalConsiderations

Disease-associatedmaternal and/or embryofetal risk

Poorlycontrolled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia,spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetesincreases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

HumanData

Publisheddata from post-marketing studies have not reported a clear association with metformin and majorbirth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy.However, these studies cannot definitely establish the absence of any metformin-associated riskbecause of methodological limitations, including small sample size and inconsistent comparator groups.

Lactation

RiskSummary

Thereis no information regarding the presence of Dapagliflozin and Metformin HCl Extended Release tabletsor dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production.

Limitedpublished 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 effectsof metformin on milk production. Dapagliflozin is present in the milk of lactating rats. However, dueto 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 exposuremay occur, there may be risk to the developing human kidney.

Becauseof the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozinand Metformin HCl Extended Release tablets is not recommended while breastfeeding.

Data

Dapagliflozin

Dapagliflozinwas present in rat milk at a milk/plasma ratio of 0.49, indicating that Dapagliflozin and its metabolitesare transferred into milk at a concentration that is approximately 50% of that in maternal plasma.Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic andtubular dilatations) during maturation.

MetforminHCl

Publishedclinical lactation studies report that metformin is present in human milk which resulted in infant dosesapproximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio rangingbetween 0.13 and 1. However, the studies were not designed to definitely establish the risk of useof Metformin during lactation because of small sample size and limited adverse event data collected ininfants.

Females and M ales of Reproductive P otential

Discussthe potential for unintended pregnancy with premenopausal women as therapy with metformin mayresult in ovulation in some anovulatory women.

Paediatric Use

Safetyand effectiveness of Dapagliflozin and Metformin HCl Extended Release tablets in paediatric patientsunder 18 years of age have not been established.

GeriatricUse

Dapagliflozinand Metformin HCl Extended Release tablets

NoDapagliflozin and Metformin HCl Extended Release tablets dosage change is recommended based on age.More frequent assessment of renal function is recommended in elderly patients.

Dapagliflozin

Atotal of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and older and 207 (3.5%) patientswere 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacyof dapagliflozin in improving glycemic control. After controlling for level of renal function (eGFR), efficacywas similar for patients under age 65 years and those 65 years and older. In patient's ≥65 years ofage, a higher proportion of patients treated with Dapagliflozin had adverse reactions of hypotension.

MetforminHCl

Controlledclinical studies of metformin did not include sufficient numbers of elderly patients to determine whetherthey respond differently than younger patients. In general, dose selection for an elderly patient shouldbe cautious, usually starting at the low end of the dosing range, reflecting the greater frequency ofdecreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and thehigher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renall m pairm ent

Dapagliflozin

Useof Dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m2 and is contraindicatedin patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) or ESRD. Dapagliflozinwas 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 m2, and an eGFR of 30 to less than 60 mL/min/1.73m2). The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73m2 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 returnedtowards baseline after treatment discontinuation. Patients with renal impairment using

dapagliflozinfor glycemic control may also be more likely to experience hypotension and may be at higherrisk for acute kidney injury. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m2, 13 patients receiving dapagliflozin experienced bone fractures compared to none receiving placebo.

MetforminHCl

Metforminis substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosisincreases with the degree of renal impairment. Dapagliflozin and Metformin HCl Extended Releasetablets is contraindicated in severe renal impairment, patients with an estimated glomerular filtrationrate (eGFR) below 30 mL/min/1.73 m2.

HepaticI m pairm ent

Useof metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis.Dapagliflozin and Metformin HCl Extended Release tablets is not recommended in patients with hepaticimpairment.

4.7Effects on ability to drive and use machines

Dapagliflozinor Metformin have no or negligible influence on the ability to drive and use machines. Patientsshould be alerted to the risk of hypoglycaemia when this medicinal product is used in combinationwith other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8Undesirable effects

Thefollowing important adverse reactions are described below and elsewhere in the labeling:

LacticAcidosis

Hypotension

Ketoacidosis

AcuteKidney Injury and Impairment in Renal Function

Urosepsisand Pyelonephritis

Usewith Medications Known to Cause Hypoglycemia

VitaminB 12 Concentrations

GenitalMycotic Infections

ClinicalTrials Experience

Becauseclinical trials are conducted under widely varying conditions, adverse reaction rates observed in theclinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and maynot reflect the rates observed in clinical practice.

