SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DAPZIN 10-N

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dapagliflozin 10 mg

Metformin Hydrochloride USP 500 mg

(as extended release form)

For Full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Recommended Dosing

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

Dapagliflozin and Metformin Extended Release should be taken once daily in the morning with fo
gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. Dapaglifl
Metformin Extended Release tablets must be swallowed whole and never crushed, cut, or
Occasionally, the inactive ingredients of Dapagliflozin and Metformin Extended Release will be eli
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
daily.
For patients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl extended-release,
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 m
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 Dapa
and Metformin Extended Release.
In patients with volume depletion, correcting this condition prior to initiation of Dapagliflo
Metformin Extended Release is recommended.

Patients with Renal Impairment

Assess renal function before initiating Dapagliflozin and Metformin Extended Release thera
periodically thereafter.
Dapagliflozin and Metformin Extended Release is contraindicated in patients with an estimated glo
filtration rate (eGFR) below 60 mL/min/1.73 m2
No dose adjustment for Dapagliflozin and Metformin Extended Release is needed in patients with m
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 c
imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patie
will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the
procedure; restart Dapagliflozin and Metformin Extended Release if renal function is stable

4.3 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 di
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 Diabeti
ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal case cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, m abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotens resistant bradyarrhythmia have occurred with severe acidosis. Metformin-associated lactic acido characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasm generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood level may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be in promptly in a hospital setting, along with immediate discontinuation of Dapagliflozin and Me Extended Release.

In Dapagliflozin And Metformin Extended Release -treated patients with a diagnosis or strong susp lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accu metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute und 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 symptom instruct them to discontinue Dapagliflozin and Metformin Extended Release and report these sy to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommen 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 occu patients with significant renal impairment. The risk of metformin accumulation and metformin-ass lactic acidosis increases with the severity of renal impairment because metformin is substantially e by the kidney. Clinical recommendations based upon the patient's renal function include

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

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

Obtain an eGFR at least annually in all patients taking dapagliflozin and metformin extended re 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 in dapagliflozin, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1. elderly patients, or patients on loop diuretics.

Before initiating Dapagliflozin And Metformin Extended Release in patients with one or more characteristics, volume status should be assessed and corrected. Monitor for signs and symp hypotension after initiating therapy.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization ha identified in post marketing surveillance in patients with type 1 and type 2 diabetes mellitus taking s glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis ha reported in patients taking dapagliflozin. Dapagliflozin and Metformin Extended Release is not in for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin and Metformin Extended Release who present with signs and sy consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood levels as ketoacidosis associated with Dapagliflozin And Metformin Extended Release may be prese if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin and Me Extended Release should be discontinued, the patient should be evaluated and prompt treatment 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 ha post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in receiving dapagliflozin: some reports involved patients younger than 65 years of age.

Before initiating Dapagliflozin And Metformin Extended Release, consider factors that may pre patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider tem discontinuing Dapagliflozin and Metformin Extended Release in any setting of reduced oral intak as acute illness or fasting) or fluid losses (gastrointestinal illness or excessive heat exposure); patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, disc Dapagliflozin and Metformin Extended Release promptly and institute treatment.

Urosepsis and Pyelonephritis

There have been post marketing reports of serious urinary tract infections including urosep pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including dapag Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients f 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 th hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents a in combination with Dapagliflozin and Metformin Extended Release.

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of could occur when caloric intake is deficient, when strenuous exercise is not compensated by supplementation, or during concomitant use with other glucose-lowering agents (such as sulfon and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or p insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycem 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 pr normal serum vitamin B12 levels, without clinical manifestations, was observed in approximatel patients. This decrease, possibly due to interference with B12 absorption from the B12-intrinsi complex is, however, very rarely associated with anemia and appears to be rapidly reversib discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic par on an annual basis is advised in patients on Dapagliflozin and Metformin Extended Release a apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appea predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitam 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 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 i Dapagliflozin and Metformin Extended Release.

Bladder Cancer

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

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

Macro vascular Outcomes

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

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

4.5 Interaction with other medicinal products and other forms of interaction *Positive Urine Glucose Test*

Dapagliflozin

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

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphe frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloraemic m acidosis. Concomitant use of these drugs with Dapagliflozin And Metformin Extended Release may i 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 t elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin ex [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase s exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients 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 medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid pr estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel b drugs, and isoniazid. When such drugs are administered to a patient receiving Dapagliflozin and Me Extended Release, the patient should be observed closely for loss of glycemic control. When such are withdrawn from a patient receiving Dapagliflozin and Metformin Extended Release, the patient be observed closely for hypoglycemia.

