SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Dapzin 5-M

1.1 Strength

5/500 mg

1.2 Pharmaceutical form

Tablets

Orange colored oval shaped, beveled edge, biconvex, film coated tablets de bossed with "DM 1" on one face and plain on other face.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dapagliflozin..... ……..5 mg

Metformin Hydrochloride USP... .....500 mg

(as extended release form)

Excipient with known effect: Each film-coated tablet contains 25.285 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Orange colored oval shaped, beveled edge, biconvex, film coated tablets de bossed with "DM 1" on one face and plain on other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Dapagliflozin and Metformin HCl extended-release is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

Dapagliflozin and Metformin HCl extended-release is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

4.2 Posology and method of administration:

Recommended Dosing

Healthcare providers should individualize the starting dose of Dapagliflozin and Metformin Extended Release based on the patient's current treatment.

Dapagliflozin and Metformin Extended Release should be taken once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.

Dapagliflozin and Metformin Extended Release tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of Dapagliflozin and Metformin Extended Release will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 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 XR should skip their last dose before starting Dapagliflozin and Metformin Extended Release.

In patients with volume depletion, correcting this condition prior to initiation of Dapagliflozin and Metformin Extended Release is recommended.

Patients with Renal Impairment

Assess renal function before initiating Dapagliflozin and Metformin Extended Release therapy and periodically thereafter.

Dapagliflozin and Metformin Extended Release is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m2

No dose adjustment for Dapagliflozin and Metformin Extended Release is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73m2 or greater).

Discontinuation for Iodinated Contrast Imaging Procedures

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

4.3 Method of administration

For oral use.

4.4 Contraindications:

Dapagliflozin and Metformin Extended Release is contraindicated in patients with:

Moderate to severe renal impairment (eGFR below 60 mL/min/1.73 m 2), end stage renal disease or patients on dialysis

History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride

Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma

Diabetic ketoacidosis should be treated with insulin.

4.5 Special warning and precautions:

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 bradyarrhythmia have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an

increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase 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 Extended Release.

In Dapagliflozin and Metformin Extended Release -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute 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 Extended Release 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 post marketing 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 Extended Release, obtain an estimated glomerular filtration rate (eGFR).

Dapagliflozin and Metformin Extended Release is contraindicated in patients with an eGFR less than 60 mL/minute/1.73 m2

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

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 Extended Release 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 post marketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Dapagliflozin and Metformin Extended Release is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin And Metformin Extended Release 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 Extended Release may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin and Metformin Extended Release should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

Acute Kidney Injury and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction, and can cause renal impairment. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin: some reports involved patients younger than 65 years of age.

Before initiating Dapagliflozin and Metformin Extended Release, 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 And Metformin Extended Release

in any setting of reduced oral intake (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, discontinue Dapagliflozin and Metformin Extended Release promptly and institute treatment.

Urosepsis and Pyelonephritis

There have been post marketing 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.

Use with Medications Known to Cause Hypoglycemia

Dapagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Dapagliflozin and Metformin Extended Release.

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

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. This decrease, possibly due to interference with B12 absorption

from the B12-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Dapagliflozin and Metformin Extended Release and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2- to 3-year intervals may be useful.

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.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C occur with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating Dapagliflozin and Metformin Extended Release.

Bladder Cancer

Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and haematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin.

There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, Dapagliflozin And Metformin Extended Release should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with Dapagliflozin and Metformin Extended Release should be considered.

Macro vascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Dapagliflozin and Metformin Extended Release.

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

4.6 Paediatric population

Not stated.