Dapagliflozinand Metformin hydrochloride

Datafrom a prespecified pool of patients from 8 short-term, placebo-controlled studies of Dapagliflozin coadministeredwith metformin immediate- or Extended Release was used to evaluate safety. This pool includedseveral add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [DPP4]inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies, and2 studies of patients with cardiovascular disease [CVD] and type 2 diabetes who received their usual treatment[with metformin as background therapy]). For studies that included background therapy with andwithout metformin, only patients who received metformin were included in the 8-study placebo-controlledpool. Across these 8 studies 983 patients were treated once daily with Dapagliflozin 10 mg and Metforminand 1185 were treated with placebo and metformin. These 8 studies provide a mean duration ofexposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years.Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or AfricanAmerican. 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 moderatelyimpaired in 10% of patients.

Theoverall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treatedwith dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformingroup. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonlyreported events leading to discontinuation and reported in at least 3 patients treated with dapagliflozin10mgandmetforminwererenalimpairment(0.7%),increasedbloodcreatinine(0.2%), decreasedrenal creatinine clearance (0.2%), and urinary tract infection (0.2%).

Table1 shows common adverse reactions associated with the use of dapagliflozin and metformin. These adversereactions were not present at baseline, occurred more commonly on dapagliflozin and metformin thanon placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin10 mg.

Table1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozinand Metformin

	%of Patients		
	Poolof 8 Placebo-Controlled Studies		
AdverseReaction	Placebo and Metformin N=1185	Dapagliflozin 5 mg and Metformin N=410	Dapagliflozin 10 mg and Metformin N=983
Female genital mycotic infections*	1.5	9.4	9.3
Nasopharyngitis	5.9	6.3	5.2
Urinarytract infections†	3.6	6.1	5.5
Diarrhea	5.6	5.9	4.2
Headache	28	5.4	3.3
Male genital mycotic infections‡	0	4.3	3.6
Influenza	2.4	4.1	2.6

	%ofPatients		
	Poolof 8 Placebo-Controlled Studies		
AdverseReaction	Placebo and Metformin N=1185	Dapagliflozin 5 mg and Metformin N=410	Dapagliflozin 10 mg and Metformin N=983
Nausea	2.0	3.9	2.6
Backpain	3.2	3.4	2.5
Dizziness	22	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
Increasedurination§	1.4	2.4	2.6
Discomfortwith urination	1.1	2.2	1.6

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

forfemales: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg andmetformin=430).

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

‡Genital mycotic infections include the following adverse reactions, listed in order of frequency reported formales: 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.

Metform in HCl
Inplacebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting werereported 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 discontinuationof study medication in 0.6% of the patients treated with metformin extended-release.

Poolof 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg for Glycemic Control
Dapagliflozin

Thedata in Table 2 are derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studiesdapagliflozin was used as monotherapy, and in 8 studies dapagliflozin was used as add-on to backgroundantidiabetic therapy or as combination therapy with metformin [see CLINICAL STUDIES (14.1)].

Thesedata reflect exposure of 2338 patients to dapagliflozin with a mean exposure duration of 21 weeks. Patientsreceived 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

AfricanAmerican. At baseline, the population had diabetes for an average of 6 years, had a mean HbA1c of8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normalor mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73m2).

Table2 shows common adverse reactions associated with the use of dapagliflozin. These adverse reactionswere not present at baseline, occurred more commonly on dapagliflozin than on placebo, and occurredin at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table2: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin

	%of Patients		
	Poolof 12 Placebo-Controlled Studies		
AdverseReaction	Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
Femalegenital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinarytract infections†	3.7	5.7	4.3
Backpain	3.2	3.1	4.2
Increasedurination‡	1.7	2.9	3.8

AdverseReaction	%of Patients Poolof 12 Placebo-Controlled Studies Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
Malegenital mycotic infections§	0.3	2.8	2.7
Nausea	2.4	2.6	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfortwith urination	0.7	1.6	2.1
Painin extremity	1.4	2.0	1.7

*Genital mycotic infections include the following adverse reactions, listed in order of frequency reported forfemales: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genitalinfection, 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: urinarytract 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 formales: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penileinfection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716,dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

Poolof 13 Placebo-Controlled Studies for Dapagliflozin 10 mg for Glycemic Control

Dapagliflozin10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 placebo-controlledstudies, 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 treatedonce daily with dapagliflozin 10 mg for a mean duration of exposure of 22 weeks. The mean age ofthe population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the populationwere 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% hadestablished microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patientsand moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m2).