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

4.6 Pregnancy and lactation Pregnancy

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

Lactation

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 (rena and tubular dilatations) during maturation. Since human kidney maturation occurs in utero an first 2 years of life when lactational exposure may occur, there may be risk to the developing human Because many drugs are excreted in human milk and because of the potential for serious adverse re in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursi discontinue Dapagliflozin and Metformin Extended Release, taking into account the importance of t to the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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 dapa coadministered with metformin immediate- or extended-release was used to evaluate safety. T included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies studies of patients with cardiovascular disease [CVD] and type 2 diabetes who received thei treatment [with metformin as background therapy]). For studies that included background thera and without metformin, only patients who received metformin were included in the 8-study p controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean d of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 7 Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately i in 10% of patients.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapa treatment. Across the clinical program, serious anaphylactic reactions and severe cutaneous reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapag treated patients. If hypersensitivity reactions occur, discontinue use of dapagliflozin; treat per stan 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 valu observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, w maximum mean difference from baseline was observed. At Week 24, the mean changes from bas hematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By W hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapaglif mg–treated patients.

Increase in Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphoru were reported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebotreated p (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
65 or ≥5.1 mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo g
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 rep
dapagliflozin-treated patients compared to placebo-treated patients. Mean percent change from
at Week 24 were 0.0% versus 2.5% for total cholesterol and −1.0% versus 2.9% for LDL cholestero
placebo and dapagliflozin 10 mg groups, respectively.

Vitamin B12 Concentrations

Metformin hydrochloride

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

4.9 Overdose

Dapagliflozin

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

Metformin hydrochloride

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dapagliflozin and Metformin Extended Release combines two antihyperglycaemic agent complementary mechanisms of action to improve glycemic control in patients with type 2 d dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochl biguanide.

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inh SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers th threshold for glucose, and thereby increases urinary glucose excretion.

Metformin hydrochloride

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both ba postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases in absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose upta utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in subjects, except in unusual circumstances, and does not cause hyperinsulinemia. With metformin t insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin respo actually decrease.

5.2 Pharmacokinetic properties

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

The administration of Dapagliflozin and Metformin Extended Release in healthy subjects after a s meal compared to the fasted state resulted in the same extent of exposure for both dapagliflo metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% re and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of foo considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of me when administered as Dapagliflozin and Metformin Extended Release combination tablets.

Absorption

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is

usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose propor with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavaila dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozi high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but d alter AUC as compared with the fasted state. These changes are not considered to be clinically mea and dapagliflozin can be administered with or without food.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, Cmax is achieved with a median va hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) f metformin extended-release tablet increased by approximately 50% when given with food. There effect of food on Cmax and Tmax of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with hepatic impairment. *Metformin hydrochloride*

Distribution studies with extended-release metformin have not been conducted; however, the a volume of distribution (V/F) of metformin following single oral doses of immediaterelease metfor mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfon 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 clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagli O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% 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 uncha the urine and does not undergo hepatic metabolism (no metabolites have been identified in hum 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 s
mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, resp
In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the
excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximat
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
secretion is the major route of metformin elimination. Following oral administration, approximat
of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elim
half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6
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 wit
moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic expo
dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patien
type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients w
2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour
excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes an
moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patien
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
the renal clearance is decreased

Hepatic Impairment

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean Cm
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 differences were not considered to be clinically meaningful. In patients with severe hepatic imp (Child-Pugh Class C), mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher, resp as compared to healthy matched controls.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairme

Geriatric

Dapagliflozin

Based on a population pharmacokinetic analysis, age does not have a clinically meaningful e systemic exposures of dapagliflozin; thus, no dose adjustment is recommended. *Metformin hydroc* Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects sugg total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is inc compared to healthy young subjects. From these data, it appears that the change in me 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 been studied.

Gender

Dapagliflozin

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

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in co clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was com 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 co clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was com 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 e carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the finding studies with dapagliflozin and metformin individually.

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both ma females. The highest doses evaluated in mice were approximately 72 times (males) and 105 times (the clinical dose of 10 mg/day based on AUC exposure. In rats, the highest dose was approxima 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 repair in rats at exposure multiples >2100 times the clinical dose.

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

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male o rats at exposure multiples ≤1708 and 998 times the maximum recommended human doses in ma females, respectively.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) a (dosing duration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively 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 female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats was, however, an increased incidence of benign stromal uterine polyps in female rats treated w mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test 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 mg/kg/day, which is approximately 3 times the MRHD based on body surface area comparisons.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystal line Cellulose
Anhydrous Lactose
Crospovidone
Polysorbate 80
Colloidal silicon dioxide
Ferric Oxide Yellow/ Yellow Iron Oxide
Povidone K-30
Glyceryl Behenate
Hydroxy Propyl Methyl Cellulose 100 M Premium
Hydroxy Propyl Methyl Cellulose 200M Premium
Magnesium Stearate
Talc
Polyethylene glycol
Opadry Pink 85F540300

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep medicine away from the reach of children

6.5 Nature and contents of container

Blister pack of 10's

7. Marketing Authorization Holder:

Micro Labs Limited No 31, Race Course Road Bangalore-560010.

INDIA

Manufacturing site

Micro Labs Limited No 31, Race Course Road Bangalore-560010.

INDIA

8. Marketing Authorization Numbers

H2022/CTD8929/19817

9. Date of first authorization

08/08/2023

10. Date of revision of the text

08/08/2023