4.7 Interaction with other medicinal products and other forms of interactions:

Positive Urine Glucose Test

Dapagliflozin

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

Interference with 1, 5-anhydroglucitol (1, 5-AG) Assay

Dapagliflozin

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

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloraemic metabolic acidosis. Concomitant use of these drugs with Dapagliflozin And Metformin Extended Release 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 Extended Release

Use with Other Drugs

Metformin hydrochloride

Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the 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 Extended Release, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving Dapagliflozin and Metformin Extended Release, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and of metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

4.8 Additional information on special populations

None stated

4.9 Paediatric population

None Stated

4.10 Fertility, Pregnancy and lactation

4.10.1 Women of childbearing potential / Contraception in males and females

None Stated

4.10.2 Pregnancy

During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Dapagliflozin and Metformin Extended Release should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4.10.3 Beast-feeding

It is not known whether Dapagliflozin and Metformin Extended Release is excreted in human milk.

Data in juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and in the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue Dapagliflozin and Metformin Extended Release, taking into account the importance of the drug to the mother.

4.10.4 Fertility

No data available.

4.11 Effects on ability to drive and use machine:

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

4.12 Undesirable effects:

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

Lactic Acidosis

Hypotension

Ketoacidosis

Acute Kidney Injury and Impairment in Renal Function

Urosepsis and Pyelonephritis

Use with Medications Known to Cause Hypoglycemia

Vitamin B 12 Concentrations

Genital Mycotic Infections

Increases in Low-Density Lipoprotein Cholesterol (LDL-C)

Bladder Cancer

Dapagliflozin and Metformin hydrochloride

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 combination with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metformin, 2 initial combinations with metformin studies, and 2 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 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%) of 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.

Hypersensitivity Reactions

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

Increase in Hematocrit

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. 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 Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported 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 patients with marked laboratory abnormalities of hypophosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if 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

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 change 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.

Vitamin B12 Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on Dapagliflozin and Metformin Extended Release and any apparent abnormalities should be appropriately investigated and managed.

4.13 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 hydrochloride

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

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

Metformin hydrochloride

Metformin improves glucose tolerance in patients with type 2 diabetes, 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. Metformin does not produce hypoglycemia in either patient 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 response may actually decrease.

5.2 Pharmacokinetic Properties:

Dapagliflozin and Metformin Extended Release combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride extended-release administered together as individual tablets.

The administration of Dapagliflozin and Metformin Extended Release 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 Extended Release combination tablets.

<u>Absorption</u>

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and

prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} 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 C_{max} and T_{max} of metformin.

Distribution

Dapagliflozin

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

Metformin hydrochloride

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 hydrochloride

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 hydrochloride

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

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 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 type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known

Metformin hydrochloride

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

Hepatic Impairment

Dapagliflozin

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

Metformin hydrochloride

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 hydrochloride

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 Extended Release 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 hydrochloride

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 antihyperglycaemic 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 hydrochloride

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 antihyperglycaemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

5.3 Preclinical safety Data:

Dapagliflozin and Metformin Extended Release

No animal studies have been conducted with Dapagliflozin and Metformin Extended Release 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/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/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 ≥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 >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 ≤1708 and 998 times the maximum recommended human doses in males and females, respectively.

Metformin hydrochloride

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 MRHD 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 MRHD based on body surface area comparisons.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystalline Cellulose

Anhydrous Lactose

Crospovidone

Polysorbate 80

Colloidal silicon dioxide

Ferric Oxide Yellow/ Yellow Iron Oxide

Povidone

Glyceryl Behenate

Hydroxy Propyl Methyl Cellulose 100 M Premium

Hydroxy Propyl Methyl Cellulose 200M Premium

Magnesium Stearate

Hydroxy Propyl Methyl Cellulose E3

Talc

Polyethylene glycol 6000

Opadry Orange 85F530162

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Store below 30°C. Keep out of reach of children.

6.5 Nature and contents of container:

Alu/Alu Blister pack Blister pack of 10 tablets, such 3 blisters are packed in printed outer carton with package insert.

6.6 Special precautions for disposal and other handling

No special requirements**.**

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

INDIA

8. MARKETING AUTHORIZATION NUMBER

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9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

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10. DATE OF REVISION OF THE TEXT

May 2024

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable

13. DOCUMENT REVISION HISTORY

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