VolumeDepletion

Dapagliflozincauses an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactionsrelated 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 theDECLARE study are shown in Table 3 [see WARNINGS AND PRECAUTIONS (5.2)].

Table3: Adverse Reactions of Volume Depletion* in Clinical Studies with Dapagliflozin

	Poolof 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	Dapagliflozin 5mg	Dapagliflozin 10mg	Placebo	Dapagliflozin 10mg	Placebo	Dapagliflozin 10mg

Overall population N(%)	N=13935 (0.4%)	N=11457 (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	n=500 (1.8%)	n=400	n=313 (9.7%)	n=2674 (1.5%)	n=2366 (2.5%)	n=9345 (6.1%)	n=8657 (6.6%)
Patients with2 moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73m2	n=1071 (1.9%)	n=1071 (0.9%)	n=891 (1.1%)	n=2684 (1.5%)	n=2655 (1.9%)	n=6583 (4.6%)	n=6035 (5.8%)
Patients ≥65 years of age	n=2761 (0.4%)	n=2161 (0.5%)	n=2043 (1.5%)	n=7116 (0.8%)	n=6651 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

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

Hypoglycemia

The frequency of hypoglycemia by study 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 5mg	Dapagliflozin 10mg
Add-onto 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 DPP 4 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-onto 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 (21.8)	55(25.9)	45(23.0)

*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 regardlessof glucose level.

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

‡OAD = oral antidiabetic therapy.

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

GenitalM ycotic I nfections

Genitalmycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections werereported 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 in0% of placebo-treated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections were morefrequently reported in females than in males (see Table 2). The most frequently reported genital mycoticinfections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a historyof genital mycotic infections were more likely to have a genital mycotic infection during the study thanthose with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin5 mg, and dapagliflozin 10 mg, respectively). In the DECLARE study, serious genital mycotic infectionswere reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treatedwith placebo. Genital mycotic infections 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.

HypersensitivityReactions

Hypersensitivityreactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment.Across the clinical program, serious anaphylactic reactions and severe cutaneous adverse reactionsand angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapagliflozin-treatedpatients. If hypersensitivity reactions occur, discontinue use of dapagliflozin; treat perstandard of care and monitor until signs and symptoms resolve.

Ketoacidosis

Inthe DECLARE study, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in thedapagliflozin-treated group and in 12 out of 8569 patients in the placebo group. The events were evenlydistributed over the study period.

LaboratoryTests

Increases in Serum Creatinine and Decreases in eGFR

Dapagliflozin

Initiationof Dapagliflozin causes an increase in serum creatinine and decrease in eGFR. In patients with normalor mildly impaired renal function at baseline, the serum creatinine and eGFR returned to baseline atWeek 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30to less than 60 mL/min/1.73 m2)

Increase in Hem atocrit

Dapagliflozin

Inthe pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observedin dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximummean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocritwere −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocritvalues >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treatedpatients.

Increase in Serum I norganic P hosphorus

Dapagliflozin

Inthe pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels werereported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebo-treated patients(mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patientswith marked laboratory abnormalities of hypophosphatemia (≥5.6 mg/dL if age 1765 or ≥5.1 - mg/dLif age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7%versus 0.9%, respectively).

Increase in Low -Density Lipoprotein Cholesterol Dapagliflozin

Dapagliflozin

Inthe pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in dapagliflozin-treatedpatients compared to placebo-treated patients. Mean percent change from baseline atWeek 24 were 0.0% versus 2.5% for total cholesterol and −1.0% versus 2.9% for LDL cholesterol in theplacebo and dapagliflozin 10 mg groups, respectively.

Vitamin B 12 Concentrations

Metforminhydrochloride

Inmetformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serumvitamin B12 levels was observed in approximately 7% of patients.

Post m ark eting Ex perience

Dapagliflozin

Additionaladverse reactions have been identified during post approval use of Dapagliflozin. Because thesereactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliablyestimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- AcuteKidney Injury
- Urosepsisand Pyelonephritis
- NecrotizingFasciitis of the Perineum (Fournier's Gangrene)
- Rash
- MetforminHCl
- Cholestatic,hepatocellular, and mixed hepatocellular liver injury

4.9Overdose

Dapagliflozin

Therewere no reports of overdose during the clinical development program for dapagliflozin. In the eventof an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measuresas dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not beenstudied.

Metforminhydrochloride

Overdoseof metformin hydrochloride has occurred, including ingestion of amounts >50 grams. Hypoglycemiawas reported in approximately 10% of cases, but no causal association with metformin hydrochloridehas been established. Lactic acidosis has been reported in approximately 32% of metforminoverdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamicconditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patientsin whom metformin over dosage is suspected.

5.PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic Properties

Pharmacotherapeuticgroup: Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs, ATCcode: A10BD15

Dapagliflozinand Metformin Extended Release tablets combine two antihyperglycaemic agents with complementarymechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin,a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a biguanide.

Dapagliflozin

Sodium-glucosecotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majorityof 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 thresholdfor glucose, and thereby increases urinary glucose excretion.

Metforminhydrochloride

Metforminimproves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandialplasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorptionof glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects,except in unusual circumstances, and does not cause hyperinsulinemia. With metformin therapy,insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin responsemay actually decrease.

5.2Pharmacokinetic Properties

Dapagliflozinand Metformin Extended Release tablets combination tablets are considered to be bioequivalentto coadministration of corresponding doses of Dapagliflozin and Metformin hydrochloride ExtendedRelease administered together as individual tablets.

Theadministration of Dapagliflozin and Metformin Extended Release tablets in healthy subjects after a standardmeal compared to the fasted state resulted in the same extent of exposure for both Dapagliflozinand Metformin Extended Release tablets. Compared to the fasted state, the standard meal resultedin 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of Dapagliflozin. Thiseffect of food is not considered to be clinically meaningful. Food has no relevant effect on the

pharmacokineticsof Metformin when administered as Dapagliflozin and Metformin Extended Release tabletscombination tablets.

Absorption

Dapagliflozin

Followingoral administration of Dapagliflozin, the maximum plasma concentration (Cmax) is usually attainedwithin 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increasein Dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozinfollowing the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fatmeal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alterAUC as compared with the fasted state. These changes are not considered to be clinically meaningfuland Dapagliflozin can be administered with or without food.

Metforminhydrochloride

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

Distribution

Dapagliflozin

Dapagliflozinis approximately 91% protein bound. Protein binding is not altered in patients with renal or hepaticimpairment.

Metforminhydrochloride

Distributionstudies with Extended Release metformin have not been conducted; however, the apparent volumeof distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mgaveraged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, whichare more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

Themetabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearancepathway 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.

Metforminhydrochloride

Intravenoussingle-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in theurine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliaryexcretion.

Metabolismstudies with Extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozinand related metabolites are primarily eliminated via the renal pathway. Following a single 50 mgdose 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% ofthe dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately12.9 hours following a single oral dose of dapagliflozin 10 mg.

Metforminhydrochloride

Renalclearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretionis the major route of metformin elimination. Following oral administration, approximately 90% ofthe absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-lifeof approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggestingthat the erythrocyte mass may be a compartment of distribution.

SpecificP opulations

RenalI m pairm ent

Dapagliflozin

Atsteady-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 ofdapagliflozinthatwere45%,2.04-fold,and3.03-foldhigher,respectively,ascomparedtopatients

withtype 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients withtype 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour glucoseexcretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes andmild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patientswith type 2 diabetes with normal renal function. The impact of hemodialysis on Dapagliflozin exposureis not known

Metforminhydrochloride

Inpatients with decreased renal function, the plasma and blood half-life of Metformin is prolonged and therenal clearance is decreased

Hepaticl m pairm ent

Dapagliflozin

Inpatients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean Cmax and AUC ofdapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjectsfollowing single-dose administration of 10 mg dapagliflozin. These differences were not consideredto be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh Class C), meanCmax and AUC of Dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthymatched controls.

Metforminhydrochloride

Nopharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Geriatric

Dapagliflozin

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

Metforminhydrochloride

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

Pediatric

Pharmacokineticsof Dapagliflozin and Metformin Extended Release tablets in the pediatric population has notbeen studied.

Gender

Dapagliflozin

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

Metforminhydrochloride

Metforminpharmacokinetic parameters did not differ significantly between healthy subjects and patients withtype 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinicalstudies in patients with type 2 diabetes, the antihyperglycaemic effect of Metformin was comparablein males and females.

Race

Dapagliflozin

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

Metforminhydrochloride

Nostudies of Metformin pharmacokinetic parameters according to race have been performed. In controlledclinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect wascomparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

BodyWeight

Dapagliflozin

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

DrugI nteractions

Specificpharmacokinetic drug interaction studies with Dapagliflozin and Metformin HCl Extended Release tabletshave not been performed, although such studies have been conducted with the individual Dapagliflozinand Metformin components.

5.3Preclinical safety Data

Dapagliflozinand Metformin Extended Release tablets

Noanimal studies have been conducted with Dapagliflozin and Metformin Extended Release tablets to evaluatecarcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findingsin the studies with dapagliflozin and metformin individually.

Dapagliflozin

Dapagliflozindid not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicitystudies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20mg/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/day based on AUC exposure. In rats, the highest dose was approximately131 times (males) and 186 times (females) the clinical dose of 10 mg/day based on AUC exposure.

Dapagliflozinwas negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicityassays in the presof S9 activation and at concentrations ≥100 µg/mL. Dapagliflozin ence wasnegative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats atexposure multiples >2100 times the clinical dose.

Therewas no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does notrepresent a genotoxic risk to humans.

Dapagliflozinhad no effects on mating, fertility, or early embryonic development in treated male or femalerats at exposure multiples ≤1708 and 998 times the maximum recommended human doses in malesand females, respectively.

Metform in hydrochloride

Long-termcarcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosingduration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively. These

dosesare both approximately 4 times the MRHD of 2000 mg based on body surface area comparisons. Noevidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there wasno tumorigenic potential observed with metformin in male rats. There was, however, an increased incidenceof benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Therewas 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. Fertilityof 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 MRHD based on body surface area comparisons.

6.PHARMACEUTICAL PARTICULARS

6.1List of excipients:

MicrocrystallineCellulose

AnhydrousLactose

Crospovidone

Polysorbate80

Colloidalsilicon dioxide

FerricOxide Yellow/ Yellow Iron Oxide

PovidoneK-30

GlycerylBehenate

HydroxyPropyl Methyl Cellulose 100 M Premium

HydroxyPropyl Methyl Cellulose 200M Premium

MagnesiumStearate

HydroxyPropyl Methyl Cellulose E3/Methocel

Talc

Polyethyleneglycol

OpadryOrange 85F530162

(PolyvinylAlcohol-part. Hydrolyzed, Titanium Dioxide, Macrogol/PEG, Talc, FD&C Yellow #6/Sunset YellowFCF Aluminium Lake, FD&C Yellow #6/ Sunset Yellow FCF Aluminium Lake)

6.2Incompatibilities:

Notapplicable

6.3Shelf life:

24months

6.4Special precautions for storage:

Storebelow 30°C, store in the original package. Protect from light

6.5Nature and contents of container:

10Tablets are packed in Alu-Alu blister pack. Such 3 blisters are packed in a carton along with pack insert.

6.6Special precautions for disposal and other handling

Anyunused product or waste material should be disposed of in accordance with local requirements

7.Marketing Authorization Holder:

MICROLABS LIMITED
31,race course road
Bangalore-560001
INDIA

8.Marketing Authorization Numbers

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9.Date of first authorization

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10.Date of revision of the text

Dec2021